Chronic Tobacco Smoking and Gastric Cancer: A Review

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ABSTRACT

Cigarette smoke contains mutagenic chemicals that are in the “probably carcinogenic” or “possibly carcinogenic” categories. In addition to free radicals, cigarette smoke is also rich in combustion toxic gases that can reach a very high concentration and become involved in more radical formation. Smoking increases the risk of cancers of the lungs, bladder, cervix, kidney, larynx (voice box), pharynx (upper throat), nose, mouth, oesophagus (foodpipe), pancreas, stomach, liver and some types of leukaemia. Within this review article we will focus on the correlation between smoking and oxidative stress and the role of smoking in increasing the risk of gastric cancer.

1. Introduction

Cancer is defined as disturbance of growth characterized by excessive proliferation of cells without apparent relation to the physiological demands of the organs involved. Cancer is the uncontrolled growth and spread of cells that may affect almost any tissue of the body. Cancer causes 6 million deaths every year or 12% of deaths worldwide.

Lung cancer is the most common world-wide, accounting for 1.2 million new cases annually, followed by cancer of the breast, just over 1 million cases; colorectal, 940,000; stomach, 870,000; liver, 5,60,000; cervical, 470,000; esophageal, 410,000; head and neck, 390,000; bladder, 330,000; malignant non Hodgkins lymphomas, 290,000; leukemia, 250,000; prostate and testicular, 250,000; pancreatic, 216,000; ovarian, 190,000; kidney, 190,000; endometrial, 188,000; nervous system, 175,000; melanoma,133,000; thyroid,123,000; pharynx, 65,000; and Hodgkin disease, 62,000 cases . The incidence of cancer is increasing worldwide causing millions of deaths every year. [Table 1]. [1]

1.1. Indian cancer incidence and mortality

From the population-based registries in India covering 28–30 million population from different parts of the country, the age adjusted incidence rates vary from 44 to 122 per 100,000 population in males and 52 to 128 per 100,000 females. Cancer incidence was higher in females compared to males. The incidence in rural areas was quite low compared to urban counterparts. It is estimated that presently nearly one million new cancer cases are being detected annually in the country. The lifetime cumulative risk indicates that an average of one of 10 to 13 people in the urban areas was stricken by cancer during their lifetime. In India, cancer mortality rates are under-reported due to poor recording of the cause of death(Figure 1). [1]

1.2. Causes of cancer-Environmental factors

Lifestyle habits like Cigarette smoking, tobacco chewing and dietary habits like Groundnuts and other foodstuffs infected with fungus like Aspergillus produce aflatoxin B1 can lead us to cancer. Occupational factors, which cause cancer, may include Asbestos, benzene, naphthylamines, beryllium, etc. Certain therapeutic drugs may also be carcinogenic.
The wealth of current knowledge about the influence of external environmental determinants of cancer provides significant potential for cancer control. Physical factors include solar radiation (which can give rise to skin cancer), and ionizing radiation (which induces cancer of the lung and certain other organs). Chemical Factors are for example, vinyl chloride (which can cause liver cancer), 2-naphthylamine (which can cause cancer of the bladder), and benzo(a)pyrene (which can cause tobacco-related cancers).

Biological factors are hepatitis B virus (which is a cause of liver cancer), and human papilloma virus (which is a cause of cancer of the cervix).

1.4. Phases in the development of cancer

Cancer develops in several phases, depending on the type of tissue affected. Typically, these phases are: dysplasia, cancer in situ, localized invasive cancer, regional lymph node involvement and distant metastasis (Figure 2). [2]

The first indication of abnormality is a change in the character of cells known as dysplasia. The lesion may regress spontaneously at the stage and sometimes even at the next carcinoma in situ (as indicated by the arrows in both directions).

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Table 1: Number of cancer deaths and new cancer cases in world as in 2000 and as predicted in 2020. [1]

<table>
<thead>
<tr>
<th>YEAR</th>
<th>REGION</th>
<th>NEW CASES (million)</th>
<th>NEW DEATHS (in millions)</th>
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<td>4.7</td>
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<tr>
<td></td>
<td>All countries</td>
<td>15.3</td>
<td>9.8</td>
</tr>
</tbody>
</table>

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Figure 2: Typical phases of cancer development [2]
When the abnormal cell growth reaches areas underlying the tissue of origin, the cancer is regarded as invasive. With further growth, there is increasing invasion and destruction of adjacent tissue. Often, the cancer extends to the regional lymph nodes that drain the area. Cancer cells may also spread through the blood or lymphatic system to affect other organs (distant metastasis). For example, cancer in the colon may spread to the liver or lungs.

Lung, colorectal and stomach cancer are among the five most common cancers in the world for both men and women. Among men, lung and stomach cancer are the most common cancers worldwide. For women, the most common cancers are breast and cervical cancer [2].

2. Stomach cancer (gastric cancer)

Cancer of the stomach, also called gastric cancer or gastric carcinoma, is a disease in which cancer (malignant) cells are found in the tissues of the stomach. Stomach cancer can develop in any part of the stomach and may spread throughout the stomach and to other organs. It may grow along the stomach wall into the esophagus or small intestine.

2.1. Incidence and mortality worldwide

In 2003, approximately 22,400 Americans were diagnosed with gastric cancer and 12,100 died of it (American Cancer Society, 2003). The disease is much more common in other countries, principally Japan, Central Europe, Scandinavia, Hong Kong, South and Central America, the Soviet Union, China, and Korea. In face, it is a major cause of death world wide especially in developing countries (American Cancer Society and Atlanta, 2002). The major type of gastric cancer is adenocarcinoma (90%). The remaining 10% include lymphomas, sarcomas and other rare types (Fine et al., 1985). Gastric adenocarcinomas can be further categorized into an intestinal type and a diffuse type (Lauren, 1965). Intestinal type lesions are frequently ulcerative and occur in the distal stomach more often than the diffuse type. These lesions are associated with a worse prognosis than the intestinal type. The intestinal type tends to predominate in geographic regions with a high incidence of gastric carcinoma. The decline in the incidence of gastric cancer worldwide is largely due to a decrease in the number of intestinal type lesions.

2.2. Incidence and mortality in India

Stomach cancer can develop in any part of the stomach and may spread throughout the stomach and to other organs. It may grow along the stomach wall into the esophagus or small intestine. In 1930, gastric cancer was the leading cause of cancer related deaths. In India the age standardized gastric cancer incidence per 100,000 by sex was found to be 7.7 in males and 3.8 in female. Epidemiological surveys have suggested the risk of gastric cancer to be greater among lower socioeconomic classes.

2.3. Pathological features

More than 90 percent of stomach cancers have been reported to be adenocarcinomas, and the remains are predominantly non-Hodgkin’s lymphomas or leiomyosarcomas. Differentiation between adenocarcinoma and lymphoma is critical, since the prognosis and treatment for these two cancers differ considerably. Gastric adenocarcinomas can be subdivided into two categories: an intestinal type characterized by cohesive neoplastic cells forming glandlike tubular structures, and a diffuse type in which cell cohesion is absent, so that individual cells infiltrate and thicken the stomach wall without forming a discrete mass. Intestinal-type lesions are frequently ulcerative, occur in the distal stomach more often than the diffuse type, and are often preceded by a prolonged precancerous phase. Diffuse carcinomas occur more often in young patients, develop throughout the stomach but especially in the cardia, and are associated with a worse prognosis. Although the intestinal type tends to predominate in geographic regions with a high incidence of gastric carcinoma and is less likely to be found in areas where the frequency is declining, the incidence of diffuse lesions is similar in most populations throughout the world. The decline in the incidence of gastric cancer during this century appears to be largely attributable to a decrease in the number of intestinal-type lesions. Although the identification of all adenocarcinomas as either diffuse or intestinal is not always possible, these two types of gastric cancer appear to represent disorders with different epidemiologic and etiologic factors [3].

2.4. Types of stomach cancer

The wealth of current knowledge about the influence of external environmental determinants of cancer provides significant potential for cancer control. Physical factors include solar radiation (which can give rise to skin cancer), and ionizing radiation (which induces cancer of the lung and certain other organs). Chemical Factors are for example, vinyl chloride (which can cause liver cancer), 2-naphthylamine, (which can cause cancer of the bladder), and benzo(a)pyrene (which can cause tobacco-related cancers).

Biological factors are hepatitis B virus (Which is a cause of liver cancer), and human papilloma virus (which is a cause of cancer of the cervix).

2.5. Etiology

Dietary factors associated with gastric carcinoma are increased consumption of: salted fish and meat, pickled vegetables, starch, smoked foods, and nitrates in drinking water or foods. Protective dietary factors are: fresh vegetables, citrus fruits, vitamin C. Genetic factors associated with increased risk are: blood group A; some familial cancer syndrome kindreds (Lynch Type II); a first degree relative with gastric cancer; and familial polyposis. Any condition causing chronic gastritis such as Hpylori infection, atrophic gastritis, relative alkalization of the gastric contents including atrophic gastritis, and duodenal reflux. Miscellaneous factors include smoking and Menetrier’s disease.

