Review of Literature

As our circle of knowledge expands, so does the circumference of darkness surrounding it.

Albert Einstein
2.1. International cancer epidemiology

According to International Union of Cancer Control and World Health Organization report of 2005, every year more than 11 million people are diagnosed with cancer worldwide. It is estimated that the number of new cases annually will rise to more than 16 million by 2020. Cancer causes more than 7 million deaths each year which is 13% of all the deaths worldwide. In the developed countries, it is the second most common cause of death with a major threat to public health. It is also increasingly much higher in the developing world. The figure 1 shows the incidence, prevalence and mortality of cancer by continent and for several larger countries41.

Based on the global cancer statistics, 2002, there were 10.9 million new cases, 6.7 million deaths, and 24.6 million persons living with cancer (within 5 years of diagnosis) in the year 2002. In the world, lung cancer is the main cancer that is estimated either in terms of number of incident cases (1.35 million) or deaths (1.18 million), due to the high case fatality (ratio of mortality to incidence is 0.87). The cancer of breast remains the second most common cancer (1.15 million new cases) and ranks 5th as a cause of mortality because of the relatively favorable prognosis (mortality to incidence ratio, 0.35). This is followed by cancers of the stomach (934,000 cases, 700,000 deaths), liver (626,000 cases, 598,000 deaths) and colon and rectum (1.02 million cases, 529,000 deaths). In men, although lung cancer is the most common cancer worldwide, it is in second place behind cancers of the prostate in developed countries. In women, after breast cancer, the cervix cancer is the second in developing countries and seventh in the developed world41.
Figure 1. Incidence, prevalence and mortality by location (global cancer statistics 2002)\(^4\)

**Incidence: 10,852,000 persons**

- **Europe**: 26.0%
- **Oceania**: 1.0%
- **Africa**: 6.5%
- **Latin America & Caribbean**: 7.7%
- **India**: 7.8%
- **Others**: 1.3%
- **North America**: 14.4%
- **USA**: 13.2%
- **Others**: 12%
- **Japan**: 4.8%
- **Asia**: 44.9%
- **China**: 20.3%

**Mortality: 6,724,000 deaths**

- **Europe**: 25.3%
- **Oceania**: 0.6%
- **Africa**: 7.3%
- **Latin America & Caribbean**: 7.1%
- **Others**: 12.9%
- **North America**: 9.4%
- **USA**: 8.4%
- **Japan**: 4.6%
- **China**: 23.8%
- **Asia**: 49.9%
- **India**: 8.6%

**Prevalence: 24,570,000 persons**

- **Europe**: 29.6%
- **Oceania**: 1.3%
- **Africa**: 4.1%
- **Latin America & Caribbean**: 6.3%
- **Others**: 10.8%
- **North America**: 21.1%
- **USA**: 19.3%
- **Japan**: 6.3%
- **China**: 12.7%
- **Asia**: 37.2%
2.2. Indian cancer epidemiology

In India, cancer has become one of the ten leading causes of death. It is estimated that there are nearly 1.5-2 million cancer cases diagnosed per year. Over 7 lakh new cases of cancer and 3 lakh deaths occur annually due to cancer. The age-adjusted cancer incidence rate per 100,000 people in the five urban centres varied between 101.2 (Bhopal) to 143.6 (Delhi) for women in 1990, whereas for males it was between 107.5 (Bhopal) and 138.9 (Mumbai). This incidence was twice the incidence rate of 56.2 in the rural area of Barsi near Pune (Maharashtra), which shows that living in polluted urban centres almost doubles the chances of developing cancer.

In 2005, the National Commission on Macroeconomics and Health had published a report on burden of disease in India. In the report, the incidence rate of cancer was estimated for the entire country in the year 2004 by selecting cancer registries on the basis of quality of the data and location. The population at risk of developing cancer was done by the exponential growth rate method from the census of 1991 and 2001 data. Estimation of the mortality rate for cancer was done by using the data from the Chennai and Mumbai registries, considering the quality of data. The cancer prevalence was estimated by assuming the average duration of disease as 2.5 years [Table 1].