2.6. Pathogenesis

A unified theory of pathogenesis is not yet possible for gastric cancer, although evidence exists for the role of nitroso compounds in the formation of many gastric cancers. The dietary factors involved often are associated with increased intake of nitrates or nitrites, or a decrease in reducing agents which prevent the
formation of nitrites from nitrates. The common pathways of gastric atrophy, intestinal metaplasia and hypochlorhydria favor the introduction of nitrite forming bacteria in the stomach. Nitroso compounds formed from nitrates have been strongly implicated as carcinogenic.

2.7. Clinical correlation

Gastric cancer is symptomatic late in its course when abdominal pain and weight loss are noted. Distal tumors late in their course may present with signs of obstruction. Grossly evident bleeding either hematemesis or melena are infrequent. These tumors may present with metastasis to Virchow’s node (left supraclavicular), ovary (Krukenberg tumor), liver or peritoneum. Laboratory findings are usually not helpful in making the diagnosis. The diagnosis is usually made following endoscopy with biopsy, sometimes with a proceeding upper GI series. Standard therapy for attempted cure is radical surgery. Radiotherapy or chemotherapy have not yet been shown to increase the disease free interval. Cure rates are dependent on the stage of disease when diagnosed and are better in countries like Japan where aggressive screening of individuals at risk results in diagnosis of early asymptomatic disease. The five year survival for localized distal disease is 50%, whereas the 5 yr survival for localized proximal disease is only 10-15% [4].

2.8. Primary gastric lymphoma

Primary gastric lymphoma is a potentially curable malignancy defined as extranodal non-Hodgkin's lymphoma (NHL) confined to the stomach and draining lymph nodes, without peripheral or mediastional lymphadenopathy, lymphomatous or leukemic involvement of peripheral blood or bone marrow, or liver and spleen involvement, except by direct contiguous extension. Primary gastric NHL also is distinct from stomach involvement by advanced systemic lymphoma, which is a frequent postmortem finding. Primary gastric lymphoma is an uncommon entity, constituting about 10% of cases of NHL and 3% of cases of gastric neoplasms. Alternatively, the stomach represents the most common site of extranodal lymphoma, accounting for 20% of cases.

Although the incidence of gastric carcinoma has been decreasing in developed countries, the incidence of primary gastric lymphoma has been increasing for unclear reasons with about 5300 new cases anticipated in 1996.

Gastric lymphoma has a peak age incidence in the mid-60s, and men are more likely to be affected than women. The disease is slightly more common in whites than in other ethnic populations. Most cases of gastric NHL in the United States are intermediate or high grade, as defined by the National Cancer Institute Working Formulation (WF). In other parts of the world, especially Southern Europe, there is a significant incidence of low-grade gastric NHL. Patients with low-grade lesions typically are much younger than patients with high grade disease.

The most important development in our understanding of gastric lymphoma in the past 5 years was the recognition that NHL of all histologic grades (>90% incidence of infection). This insight has profound implications for the treatment and prevention of gastric lymphoma and has broader implications for lymphoma pathogenesis in all sites.

2.9. Clinical features

The clinical presentation of gastric lymphoma mimics that of gastric cancer. Persistent epigastric pain predominates and may occur a few weeks before diagnosis but is more often present for a long time, often longer than 6 months. Some case series have recorded persistent dyspepsia or epigastric pain for up to 6 years before the diagnosis of lymphoma. About half of patients present with recurrent gastric ulcers, gastritis, or non-specific gastric bleeding, and these symptoms also may precede the diagnosis by years. Weight loss occurs in about half of patients and appears to be related to early satiety rather than systemic effects of disease. Other constitutional symptoms, such as night sweats of fevers, are less common in patients with gastric lymphoma than in those with other hematologic malignancies. Vomiting occurs in about one third of patients. An abdominal mass is palpable in one third of cases, whereas over peripheral lymphadenopathy is unusual. The average size of the primary lesion at diagnosis is 7 to 8 cm. More than half of gastric lymphomas occur in the antrum and pre-pyloric areas. About one quarter occur in the corps, and few originate in the fundus. Fewer than 10% involve more than one region by direct extension or present as multifocal lesions.

2.10. Diagnosis

An adequate endoscopic biopsy and accurate pathologic interpretation are critical to the diagnosis of gastric lymphoma.

2.11. Gastric (nonlymphoid) sarcoma

Leiomyosarcomas are the most common of this group of gastric malignancies and make up approximately 1 to 3 percent of all gastric neoplasms. They most frequently involve the anterior and posterior walls of the gastric fundus and often ulcerate and bleed. Even those lesions that appear benign on histologic examination may behave in a malignant fashion. Leiomyosarcomas rarely invade adjacent viscera and characteristically do not metastasize to lymph nodes, but they may spread to the liver and lungs [5].

2.12. Risk factors for gastric cancer

Gastric cancer risk factors have been identified, such as Helicobacter pylori (H. pylori) infection, blood type A, chronic gastric diseases, cigarette smoking, alcohol drinking, occupational exposure and environmental exposure as well as consumption of meat including salted and cured meat, as well as smoked food, fried food, and fermented beans. In contrast, a significant negative association has been found between gastric cancer and eating fruit and vegetables, and drinking green tea. Exposure to these risk factors depends, however, on time, place, and the social background of the population at risk. In this report, we aimed at elucidating the significant risk factors of gastric cancer in India, their dose-response relationship, and, in particular, their significant synergistic effects.

2.13. Molecular biology of gastric cancer

The role of oncogenes and tumor-suppressor genes in the pathogenesis of gastric cancer has recently received considerable
attention. As in studies of colorectal cancer, allelic deletions of the MCC (mutated in colon cancer), APC (adenomatous polyposis coli), and p53 tumor-suppressor genes have been reported in 33, 34 per cent and 64 per cent of gastric cancers, respectively. Unlike both colon and pancreatic cancers, gastric cancer rarely involves mutations in the ras oncogene. Abnormalities of several growth factors and receptor systems have also been identified in gastric cancer. Patients with intestinal-type cancers have an increased frequency of overexpression of epidermal growth-factor receptor, erb B-2, and erbB-3. In contrast, diffuse lesions have been linked to abnormalities of fibroblast growth-factor systems, including the K-sam oncogene. These disparities between mutations associated with the intestinal and diffuse types of gastric cancer underscore the unique pathogenesis of each.

When superficial and surgically curable, gastric carcinoma typically produces no symptoms. Consequently, at the time of presentation, the disease is often locally advanced or metastatic. As the tumor becomes more extensive, an insidious upper abdominal discomfort may develop, ranging in intensity from a vague sense of postprandial fullness to a severe, steady pain. Anorexia, often with slight nausea, is quite common but usually not the presenting symptom. Weight loss is also frequently reported at the time of presentation. Abdominal pain and weight loss were the most frequent initial symptoms in a review of 18,365 patients performed by the American College of Surgeons. Vomiting occurs more often when the tumor invades the pylorus, whereas dysphagia may be the main symptom associated with a lesion of the cardia. Hematemesis or melena is reported by 20 percent of patients, although frank gastrointestinal hemorrhage is uncommon and more likely to be associated with leiomyoma and leiomyosarcoma. There are no physical findings associated with early gastric cancer, and the presence of a palpable abdominal mass generally indicates longstanding growth and regional extension.

Gastric carcinomas spread by direct extension through the stomach wall to perigastric tissue, occasionally adhering to or invading adjacent structures, such as the pancreas, colon, or liver. Direct extension into the colon may be associated with foul-smelling emesis or the passage of recently ingested material in the stool. The disease may also spread by lymphatic vessels to intraabdominal lymph nodes and supraclavicular nodes (Virchow’s node).

A tumor that spreads along the peritoneal surfaces may result in a periumbilical nodule (Sister Mary Joseph’s node), an enlarged ovary (Krukenberg’s tumor), a mass in the Cul-de-sac (Blumer’s shelf), or frank peritoneal carcinomatosis and malignant ascites. The liver is the most common site of hematogenous dissemination, although pulmonary metastases are also seen. Laboratory tests may demonstrate anemia (in 42 percent of patients), hypoproteinemia (in 26 percent), abnormal liver function (in 26 percent), and fecal occult blood (in 40 percent). Patients with gastric carcinoma infrequently present with various paraneoplastic conditions, such as microangiopathic hemolytic anemia, membranous nephropathy, the sudden appearance of seborrheic keratoses (the Leser–Trélat sign), filiform and popular pigmented lesions in skin folds and mucous membranes (acanthosis nigricans), (Brown, et al., 1968) chronic intravascular coagulation leading to arterial and venous thrombi (Trousseau’s syndrome), and in rare cases, dermatomyositis.

2.14. Diagnostic studies

An upper gastrointestinal series is often the first diagnostic test performed to evaluate symptoms related to the upper gastrointestinal tract. Double-contrast techniques allow improved visualization of mucosal detail and may indicate diminished distensibility of the stomach, which may be the only indication of a diffuse infiltrative carcinoma. For lesions between 5 and 10 mm in diameter, however, false negative rates as high as 25 percent have been reported. Differentiating a benign tumor from a malignant ulcer or even a lymphoma may be impossible, and knowing the anatomical location of the ulcer is not enough to predict the presence or absence of a tumor.

Less than 3 percent of all gastric ulcers that are evaluated by endoscopy and biopsy are malignant. Thus, if the radiographic features of an ulcer appear benign and complete healing can be demonstrated on a repeated examination, endoscopy may not be necessary. Endoscopy and biopsy should be performed, however, if an upper gastrointestinal examination indicates the possible presence of a tumor or if a lesion has not completely healed within approximately six weeks.

Fiberoptic endoscopy and biopsy have been reported to have a diagnostic accuracy of 95 per cent. Since the accuracy increases with the number of biopsies, multiple biopsies are recommended. Gastric carcinomas may be difficult to distinguish from gastric lymphomas, and because of the submucosal location of lymphoid neoplasms, it is important to obtain biopsy specimens at an adequate depth.

Computed Tomographic (CT) scans of the abdomen can delineate the extent of the primary tumor, as well as the presence of nodal or distant metastases. Comparisons of the findings on CT scans with the findings at laparotomy, however, indicate that preoperative scans often underestimate the extent of disease, principally because of radiographically undetectable metastases to the lymph nodes, liver, and omentum. Investigators have recently used a high-frequency ultrasound probe attached to the end of an endoscope to assess the condition of patients with gastric cancer. Preoperative ultrasonic endoscopy can determine the depth of tumor penetration and the presence of nodal metastases with an accuracy of approximately 85 and 70 percent, respectively — higher than that of preoperative CT scanning. Because of the inability to examine the entire abdomen with ultrasonic endoscopy, however, the sensitivity of this technique cannot approach that of CT scanning in detecting distant metastases. Without additional data on the effect of ultrasonic endoscopy on the clinical outcome, routine use of this technique cannot be recommended.

2.15. Staging and prognosis

The pathological stage of gastric cancer remains the most important determinant of the prognosis. Analyses from multiple clinical trials confirm the importance of the depth at which the tumor has penetrated the stomach wall and the presence or absence of metastases to regional lymph nodes or distant organs in
predicting disease-free and overall survival. The American Joint Committee on Cancer has incorporated these factors in a comprehensive tumor–node–metastasis (TNM) staging system (Table 2)[6]. Beyond the stage of disease, intestinal-type cancer is associated with a higher rate of five-year survival than diffuse cancer (26 and 16 per cent, respectively). Similarly, poorly differentiated tumors, tumors with abnormal DNA content (i.e., aneuploidy), and tumors with genetic alterations in proto-oncogenes or tumor suppressor genes, all of which are common among patients in the United States, have been associated with a diminished survival rate. The location of the primary tumor also appears to predict the outcome. Approximately 37 per cent of gastric carcinomas in the United States originate in the upper third of the stomach, whereas 20 per cent originate in the middle third, and 30 per cent in the lower third; 12 per cent of gastric carcinomas involve the entire stomach. The rate of survival five years after resection is approximately 20 to 25 per cent for patients with distal tumors, 10 per cent for patients with proximal tumors, and less than 5 per cent for those whose entire stomach is involved.

The diminished survival of patients with proximal tumors may reflect the more aggressive, diffuse histologic features of such lesions or the considerable technical difficulty of resecting proximal tumors and obtaining sufficiently wide radial margins [6].

### Table 2: TNM classification of gastric cancer: diagnosis and staging[6]

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
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<tr>
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### Staging

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<td>M0</td>
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<tr>
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<td>M0</td>
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<td>T4</td>
<td>N1-2</td>
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### 2.16. Treatments available for stomach cancer

Surgery to remove the tumor is the only means of curing stomach cancer. Cure can be achieved in 80% or more of patients with tiny early gastric cancers, but unfortunately, such cases are uncommon outside Japan. For the majority of patients surgery involves removing part of all of the stomach and possibly a portion of the lower gutter, depending upon the exact location of the tumor.

Surgery may also be necessary in patients who cannot be cured as this may be the only means of relieving distressing symptoms such as blockage of the stomach.

Chemotherapy and radiotherapy treatment given after surgery are not very effective in preventing recurrence of the disease or improving survival. Recently, however, better results have been obtained by giving chemotherapy pre-operatively, (“neoadjuvant therapy”).

For patients with inoperable tumors, it is sometimes possible to control symptoms (i.e. difficulty swallowing or recurrent bleeding) by laser therapy performed using an endoscope. Similarly, difficulty swallowing or obstruction at the junction between the stomach and duodenum (pylorus) can sometimes be controlled by inserting an expandable metallic tube (stent) through the blocked region to hold it open. Some improvement in symptoms may also be obtained with chemotherapies.

Besides the therapies described above, scientists are seeking other new therapies for cancer. Based on mechanisms of cancer and key role of ROS, scientists have found that elevation of antioxidant enzymes combined with anticancer drugs can inhibit tumor cell growth in vitro and in vivo. We hope that this promising antioxidants combination will be applied to clinical trials in the future [7].

### 3. Tobacco and cancer: prevalence of smoking

Tobacco is a plant used in many ways and forms. It can be smoked in cigarettes, cigars, pipes, water pipes, or chewed to name a few of its uses. Cigarette smoking, the most popular method of smoking tobacco, is one of the most prevalent social habits practiced worldwide today. The World Health Organization (WHO) estimated that almost 1.1 billion people are smokers. In the United States, the National Cancer Institute estimated that almost 50 million Americans are tobacco smokers. In China, the most populous country in the world, more than 300 million men and 20 million women or 27% of the 1.2 billion population were reported to be smokers in 1995.

Tobacco consumption remains the most important avoidable cancer risk. Between 25 and 30% of all cancers in developed countries are tobacco-related. India is the third largest producer and consumer of tobacco. The country has along history of tobacco use in a variety of ways of chewing and smoking. The habits of chewing (15–70%) and smoking (23–77%) vary considerably from area to area (WHO, Geneva 1995). It has been estimated that in 1996, 184 million persons used tobacco in the country in one or other form. The cancer risk of tobacco use has been extensively investigated. The principle impact of tobacco smoking is seen in higher incidence of cancers of the lung, larynx, oesophagus, pancreas and bladder. Bidi smoking is associated with cancer of oropharynx as well as larynx.
There are predictions of incidence of 7-fold increase in tobacco-related cancer morbidity between 1995 and 2025 (Figure 3). [8] Further there will be an overall increase by 220% of cancer deaths simply related to tobacco use by the year 2025 (National Cancer Control Programme).

**Figure 3: Tobacco and cancer incidence [8]**

![Tobacco and cancer incidence graph](image)

WHO has estimated the excess premature mortality attributable to tobacco use amounting to 4 million deaths per year. According to WHO estimates, the annual cigarette consumption per adult in developing countries is on the rise.

The WHO has estimated that 91% of oral cancer in this part is directly attributable to tobacco usage. Even for coronary artery disease, cigarette smokers have 70% greater mortality than non-smokers do. In India, the smoking prevalence among adults were 29.4 per cent of the total population for males and 2.5 per cent in females in 1999. Cigarette smoke is known to contain a large number of oxidant it has been hypothesized that many of the adverse effects of smoking may result from oxidative damage to critical biologic substances. Such damage could result both from oxidants present in cigarette smoke and from the activation of phagocytic cells that generate reactive oxygen species [9].

### 3.1. Composition of cigarette smoke

Cigarette smoke is a complex mixture of chemicals containing more than 4000 different constituents. In the last 30–40 years, a large body of knowledge has accumulated identifying the exact chemical composition of cigarette smoke both qualitatively and quantitatively. Some of the compounds identified include different pyridine alkaloids such as nicotine, ammonia, acrolein, phenols, acetaldehyde, N-nitrosamine; polycyclic aromatic hydrocarbons such as benzo[α]pyrene (Table 3). [10]

Combustion gases such as carbon monoxide, nitrogen oxides, hydrogen cyanide; trace metals; emitter radioactive elements such as polonium, radium, and thorium. Most of these compounds are produced by pyrolysis and distillation in the zone immediately behind the lit tip of a cigarette where the temperature can reach 950°. Undiluted mainstream cigarette smoke was found to contain up to 1.3 x 1010 particles/cm3 ranging in diameter from 0.2–1.0 m. It should be noted that the particulate phase in cigarette smoke displays most of the tobacco-associated carcinogenicity. It was estimated that undiluted mainstream smoke might contain as high as 30 mg of tar and 5 mg of nicotine in an unfiltered regular tar cigarette or as low as 0.5 mg tar and 0.05 mg nicotine in a filtered low-tar cigarette.

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<th>SUBSTANCE</th>
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<tr>
<td>Polynuclear aromatic hydrocarbons</td>
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<td>Nicotine</td>
<td>Neurendocrine</td>
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<td>Cocarcinogen</td>
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</table>

### 3.1.1. Nicotine

Nicotine, an active ingredient in tobacco smoke, is a pharmacological reinforcer of the use of tobacco. It is a natural liquid alkaloid, which was isolated from the leaves of tobacco plant, Nicotiana tabaccum, in 1828 by Posselt and Reiman. It is generally accepted to be an active alkaloid in tobacco, typically comprising of 1-2% weight of tobacco. It was first prescribed as medical drug to treat rodent ulcer and constipation. The administration of nicotine mimics most of the subjective effects of smoking, which is the major risk factor for cardiopulmonary diseases and several types of cancers.
3.1.1.1. Physicochemical properties of nicotine

Nicotine is a clear liquid with a characteristic tobacco odour and turns brown on exposure to air. It is a tertiary amine composed of pyridine and pyrolidine ring with an empirical formula of C10H14N2. It is a weak base with a pKa of 8.0. It exists in two different isomers (S)-nicotine and (R)-nicotine. It boils at 246°C under atmospheric pressure.