The data from population-based registries under National Cancer Registry Programme also indicated that the leading sites of cancers are oral cavity, lung, pharynx, oesophagus and stomach amongst men and cervix, breast, ovary, oral cavity and esophagus in women. Cancers mainly those of oral cavity and lungs in males, and cervix and breast in females account for over 50% of all cancer deaths in India [Table 2]. Similarly, another study related to the evaluation of incidence trend and cumulative risk of oral cancer confirmed its major contribution to the cancer burden in India.
Table 1. Cancer Incidence, prevalence and mortality: Estimate for India, 2004

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence, all ages</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIR/10^5</td>
<td>66.2</td>
<td>81.6</td>
<td>73.6</td>
</tr>
<tr>
<td>ASR/10^5</td>
<td>95.1</td>
<td>112.1</td>
<td>104.2</td>
</tr>
<tr>
<td>Cumulative risk (0-74 years)</td>
<td>1 in 9</td>
<td>1 in 8</td>
<td>1 in 9</td>
</tr>
<tr>
<td>Incident cases</td>
<td>374,506</td>
<td>432,174</td>
<td>806,680</td>
</tr>
<tr>
<td>Prevalent cases</td>
<td>936,265</td>
<td>1,080,435</td>
<td>2,016,700</td>
</tr>
<tr>
<td><strong>Incidence, 35-64 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIR/10^5</td>
<td>119.5</td>
<td>176.5</td>
<td>153.7</td>
</tr>
<tr>
<td>ASR/10^5</td>
<td>155.1</td>
<td>234.3</td>
<td>202.6</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMR/10^5</td>
<td>51.8</td>
<td>48.4</td>
<td>49.1</td>
</tr>
<tr>
<td>Deaths</td>
<td>293,219</td>
<td>245,638</td>
<td>538,858</td>
</tr>
</tbody>
</table>

CIR: Crude incidence rate; ASR: Age standardized rate; CMR: Crude mortality rate

Table 2. Common cancers in India, 2004

<table>
<thead>
<tr>
<th>Site of Cancer</th>
<th>Incident cases (%)</th>
<th>Crude incidence rate/10^5</th>
<th>Age standardized rate/10^5</th>
<th>Ratio of risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All ages</td>
<td>35-64 years</td>
<td>All ages</td>
<td>0-74 years</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>40,700 (10.9)</td>
<td>7.2</td>
<td>17.6</td>
<td>10.3</td>
</tr>
<tr>
<td>Lung</td>
<td>34,983 (9.3)</td>
<td>6.2</td>
<td>9.8</td>
<td>9.4</td>
</tr>
<tr>
<td>Pharynx</td>
<td>31,716 (8.5)</td>
<td>5.6</td>
<td>11.5</td>
<td>8.3</td>
</tr>
<tr>
<td>Esophagus</td>
<td>24,729 (6.6)</td>
<td>4.4</td>
<td>9.7</td>
<td>6.6</td>
</tr>
<tr>
<td>Stomach</td>
<td>22,222 (5.9)</td>
<td>3.9</td>
<td>7.9</td>
<td>5.8</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervix</td>
<td>112,609 (26.1)</td>
<td>21.3</td>
<td>57.4</td>
<td>28.5</td>
</tr>
<tr>
<td>Breast</td>
<td>90,723 (21.0)</td>
<td>17.1</td>
<td>39.7</td>
<td>22.8</td>
</tr>
<tr>
<td>Ovary</td>
<td>24,246 (5.6)</td>
<td>4.6</td>
<td>9.8</td>
<td>6.2</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>22,741 (5.9)</td>
<td>4.3</td>
<td>9.7</td>
<td>6.5</td>
</tr>
<tr>
<td>Esophagus</td>
<td>17,220 (4.0)</td>
<td>3.3</td>
<td>6.8</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Table 3. Incidence and mortality by sex and UADT cancer site worldwide, 2002

<table>
<thead>
<tr>
<th>Site of Cancer</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td></td>
<td>Cases</td>
<td>ASR (world)</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>175,916</td>
<td>6.3</td>
</tr>
<tr>
<td>Pharynx</td>
<td>106,219</td>
<td>3.8</td>
</tr>
<tr>
<td>Larynx</td>
<td>139,230</td>
<td>5.1</td>
</tr>
</tbody>
</table>

CR-Cumulative risk (age 0-64)

ASR- Age standardized rate
2.3. UADT cancer incidence and mortality - International scenario

Oral and pharyngeal cancers are the sixth most common malignancy reported worldwide, behind lung, stomach, breast, colon and rectum, cervix and uterus. They are also one of the cancers with high mortality ratios. The cancer incidence globally was estimated to be 405,318 and about two-thirds of them arising in developing countries. The highest rates of these cancers were reported in South Asian countries such as India and Sri Lanka.