3.1.1.2. Absorption of nicotine

Nicotine can be readily absorbed to the arterial circulation from the respiratory tract, buccal and nasal mucosa, lung, the gastrointestinal tract, skin, and also the urinary bladder, depending on the pH of the tissue and the nicotine delivery system. The pH of the aqueous fraction of cigarette smoke is generally around 8.5 and the pH of the alveoli is about 7.4 and at this pH about 30% of the nicotine is uncharged and therefore easily crosses the cell membranes and enters into the circulation. Nicotine is also absorbed through the skin during tobacco harvesting and nicotine replacement therapies. The reabsorption of the nicotine occurs through the urinary bladder and seems to be dependent on pH of the urine. Absorption from the stomach is poor because of acidic nature of stomach, whereas intestinal absorption is far more efficient.

3.1.1.3. Nicotine and free radicals

Nicotine, a potential oxidant is capable of producing free radicals and reactive oxygen species (ROS). The nicotine induced free radicals react with biomembranes causing oxidative destruction of polyunsaturated fatty acid (PUFA) forming cytotoxic aldehydes by a process known as lipid peroxidation. Nitric oxide (NO), a small highly reactive free radical produced by nicotine, can lead lipid peroxidation directly or indirectly by reacting with hydroxyl radical forming peroxynitrite which can cause relative high cytotoxicity.

The increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) by nicotine can produce a condition of oxidative stress which has been suggested to play a major role in the pathogenesis of several tobacco-related diseases such as cancer, cardiovascular diseases [11].

3.2. Tobacco smoke as a carcinogenic agent

Tobacco smoke has long been recognized as a chemical carcinogen. Tobacco smoke contains some deadly carcinogenic chemicals. Some of these cancer-causing chemicals, such as the tobacco-specific nitrosamines, N-Nitrosomorpholine N’-Nitrosonornicotine (NNN), 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNK), N’-Nitrosomethylamine (NAT) and N’-Nitrosoanabasine (NAB), are formed from natural components of the tobacco plants.

Cigarette smoke contains numerous known or suspected human carcinogens. The International Agency for Research on Cancer (IARC) has listed 36 chemicals that are “known to cause cancer” (Group 1) in humans (Table 4) [12]. Accordingly, cigarette smoke is in the United States Environmental Protection Agency’s (USEPA) Group A and the IARC Group 1 classification for carcinogens (known to cause cancer in humans)[12].

<table>
<thead>
<tr>
<th>Table 4: Carcinogens in tobacco smoke [12]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1: Carcinogenic to Humans</strong></td>
</tr>
<tr>
<td>Tobacco Products, Smokeless</td>
</tr>
<tr>
<td>4-Aminobiphenyl</td>
</tr>
<tr>
<td>Benzene</td>
</tr>
<tr>
<td>Cadmium</td>
</tr>
<tr>
<td>Chromium</td>
</tr>
<tr>
<td>2-Naphthylamine</td>
</tr>
<tr>
<td>Nickel</td>
</tr>
<tr>
<td>Polonium-210(Radon)</td>
</tr>
<tr>
<td>Vinyl Chloride</td>
</tr>
<tr>
<td><strong>Group 2A: Probably Carcinogenic to Humans</strong></td>
</tr>
<tr>
<td>Acrylonitrile</td>
</tr>
<tr>
<td>Benzo[a]anthracene</td>
</tr>
<tr>
<td>Benzo[a]pyrene</td>
</tr>
<tr>
<td>1,3-Butadiene</td>
</tr>
<tr>
<td>Dibenzo(a,h)anthracene</td>
</tr>
<tr>
<td>Formaldehyde</td>
</tr>
<tr>
<td>N-Nitrosodiethylamine</td>
</tr>
<tr>
<td>N-Nitrosodimethylamine</td>
</tr>
<tr>
<td>Acetaldehyde</td>
</tr>
<tr>
<td>Benzo[b]fluoranthene</td>
</tr>
<tr>
<td>Benzo[k]fluoranthene</td>
</tr>
<tr>
<td>Dibenzo[a,j]acridine</td>
</tr>
<tr>
<td>Dibenzo[a]carbazine</td>
</tr>
<tr>
<td>7H-Dibenzo[c,g]carbazole</td>
</tr>
<tr>
<td>Dibenzo(a)pyrene</td>
</tr>
<tr>
<td>Dibenzo(a)pyrene</td>
</tr>
<tr>
<td>1,1-Dimethylhydrazine</td>
</tr>
<tr>
<td>Hydrazine</td>
</tr>
<tr>
<td>Indeno[1,2,3-cd]pyrene</td>
</tr>
<tr>
<td>5-Methylchrysenene</td>
</tr>
<tr>
<td>4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNK)</td>
</tr>
<tr>
<td>N-Nitrosodiethanol amine</td>
</tr>
<tr>
<td>N-Nitrosomethyl ether amine</td>
</tr>
<tr>
<td>N-Nitrosomorpholine</td>
</tr>
<tr>
<td>N’-Nitrosonornicotide (NNN)</td>
</tr>
<tr>
<td>N-Nitrosophyrrolidine</td>
</tr>
<tr>
<td>Quinoline</td>
</tr>
<tr>
<td>Ortho-Toluidine</td>
</tr>
<tr>
<td>Urethane (Ethyl Carbamate)</td>
</tr>
<tr>
<td><strong>Group 3: Unclassifiable as to Carcinogenicity to Humans</strong></td>
</tr>
</tbody>
</table>
3.3. Damage to DNA caused by cigarette smoking

Cigarette Smoking produces superoxide, hydrogen peroxide, and the hydroxyl radical, and thus become potent oxidants. These Cigarette smoking can initiate lipid peroxidation, oxidize proteins, and nick DNA. The quinone-hydroquinone-semi-quinone system can penetrate viable mammalian cells, bind to, and nick cellular DNA. The nicks produced by the tar radical require multi-step repair, suggesting a process that could be error prone. These Cigarette Smoking (ACT solutions) also interfere with mitochondrial electron transport showed in an interesting study the role of the tar radical in Cigarette Smoldering (ACT) extracts in the DNA damage that is caused by cigarette smoke.

The free radicals are involved in many of the biological processes that occur when chemicals transform cells. Since cigarette smoking increases the concentrations of radicals in the lungs, it appears reasonable to assume that some of the tumorigenicity of smoke derives from the free radicals it contains or causes to be produced in the lung. The DNA strand breaks caused by ACT are the type of strand break that cannot be repaired in a single step, and the likelihood for mutation is increased by the possibility for error at each step of a multi-step repair process. A group of enzymes similar to that suggested for repairing breaks induced by ionizing radiation is probably necessary for repair of strand breaks induced by ACT. At least two possibilities for mutation exist in this repair scheme. The DNA ligase may join DNA strands across nucleotide gaps after excision of the 3' phosphate or the 5' nucleoside; thus, deletion mutation might occur by ligation across tar-induced lesions where base release accompanies strand scission. Mutation might also result from base misincorporation during gap filling by a polymerase. Regardless of the detailed mechanism, it seems clear that the types of DNA nicks produced by cigarette smoke and ACT must lead to mutations; and these mutations may be related to the known ability of cigarette smoke to induce cancer.

Enhanced lipid peroxidation in the blood of tumour-bearing animals was accompanied by significant decreases in the levels of reduced glutathione (GSH), ascorbic acid and vitamin E and the activities of glutathione peroxidase (GPx), glutathione-S-transferase (GST) and glutathione reductase (GR). Serum superoxide dismutase, plasma ascorbic acid and lipid peroxidation in H.pylori gastritis and gastric cancer patients were compared with values for age matched healthy subjects. The concentration of serum superoxide dismutase and serum malondialdehyde was significantly higher in gastric cancer as compared to H.Pylori gastritis patients. Study was undertaken to investigate the relationship between exposure to cigarette smoke and apoptosis in the rat gastric mucosa and the mechanism involved. Exposure to cigarette smoke can increase apoptosis in the rat gastric mucosa through a reactive oxygen species (ROS) mediated and a p53-independent pathway.

The circulation of cervical cancer patients may be due to their increased utilization to scavenge lipid peroxides as well as their sequestration by tumor cells.

There was a significant association between cigarette smoking and gastric cancer risk: the hazard ratio (HR) for ever smokers was 1.45 (95% confidence interval (CI). The HR of current cigarette smoking was 1.73 (95%) in males and 1.87 (95%) in females. Hazard ratios increased with intensity and duration of cigarette smokers has a higher HR of gastric cancer (GC) in the cardia than in the distal part of the stomach.

ATS (α-tocophenol succinate) inhibits gastric carcinoma cell growth. In vitro studies are indicated to further evaluate the potential benefit of this antioxidant against gastric cancer. Smoking has recently been recognized as causally associated with the development of gastric cancer.

Endogenous oxidative damage to proteins, lipids, and DNA is thought to be an important etiologic factor in ageing and the development of chronic diseases such as cancer. The pathology associated with these diseases is likely to occur only after the production of reactive oxygen species has exceed the body or cell capacity to protect itself and effectively repair oxidative damage.

Associations between the high consumption of certain highly salted foodstuffs, particularly in some oriental countries, and increased risk of cancer. A randomized double-blind placebo-controlled study involving 128 male normalipidemic chronic smokers the effect of a 2-year α-tocopherol treatment on plasma levels of sCAM-1 and autoantibodies against oxLDL was evaluated. After supplementation with α-tocopherol concentration of TBARS in plasma and in vitro oxidizability of LDL had decreased.

The oxidant-antioxidant balance is thought to be important in the initiation, promotion, and therapy resistance in cancer. In the present study we assessed the expression of the antioxidants manganese superoxide dismutase and copper/zinc superoxide dismutase in gastric and carcinomas. The superoxide dismutase levels were not found to be associated with major clinicopathological features of the gastric cancer patients. Univariate analysis revealed, however, that a high Mn-SOD level in gastric carcinomas, a low level in the normal gastric mucosa, and a high ratio of these two levels in gastric cancer patients are indicative of a poor overall survival. Multivariate analysis, including all clinicopathological parameters, revealed that the Mn-SOD ratio in particular is an independent prognostic parameter in gastric cancer patients.

Cigarette smoking is a major risk factor for cancer and also affects the incidence and healing of peptic ulcer. There is an evidence suggesting that tobacco smoke may also be associated with gastric cancer, which is estimated to be the second most common cancer worldwide.
Demonstrated that a correlation existed between the levels of serum ascorbic acid and beta-carotene, alpha-tocopherol and lipid peroxidation in gastric carcinoma [13].

4. Free radicals

Any atom or molecule capable of independent existence that contains one or more unpaired electrons in its outermost orbital is called a free radical.

Table 5: Reactive oxygen species (ROS) [16]

<table>
<thead>
<tr>
<th>The Radicals</th>
<th>( \text{ROS} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superoxide</td>
<td>( \text{O}_2^- ) Oxygen-centered radical with selective reactivity. This species is produced by a number of enzyme systems, by autoxidation reactions and by nonenzymatic electron transfer that univentionally reduce molecular oxygen. SOD accelerates the dismutation of ( \text{O}_2^- ), converting it into hydrogen peroxide (H2O2) and oxygen (O2).</td>
</tr>
<tr>
<td>Hydroxyl</td>
<td>( \text{OH}^- ) A highly reactive oxygen centered radical that attacks all molecules in the human body.</td>
</tr>
<tr>
<td>Peroxyl, alkoxy</td>
<td>( \text{RO}^- \times \text{RO}^- ) Typically, organic radicals often encountered as intermediates during the breakdown of peroxides of lipids in the free radical reaction of peroxidation.</td>
</tr>
<tr>
<td>Oxides of nitrogen</td>
<td>( \text{NO}, \text{NO}_2 ) Nitric oxide is formed in vivo from the amino acid L-arginine. Nitrogen dioxide is formed when No reacts with O2- and is found in polluted air and smoke.</td>
</tr>
<tr>
<td>The Non Radicals</td>
<td></td>
</tr>
<tr>
<td>Hydrogen peroxide</td>
<td>( \text{H}_2\text{O}_2 ) Formed in vivo when O2- dismutates and also by many oxidase enzymes. Higher levels of ( \text{H}_2\text{O}_2 ) can attack several cellular energy-producing systems. ( \text{H}_2\text{O}_2 ) also forms ( \text{OH}^- ) in the presence of transition metal ions (Fe2+). O2- can facilitate this reaction.</td>
</tr>
<tr>
<td>Hypochlorous acid</td>
<td>( \text{HOCl} ) A powerful oxidant formed in the human neutrophils at sites of inflammation by action of the enzyme myeloperoxidase. May also react with O2- to generate ( \text{OH}^- ) in neutrophils.</td>
</tr>
<tr>
<td>Ozone</td>
<td>( \text{O}_3 ) This noxious gas has been shown to deplete plasma antioxidants vitamin D, vitamin E, and uric acid.</td>
</tr>
<tr>
<td>Singlet oxygen</td>
<td>( \text{O}_2 ) Here the spin of one of the electrons of the two outer orbitals is inverted, removing the quantum mechanical spin restrictions of molecular oxygen.</td>
</tr>
</tbody>
</table>

Reactive oxygen species (ROS) are the side-products generated endogenously by all aerobic cells as a result of the metabolism of oxygen. They are oxygen-containing molecules that have higher chemical reactivity than ground-state molecular oxygen. ROS include not only oxygen-centered radicals such as superoxide oxygen anion (O2-) and hydroxyl radical (HO.), but also molecules such as singlet oxygen (1O2) and hydrogen peroxide (H2O2). ROS are generated during normal aerobic metabolism, and increased amounts of these species are produced during various forms of oxidative stress (Table 5) [14].

ROS are known to react with various intracellular targets, including lipids, proteins, and DNA. ROS-induced damage can result in cell death, mutations, chromosomal aberrations or carcinogenesis. Mitochondria are believed to be a major site of ROS production according to an endogenous and continuous physiological process under aerobic conditions.

4.1. The basic properties of free radicals

A free radical is any atom or molecule, capable of independent existence that possesses one or more unpaired electrons. Electrons are more stable when paired together in orbitals: the two electrons in a pair have different directions of spin. Hence, radicals are generally less stable than non-radicals, although their reactivity vary (Table V). The free radicals are capable of reacting indiscriminately with any molecules with which they come in contact. Once radicals are formed they can either react with another radical or with another non-radical molecule by various interactions. If two radicals meet they can combine their unpaired electron, thus forming a covalent bond. However, most molecules found in vivo are non-radicals. In this case a radical might donate its unpaired electron to the other molecule, or might take one electron from it, thus transforming its radical character. At the same time a new radical is formed. The feature that is becoming clear is that a radical generates another radical, leading to the chain reaction. In biological and related fields, the major free radical species of interest are oxygen free radicals. Step-wise single electron additions to (reduction of) molecular oxygen generates a unique spectrum of more reactive intermediates, the oxygen free radicals. The term OFRs includes the superoxide anion free radical (O2-), the hydroxyl radical (HO.), and lipid (L) and other (X) peroxy radicals (LOO- and XOO-). More recently through research into nitric oxide (NO), the active moiety of endothelial derived relaxing factor, and into air-borne pollution, there has been growing interest in nitrogen-centered free radical species such as peroxynitrate (•ONO2) and peroxynitrite (•ONONO).

Oxygen free radicals (OFRs) are part of a greater group of molecules often called reactive oxygen species (ROS) that are all more strongly oxidizing than molecular oxygen itself. These include hydrogen peroxide (H2O2), lipid peroxide (LOOH), singlet oxygen (1O2), hypochlorous acid (HOCL) and other N-chloramine compounds (Table V) [12].

4.2. Free radical-generating systems in normal processes in vivo

Oxygen free radicals (OFRs) and other free radicals are constantly formed in the human body by normal metabolic processes, as the reduction of oxygen to water by the mitochondrial electron transport chain. In this reaction oxygen...
itself is reduced in such a way that two electrons (and two pairs of protons) are accepted by each oxygen atom leading to the formation of a water molecule. A small percentage of electrons leak away from the main stream of the mitochondrial respiratory chain, leading to univalent reduction of molecular oxygen, which generates superoxide anion (Figure 4). [15]

The quantitative importance of oxygen-derived free radicals can be realized by the fact that about 250 grams of oxygen are consumed every day by the human organism. Of this, about 2-5% would be converted to the superoxide.

In human cells superoxide is quickly transformed into hydrogen peroxide ($H_2O_2$). This reaction is greatly accelerated by superoxide dismutase (SOD), a widely distributed enzyme. $H_2O_2$ is a potent oxidant and, in sufficient concentrations, will kill any cell. The further reduction of $H_2O_2$ stabilizes the inter-oxygen bond, resulting in a cleavage to produce $OH^-$ and $OH$. species. The latter one, hydroxyl radical is a highly reactive radical species. Free transition metal ions (Fe, Cu) often act as electron donor necessary for generation of hydroxyl radical from $H_2O_2$. In the presence of excess iron, the toxicity of $H_2O_2$ may be magnified 10 to 1000 times. Because of this sequestration of transition metals can be considered as an important mechanism of antioxidant defense.

Lipids, particularly polyunsaturated fatty acids (PUFA) are the major class of biomolecules susceptible to oxidative damage by free radicals. Lipid peroxidation is a chain reaction, which is initiated by the attack of free radicals on the membrane lipids that are capable of abstracting a hydrogen atom from the methylene group. This is known as initiation phase.

The carbon radical thus formed is stabilized by molecular rearrangement to produce conjugated diene, which easily reacts with an oxygen molecule to give a peroxy radical. The peroxy radical can further abstract a hydrogen atom from another lipid molecule to form lipid hydroperoxides. This is the propagation stage of lipid peroxidation.

Alternatively, the peroxy radical can form cyclic peroxy and cyclic endoperoxide which undergo fragmentations leading to the formation of cytotoxic aldehydes like malonaldehyde. Once started, LPO proceeds as a chain reaction until the polyunsaturated fatty acid is consumed or until the radical self annihilates. This is referred to be termination phase of LPO.