Based on the global cancer statistics report of 2002, the worldwide incidence of UADT cancers was 563,826 and the total number of deaths reported due to these cancers were 301,408. The oral cavity cancers accounted for 274,000 cases, with almost two-thirds of them in men. The highest incidence was found in Melanesia (31.5 per 100,000 in men and 20.2 per 100,000 in women). In men, rates were high in Western Europe (11.3 per 100,000), southern Europe (9.2 per 100,000), south Asia (12.7 per 100,000), southern Africa (11.1 per 100,000), and Australia/New Zealand (10.2 per 100,000). In females, incidence is relatively high in southern Asia (8.3 per 100,000). Cancer of the larynx accounts for 159,000 new cases and 90,000 deaths. It is a predominant cancer in men and comprises 2.4% of cases and 2.1% of deaths. The male to female sex ratio (almost 7:1) is greater than for any other site and it is a rare cancer in women, particularly in developed countries. High-risk countries include southern Europe (France, Italy, Spain), eastern Europe (Russia, Ukraine), south America (Uruguay, Argentina) and western Asia (Turkey, Iraq). In western Asia, larynx cancer accounts for 4.7% of cancers in men.

The incidence of head and neck cancers in the United States of America was 40,490 in 2006, accounting for about 3% of adult malignancies. Almost 11,170 patients died of the disease in 2006. In North America and Europe, the tumors usually arise from the oral cavity, oropharynx or larynx, whereas nasopharyngeal cancer is more common in the
Mediterranean countries and in the Far East. In Canada, approximately 3,200 new oral cancers and 1,050 deaths from these cancers are estimated to occur each year; while the incident cases and deaths due to laryngeal cancers are 1,150 and 510 respectively. In southeast China and Taiwan, head and neck cancer, specifically nasopharyngeal cancer is the most common cause of death in young men. The head and neck cancer among the African Americans affect younger ages with increased mortality, and more advanced disease at presentation.

2.4. UADT cancer incidence and mortality- National scenario

Mouth and pharynx are the third most common site among males and fourth among females in the developing countries. In India, the head and neck cancers account for 30-40% of all cancers, of which 9.4% being oral cancers. It constitutes 23% of all cancer in males and 6% in females. It ranks first in males and third in females among all the cancers. The age adjusted incidence for these sites ranges from 10.8-38.8 and 6.4-14.9 per 100,000 in males and females respectively in the population. The most common UADT cancers are those of the oral cavity and pharynx in Indians. It is the sixth commonest cause of death in males and seventh in females.

Districts in central, south, and northeast India had the world's highest incidence of cancers associated with tobacco, which is chewed as well as smoked. Aizawl district in the northeastern state of Mizoram has the world's highest incidence of cancers in men of the lower pharynx (11.5 per 100,000 people) and tongue (7.6 per 100,000 people). The incidence of mouth cancer among men in Pondicherry was 8.9 per 100,000, one of the highest rates in the world for men.

The people of lower socio-economic strata consume unstandardised quality of pan masala and tobacco that might contain more carcinogens. Changing food habits & lifestyles, increasing use of oral tobacco, environmental pollution and other factors...
contribute to the occurrence of high cancer rates. The tobacco related cancers accounted for nearly 48.2% of all cancers in Indian men and 20.1% in women\textsuperscript{56}. National sample survey organization data from India has shown that the tobacco consumption has decreased in both urban and rural males and females over the period 1987-88 to 1993-94. In spite of the decreasing trend reported, the incidence of oral cavity cancers in India is still one of the highest in the world\textsuperscript{56}. The possible reasons could be the easy availability of tobacco products and the lack of awareness in the community.