4.3.1. Mechanism of Lipid Peroxidation

Lipid peroxidation includes three stages namely initiation, propagation and termination (Figure 5).[16]

In a peroxide free lipid system, the initiation of a peroxidation sequence refers to the attack of a ROS with sufficient reactivity to abstract a hydrogen atom from a methylene group (-CH2), these hydrogens have very high mobility. This attack easily generates free radicals from PUFA. The presence of a double bond in the fatty acid weakens the -CH bonds in the carbon atom adjacent to the double bond and makes the 'H' removal easier. The 'C' radical level is stabilised by a molecular rearrangement to form conjugated diene. Under aerobic condition, conjugated diene combines with oxygen to give peroxy radicals.

4.3.1.1. Initiation

In a peroxide free lipid system, the initiation of a peroxidation sequence refers to the attack of a ROS with sufficient reactivity to abstract a hydrogen atom from a methylene group (-CH2), these hydrogens have very high mobility. This attack easily generates free radicals from PUFA. The presence of a double bond in the fatty acid weakens the -CH bonds in the carbon atom adjacent to the double bond and makes the 'H' removal easier. The 'C' radical level is stabilised by a molecular rearrangement to form conjugated diene. Under aerobic condition, conjugated diene combines with oxygen to give peroxy radicals.

4.3.1.2. Propagation

The peroxy radical abstracts 'H' from another lipid molecule (adjacent fatty acid), especially in the presence of metals such as copper or iron and cause an autocatalytic chain reaction. The peroxy radical combines with 'H' to give a lipid hydroperoxide.
This reaction characterises the propagation stage. Probable alternative fates of peroxy radicals are to be transformed into cyclic peroxides or even cyclic endoperoxides (from PUFA’s such as arachidonic or eicosapentaenoic acids).

4.3.1.3. Termination

Termination (formation of a hydroperoxide) is most often achieved by reaction of a peroxy radical with -tocopherol, which is the main lipophilic “chain breaking molecule” in the cell membranes. Furthermore, any kind of alkyl radicals can react with a lipid peroxide LOO to give non-initiating and non-propagating species such as the relatively stable dimers LOOL or two peroxy molecules combining to form hydroxylated derivatives (LOH).

Membrane lipid peroxidation results in loss of PUFA, decreased membrane fluidity and loss of enzyme and receptor activity. The products of LPO are capable of interacting with DNA and cause oxidative damage [17].

4.4. Free radical induced oxidative stress in cancer processes

All aerobic organisms are continually exposed to oxidative stress. Normally there is equilibrium between free radical formation and antioxidant defense mechanisms. An imbalance between formation of ROS and antioxidant defense mechanisms could lead to oxidative stress (Figure 6). [18] Oxidative stress can be produced endogenously (or) exogenously.

Figure 6: ROS generation and detoxification [18]

OFR are known to be involved in various processes such as carbohydrate damage, membrane damage, lipid peroxidation, mutagenesis and carcinogenesis. Free radical induced oxidative stress has been implicated in all stages of cancer development. About 10,000 to 20,000 oxidative hits to DNA/cell/day are estimated to occur in humans.

Chemically induced cancer is a multistage process definable by initiation, promotion and progression. Initiation involves a non-lethal and inheritable mutation in cells by nitration of a chemical with DNA and this mutation cancers a growth advantage to that cell. Promotion involves the selective clonal expansion of the initiated cell population through either increased cellular proliferation and/or inhibition of cell death. ROS specifically in initiated cell population has an important role in the clonal expansion of the initiated cells (Klauing et al., 1999). Tumor progression results in the development of malignant growth from benign lesion. In this stage, oxidative stress may play a direct role in the development of cancer characteristics such as uncontrolled growth, genomic instability, chemotherapy resistance, invasion and metastasis [19].

4.5. Free radicals in cigarette smoke-cigarette smoke chemistry

Two major phases were identified in cigarette smoke: a tar phase and a gas phase; both phases are rich in oxygen-centered, carbon-centered and nitrogen-centered free radicals as well as non-radical oxidant. From the analysis of each phase, it was estimated that a single cigarette puff contains approximately, 1014 free radicals in the tar phase, and 1015 radicals in the gas phase. As a comparison, one billion = 109.

4.5.1. Tar phase radicals

Tar phase radicals are mostly quinone-hydroquinone complexes that are not highly reactive. However, they are long-lived radicals that could linger in the air for hours or perhaps days and potentially contribute to the environmental cigarette smoke (side-stream or passive smoking) and the damage observed in non-smokers. Moreover, tar phase radicals can attack or bind to DNA causing strand breaks and leading to DNA damage and eventually cancer. The relationship between tar concentration and DNA damage is linear as shown in a study by Pryor and Stone, (Pryor and Stone, 1993) where rat spleen lymphocytes exposed to cigarette tar extract showed increasing DNA damage with increased exposure to tar filter extracts.

4.5.2. Gas phase radicals

Gas phase radicals on the other hand, are generally more reactive, but short-lived and may not survive the journey through the cigarette. However some can live long enough to interact with natural endogenous oxidants generated during an oxidative burst induced by a phagocytic inflammatory response to irritation caused by cigarette smoke (Anderson and Theron, 1990; Anderson, 2001). Cigarette smoke-induced oxidants include nitric oxide (NO), an air pollutant, which is capable of reacting with superoxide anion radical (O2-) to form peroxynitrite (ONOO-) and with organic peroxy radicals to form alkyl peroxynitrates (ONOOR).

In addition to free radicals, cigarette smoke is also rich in combustion toxic gases that can reach a very high concentration and become involved in more radical formation. For example, Abelson estimated that cigarette smoke contains 42,000 ppm carbon monoxide, which can significantly elevate the level of carbonyhemoglobin and reduce the oxygen carrying capacity of smokers’ blood. Pryor and Stone, (Pryor and Stone, 1993) reported nitric oxide (NO) concentrations of 500-1000 ppm, and nitrogen dioxide (NO2) of up to 250 ppm. It should be noted that nitrogen oxides (NOx) along with ozone are the most damaging reactive oxidant gases in photochemical smog that pollutes the air of major metropolitan areas with significant adverse health effects [20].

4.6. Mechanism(s) of free radical induced injury from cigarette smoking
Despite the large body of epidemiological evidence that exists today establishing a strong correlation between smoking and morbidity and mortality, the exact molecular and biochemical mechanisms of smoke-related disease remains not completely clear. Recent findings however, suggest that lung damage resulting in respiratory dysfunction, and induction of carcinogenesis, particularly in the lung, are processes mediated by free radicals generated in cigarette smoke. This is in agreement with the concept that free-radical mediated oxidative stress is capable of causing tissue damage and disease states, and oxidative damage is strongly suspected to initiate carcinogenesis. Oxidative stress has been defined by Helmut Sies as a condition in which “a disturbance of the pro-oxidant/anti-oxidant balance occurs in favour of the former leading to biological damage.” Indeed numerous studies indicate that cigarette smoking is associated with increased oxidant generation and antioxidant depletion tipping the oxidant/antioxidant balance towards the oxidant side and producing oxidative stress [21].

5. Antioxidants

Oxidative stress occurs when there is an imbalance between prooxidants and antioxidants, either due to the increased generation of oxidizing species or due to a relative lack of antioxidant defense capacity.

An antioxidant is “any substance when found at low concentration compared to that of an oxidisable substrate, significantly delays or prevents oxidation of that substrate”. Normal cells have a number of endogenous antioxidants, which act co-operatively in vivo to eliminate toxic oxymetabolites.

5.1. Antioxidant enzymes

The antioxidants found in biological systems include enzymes, vitamins, metal ion chelators and a variety of small molecules. The important enzymic antioxidant include superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). The non-enzymic antioxidants and other small molecules with antioxidant property include reduced glutathione (GSH), ascorbic acid, tocopherol, -carotene, uric acid and bilirubin. Metal ion chelators that sequestrate metal ions include haptoglobin, albumin, transferrin, ceruloplasmin and metallothionein.

5.2. Antioxidant systems

As mentioned above, ROS are produced naturally and continuously within the cell. In order to prevent their accumulation and possible deleterious effects, antioxidant systems act as ROS scavengers (Figure VIII). Thiol-containing moieties (such as the cysteine residue found in glutathione) have a reducing power (i.e. a low E0). They therefore display antioxidant properties because they can trap ROS (ie. Supply them with electrons, therefore abolishing their oxidative power. The intracellular glutathione content varies within the range 5-10mM, depending on cell type and cellular compartment. Owing to its ubiquitous prevalence, glutathione acts as an antioxidant buffer within the cell. More over, several enzymic systems detoxify ROS: catalase dismutates H2O2, and SO Delinimates O2- (but generates H2O2). Glutathione peroxidase catalyses the reduction of peroxides (ROOH; including H2O2) into alcohols (ROH), using the reducing potential of glutathione.. The cysteine-rich metallothionein protein also displays antioxidant properties. Other enzymes, including quinone reductase and haem oxygenase, can prevent the formation of oxygen-derived radicals. These enzymes are induced as part of a concerted response to oxidative stress. Cells also protect themselves with antioxidant systems involving a cascade of functional redox molecules, such as thioredoxin (trx) and redox factor 1, the radical-scavenging vitamins C (cytosol) and E (membrane-bound). The expression of antioxidant proteins and of enzymes that regenerate them (such as glutathione reductase and Trx reductase) is induced at the transcriptional level (see below) by oxidative stress.

Antioxidant protection can be viewed as consisting of four sequential levels of defensive activity: preventive; chain breaking; repairing and adaptive. The first level of defense, which is largely enzymatic, involves enzymes whose activity depends principally on trace amounts of minerals Mn, Cu, Zn and Se (superoxide dismutases, glutathione peroxidases and catalase); it is concerned with the control of formation and proliferation of primary radical species derived from molecular oxygen. The second, which involves the two vitamins C and E, and probably carotenoids, is secondary radicals in chain reactions such as lipid peroxidation, initiated and driven by primary radicals. The third level is the enzymatic prevention of formation of secondary radicals from chain-terminated derivatives and enabling the removal of such molecules from an environment in which metal catalyzed reactions might cause further oxidative damage. Finally, adaptation can also be included in antioxidant mechanisms. Namely, free radicals also work as a signal capable of inducing the synthesis and the transport of the appropriate antioxidant to its site of action [22].

5.3. Antioxidant enzymes and cancer

5.3.1. Superoxide dismutase (SOD)

Superoxide dismutase (SOD) is an endogenously produced intracellular enzyme present in every cell of the body. Cellular SOD is represented by a group of metalloenzymes with various prosthetic groups. The prevalent enzyme is Cu-Zn SOD, which is a stable dimeric protein. SOD appears in three forms (1) Cu-Zn SOD in the cytoplasm with two subunits, (2) Mn-SOD in the mitochondria and (3) SOD in the extracellular space (Cu-SOD). SOD catalyses the destruction of superoxide free radical to hydrogen peroxide. It protects oxygen metabolising cells against harmful effects of superoxide free radicals.

\[ \text{SOD} + \text{2O}_2^- + \text{2H}^+ \rightarrow \text{H}_2\text{O}_2 + \text{O}_2 \]

5.3.2. Catalase (CAT)

Catalase (CAT) is a tetrameric hemeprotein of molecular weight 240,000 largely located in peroxisomes. CAT is also present in liver, kidney and erythrocytes. It contains a heme group at the active site of each monomer with NADPH as a stabilising compartment (Chance et al., 1952). It catalyses the reduction of hydrogen peroxide and thereby protects the cellular constituents from oxidative damage by highly reactive hydroxyl radicals. Catalase uses H2O2 as a substrate as well as hydrogen acceptor.
5.3.3. Glutathione (GSH)

Glutathione, a low molecular weight tripeptide consisting of glutamate, cysteine and glycine, is synthesised intracellularly by two glutathione synthesising enzymes, γ-glutamyl cysteine synthetase (GCS) and glutathione synthetase. Glutathione plays an important role in cellular defense against oxidative stress by reducing protein disulfides and other cellular molecules. It also acts as a scavenger of free radicals. It participates in the protection of sulfhydryl groups, detoxification of electrophile substances, amino acid transport, production of coenzymes and recycling of vitamin E and C.

Glutathione exists both in the thiol reduced (GSH) and disulfide oxidised (GSSG) forms. Glutathione scavenges hydrogen peroxide in the reaction catalysed by glutathione peroxidase

\[ \text{H}_2\text{O}_2 + 2\text{GSH} \rightarrow \text{GPX} \rightarrow 2\text{H}_2\text{O} + \text{GSSG} \]

In addition to its role as substrate in glutathione redox cycle, GSH is also a scavenger of hydroxyl radicals and singlet oxygen.

5.3.4. Glutathione peroxidase (GPx)

Glutathione peroxidase (GPx) catalyses the reduction of various organic hydroperoxides as well as hydrogen peroxide to non-toxic products with glutathione as hydrogen donor.

\[ \text{H}_2\text{O}_2 + 2\text{GSH} \rightarrow \text{GPX} \rightarrow 2\text{H}_2\text{O} + \text{GSSG} \]

\[ \text{ROOH} + 2\text{GSH} \rightarrow \text{GPX} \rightarrow \text{ROH} + \text{H}_2\text{O} + \text{GSSG} \]

GPx, a tetrameric enzyme of molecular weight 84,000, consists of four identical protein subunits with one atom of selenium in the form of selenocysteine at its catalytic site.

5.3.5. Glutathione-S-transferase (GST)

Glutathione-S-transferase (GST) is a detoxification enzyme, which catalyses the conjugation of the tripeptide-glutathione to an electrophilic site of toxic compounds thereby protecting cells against xenobiotics. GST provides protection to the tissues by catalysing conjugation of a wide variety of electrophilic xenobiotics to GSH and by binding some of the toxic compounds covalently and non-covalently (Jakoby et al., 1984). It possesses peroxidase activity and participates in the reduction of fatty acid hydroperoxides to non-toxic alcohols. Based on structural, physiochemical, enzymic and immunological properties, GSTs are categorised into four classes namely α,μ,π and θ.

5.3.6. Ceruloplasmin

Ceruloplasmin is a glycoprotein present in plasma. It is synthesised in hepatocytes and secreted into plasma with 6-7 copper ions bound per molecule. Ceruloplasmin inhibits iron dependent lipid peroxidation by its ferroxidase activity. Ceruloplasmin oxidises iron from ferrous to ferric state and thereby prevents iron catalysed lipid peroxidation, since it requires both Fe(II) and Fe(III), the maximum rate occurs when the ratio is approximately one.

\[ \text{2H}_2\text{O}_2 \rightarrow \text{CAT} \rightarrow 2\text{H}_2\text{O} + \text{O}_2 \]

5.3.7. Vitamin E

Vitamin E is the major fat soluble antioxidant of biological membrane. It is regarded as the major free radical chain terminator because of its lipophilic property. Vitamin E quenches the singlet oxygen and also reacts with lipid peroxy radicals to form vitamin E radical and thereby it acts as a chain terminator.

\[ \text{LOO}^+ + \text{Vit E-OH} \rightarrow \text{Vit E-OH} + \text{A}^+ \]

Vitamin E radical can be reduced back to vitamin E by ascorbic acid.

\[ \text{AH} + \text{Vit E-O}^- \rightarrow \text{Vit E-OOH} + \text{A}^- \]

5.3.8. Vitamin C

Vitamin C is a water soluble, chain breaking antioxidant found in both intracellular as well as extracellular fluid. Vitamin C is a potent quencher of singlet oxygen and protects plasma lipids against peroxidation. It can serve both as an antioxidant and a proxidant. It scavenges O2, H2O2, thiol radicals as well as peroxy and sulphenyl radicals. Vitamin C along with GSH and vitamin E plays a key role in protecting cells against oxidative damage due to its ability to interact with variety of oxygen species. Ascorbate reacts rapidly with O2 and O2 and forms semi dehydroascorbate. The dehydroascorbate can be reduced back to ascorbate by GSH.

\[ \text{AH}_2 + \text{O}_2 \rightarrow \text{AH}^+ + \text{H}_2\text{O} \]

\[ \text{AH}^+ + \text{AH} \rightarrow \text{A} + \text{AH}_2 \]

Dehydro ascorbate

\[ \text{A} + 2\text{GSH} \rightarrow \text{GSSG} + \text{AH}_2 \]

Vitamin C can also regenerate vitamin E from the -tocopheroxyl radical. It also protects the oxidative breakdown of collagen fibrils by O2 in the extracellular matrix (19).

5.4. Tobacco smoking and antioxidants

Cigarette smoking is a serious health problem in worldwide. Smoking has been strongly implicated as a risk factor for chronic obstructive pulmonary disease, cancer and atherosclerosis. Because cigarette smoke is know to contain a large number of oxidants.

Free radicals and non-radicals oxidants generated in the smoke or induced by it will interact with endogenous antioxidants leading to disease states, dysfunction or even death as outlined in (Figure IX) The rate by which these adverse effects are manifested is thought to be associated with the depletion or accelerated turnover of endogenous antioxidant nutrients. Several nutrition surveys indicate that smokers in general consume less antioxidants than nonsmokers. As a result attempts have been made to alleviate the adverse effects of smoking by increasing the intake of dietary antioxidants, either individually or in combinations.

Carotenoids such as β-carotene are suggested to have antioxidant properties capable of quenching free radicals such as singlet oxygen (102) (Stratton et al., 1993). It was also suggested that a cooperative interaction exists between fat-soluble...
antioxidants; the relation between -carotene and vitamin E was reported to be synergistic. In humans, the protective effects of β-carotene can be seen in those experiencing the stress of smoking, but not in nonsmokers. For examples, in a randomized, double-blind, controlled, interventional study, 4 weeks of supplementation with 20 mg/day β-carotene had no effect on lipid peroxidation in non-smokers, but caused a 37% reduction in smokers.

Exposure of human plasma in vitro to cigarette smoke showed that -carotene are depleted to a greater extent than vitamin E. Whether this decline represents sparing of vitamin E or direct reaction with oxidants is not clear. The findings of the Physicians’ Health Study (PHS), and the β-Carotene and Retinol Efficacy Trial (CARET), studies questioned the protective role of β-carotene under conditions of cigarette smoke-induced oxidative stress.