The National Cancer Registry programme had estimated the cancers related to UADT from five different hospital based cancer registries (HBCRs), over the period of three years from 1st January 2001 to 31st December 2003\textsuperscript{57}. The mouth cancer, among males was common in Mumbai (12.2%) followed by Thiruvananthapuram (9.4%) and Chennai (8.4%) and for females, the highest proportion was in Bangalore (10.5%). An almost similar distribution of tongue cancer was reported among males in Mumbai and Chennai (6.8% and 6.7% respectively) while it was between 1% and 2.8% among females. The highest rate for hypopharynx was in Dibrugarh, Assam (16.7%) among males and in females it varied from 0.5% to 2.6%. The cancer of larynx among males ranges from 4% to 4.9% while the data was not available for females [Table 4].
According to the consolidated report of the hospital based cancer registry (2001-2003), the figures of the leading sites of cancer among males and females, and the leading sites based on the age groups (35-64 and 65 & above) among males and females in Chennai, the capital of Tamilnadu are given below [Figures 2-7].

According to the report, stomach (9.1%) and mouth (8.4%) cancers were the leading sites among the males. These two sites were followed by the cancers of tongue, hypopharynx and larynx that accounted for 6.7%, 5.8% and 4.2% respectively [Figure 2]. Among the females, cancer of the cervix was the leading site, accounting for about 30.7%, followed by breast (21.7%) and mouth (5.7%) [Figure 3].

The relative proportions of cancers in the broad age groups, 35-64 and 65 years and above, for both sexes from the hospital based registry of Chennai are shown below [Figures 4-7]. Between 35-64 years, mouth cancer was the second leading among the males followed by tongue, hypopharynx and larynx that accounted for 7.7%, 6.5% and 4.9% respectively. Among females, mouth cancer was the third leading cancer while hypopharynx and tongue was among the first ten sites [Figures 4 and 5]. Among the males above 65 years of age, mouth was the leading site, while third in females [Figures 6 and 7].

**Table 4. Relative proportion of UADT cancers**

<table>
<thead>
<tr>
<th></th>
<th>Mouth</th>
<th></th>
<th>Tongue</th>
<th></th>
<th>Hypopharynx</th>
<th></th>
<th>Larynx</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>%</td>
<td>Female</td>
<td>%</td>
<td>Male</td>
<td>%</td>
<td>Female</td>
<td>%</td>
</tr>
<tr>
<td>Mumbai</td>
<td>12.2</td>
<td></td>
<td>5.0</td>
<td></td>
<td>6.8</td>
<td>2.6</td>
<td>4.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Bangalore</td>
<td>5.3</td>
<td>10.5</td>
<td>5.3</td>
<td>1.1</td>
<td>9.3</td>
<td>1.6</td>
<td>NDA</td>
<td></td>
</tr>
<tr>
<td>Chennai</td>
<td>8.4</td>
<td>5.7</td>
<td>6.7</td>
<td>1.8</td>
<td>5.8</td>
<td>2.0</td>
<td>4.2</td>
<td>NDA</td>
</tr>
<tr>
<td>Thiruvananthapuram</td>
<td>9.4</td>
<td>5.9</td>
<td>5.9</td>
<td>2.8</td>
<td>2.9</td>
<td>0.5</td>
<td>NDA</td>
<td></td>
</tr>
<tr>
<td>Dibrugarh, Assam</td>
<td>6.6</td>
<td>7.4</td>
<td>5.4</td>
<td>2.4</td>
<td>16.7</td>
<td>2.6</td>
<td>4.5</td>
<td></td>
</tr>
</tbody>
</table>

NDA- No data available
Figure 2. Ten leading sites of cancer among males in Chennai

- Lymp. Leuk. 25%
- Myel. Leuk. 34%
- NHL. 39%
- Larynx 4.2%
- Hypopharynx 5.8%
- Tongue 8.7%
- Esophagus 6.8%
- Lung 6.9%
- Mouth 8.4%
- Stomach 9.1%

Figure 3. Ten leading sites of cancer among females in Chennai

- Tongue 1.8%
- Hypopharynx 2.0%
- Myel. Leuk. 2.0%
- Thyroid 2.0%
- Stomach 3.1%
- Esophagus 3.6%
- Ovary 5%
- Mouth 5.7%
- Breast 21.7%
- Cervix 30.7%
Figure 4. Leading sites in broad age