Vitamin E (α-tocopherol) is the major intracellular lipophilic chain breaker, and efficient antioxidant capable of trapping peroxyl radicals and quenching free radicals and reactive oxygen species. It is also essential for structural membrane stability. Vitamin E concentration in the lung, however, does not decrease in response to cigarette smoke or inhaled environmental oxidants, rather it was found to increase following exposure to cigarette smoke.

Ascorbic acid (vitamin C) is the major essential water-soluble antioxidant in human serum. Vitamin C can function as an antioxidant and scavenge the superoxide anion radical (O2-), singlet oxygen (1O2), hydroxyl radicals (OH), neutralize hypochlorous acid (HOCl), and prevent lipid peroxidation, but can not scavenge or neutralize hydrogen peroxide (H2O2), rather it may potentiate its toxicity by inhibiting catalase activity. Vitamin C can protect DNA from oxidant-mediated damage, and has been reported to neutralize phagocyte-derived oxidants protecting the 1-protease inhibitor (API) from oxidant-mediated functional inactivation. The vitamin C concentration is lower in blood plasma of cigarette smokers compared to non-smokers, possibly due to increased turnover of the vitamin, increased oxidant stress in smokers, or other mechanisms as yet unknown. It could also be due to its increased consumption during recycling of vitamin E or -carotene that are directly oxidized in the course of scavenging free radicals and reactive oxygen species in cigarette smoke. Nevertheless, it has also been suggested that neither of these antioxidants is an extremely efficient scavenger of cigarette smoke-induced radicals. Another potential reason for declining vitamin C concentration is reduced dietary intake of the vitamin by smokers relative to non-smokers. This factor is often overlooked in studies of vitamin C concentration comparing smokers to nonsmokers. It is also suggested that a close correlation exists between vitamins C and E, and several studies have proposed that vitamin C can act synergistically to preserve vitamin E either by sparing it from oxidation or by regenerating it after it is oxidized. Glutathione (GSH), in its reduced form, is an important water-soluble antioxidant. Its main function is to detoxify xenobiotic toxins by conjugation giving rise to oxidized glutathione disulfide (GSSG). It can also provide reducing equivalents to regenerate reduced vitamin E or vitamin C yielding thiomyl radical (GS) in the process. Exposure of human plasma to cigarette smoke was shown result in depletion of protein thiol including GSH. Unlike other antioxidants, GSH can act sacrificially to prevent protein carbonyl formation associated with cigarette smoke exposure to plasma and is depleted in the process [23].

Vitamin E, and possibly vitamin C, being able to significantly lower lipid oxidative damage in both smokers and nonsmokers, the current evidence is insufficient to conclude that antioxidant vitamin supplementation materially reduces oxidative damage in humans.

Malnutrition may also be a significant cause for the increased prevalence of cervical cancer in women with a low socioeconomic status. Folate, Vitamin C, and β-cryptoxanthin might be better protective agents against lung cancer in smokers. The Chemoprevention of gastric dysplasia an intervention study of 1, 219 subjects confirmed the protective effect of specific dietary antioxidants on the severity of gastritis. Dietary vitamin C, and to a lesser extent, dietary vitamin E are potentially important for the prevention of gastric cancer.

Vitamin C prevented, smoke induced decrease in plasma TRAP and the accelerated formation of serum thiobarbituric acid reactive substances. Vitamin C protected nonsmoking subjects against the harmful effects of free radicals during exposure to secondhand smoke.

Increased levels of F2-isoprostanest in the circulation of persons who smoke support the hypothesis that smoking can cause the oxidative modification of important biologic molecules in vivo. Smoking also increases plasma vitamin E disappearance, the main chain breaking antioxidant, which may increase the risk for carcinogenesis through oxidative stress.

There is evidence, which suggests that supplementation with antioxidants like AT (Alpha Tocopherol), might protect smokers from oxidative damage and could reduce risk from cancer or other diseases caused by free radicals associated with smoking. However, there are reports suggesting that the supplementation of vitamins like AT might not have a beneficial role in combating oxidative stress. Therefore, the present study was designed to investigate the antioxidant role of AT in lungs of mice exposed to cigarette smoking (CS) insult for varying duration.

Free radicals generated in biological systems by cigarette smoke (CS) inhalation can cause oxidative stress in tissues, resulting in lipid peroxidation (LPO). In view of the antioxidant properties of α-tocopherol (AT), effects of AT on antioxidant defense system and LPO were investigated in mice inhaling CS for different time intervals. It appears from our studies that AT inhibits its antioxidant role either directly by scavenging the oxidative species or indirectly by modulating the GSH levels.

Cigarette smoke exposure induces peroxidation of microsomal lipids evidenced by the formation of conjugated dienes, malonadehyde, and fluorescent pigment. Cigarette smoke-induced oxidative damage of proteins and peroxidation of lipids are accompanied by marked drop in the tissue ascorbate level indicate that comparatively large doses of vitamin C may protect the smokers from cigarette smoke – induced oxidative damage and associated degenerative diseases.
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5.5. Antioxidants and lipid peroxidation in gastric cancer

Dietary, as well as antioxidative, vitamin levels have been associated with altered cancer risk. A number of epidemiological studies show that low dietary intakes of vitamin A or carotenoids were correlated with the increased incidence of mortality from lung or breast cancer. Change in serum antioxidative vitamin levels are also often observed in cancer patients. For example, the level of serum ascorbic acid has been shown to decrease in colon, lung, breast, and stomach cancers. The antioxidative vitamins have a number of biological activities which relate to the their cancer preventive properties such as immune stimulation, inhibition of nitrosamine formation, and an alteration of metabolic activation of carcinogen. The major protective function of the vitamins against cancer is the scavenging of free radicals, which are capable of initiating lipid peroxidation. An association between serum alpha-tocopherol and lipid peroxidation in breast cancer has been hypothesized. Stomach cancer is the most prevalent malignant tumor. The purpose of the present study was to determine the relationships among the serum levels of antioxidative vitamins, lipid peroxidation.

A high dietary salt intake does not necessarily entail exposure to salt in concentrations high enough to damage the gastric mucosa. Glutathione independently reduced cytotoxicity of cigarette smoke constituents (CSC) and incidence of cancer. Vitamin E in the form of alpha-tocopherol succinate (ATS), has been shown to inhibit growth of several cancer cell lines in vitro. ATS inhibits gastric carcinoma cell growth in vitro in a dose and time dependent fashion.

Vitamin C, Vitamin E, and β-carotene, often referred to as “antioxidant vitamins,” have been suggested to limit oxidative damage in humans. Because of their antioxidant properties, Carotenoids may have beneficial effects in preventing cancer and cardiovascular disease.

Various organs may control or prevent the damaging effects of the oxidant species by enzymatic and non-enzymatic antioxidant defense systems. These include enzymes like superoxide dismutase (SOD), catalase and GSH-Px certain vitamins like α-tocopherol and ascorbic acid are also suggested to have a strong free radical scavenging properties. The deleterious effects of the free radicals are kept under check by a delicate balance between the rate of their production and elimination by the different antioxidant systems. Any shift in this critical balance could result in an increase in the per oxidative stress and may lead to cellular damage.

The possible protective compounds in vegetables and fruit include a wide variety of phytochemicals. The carotenoids, colourful compounds that are abundant as pigments in plants. The main carotenoids are β-carotene, β-carotene, lutein, zeaxanthin, β-cryptoxanthin and lycopene. They are potent quenchers of free radicals, which are by products of metabolic processes originating from environmental pollutants such as cigarette smoke [23].

5.6. Conclusion

Cigarette smoke is a heterogeneous aerosol, which contains more than 4000 chemical. These include various compounds, which are capable of causing an increase in the generation of various reactive oxygen species like O2, H2O2, OH, ROO-. These reactive oxygen species in turn are capable of initiating and promoting oxidative damage in the form of lipid peroxidation. Cigarette smoking may thus be associated with an increase in the incidence and severity of various diseases like gastric cancer, chronic obstructive lung disease and Atherosclerosis.

Cigarette contains some of the same poisons (toxins) and cancer causing agents (carcinogens) as does cigarette smoke but in higher concentrations. Cigarette tobacco has a high concentration of nitrogen compounds during fermentation and smoking these compounds give rise to several tobacco specific nitrosamines (TSNA’s). The higher concentration of nitrogen oxides, ammonia, carbon monoxide and tar all very harmful. Nicotine is the substance in tobacco that causes addiction.

Each puff of a cigarette contains ~1014 free radicals in the tar phase and ~1015 in the gas phase. In addition to high concentrations of oxides of nitrogen, smokers also have increased phagocyte activities, and are therefore under a high and sustained free radical load. It is thus not surprising that smokers have an increased incidence of diseases associated with oxidative stress. It has been hypothesized that many of the adverse effects of smoking may result from oxidative damage to critical biologic substances. Such damage could result both from oxidants present in cigarette smoke and from the activation of phagocytic cells that generate reactive oxygen species.

Oxidative inactivation of antiproteases may be involved in the development of chronic obstructive modification of DNA and can lead to the development of cancer. Thus cigarette smoking can moderately increase the risk of gastric cancer.
References:


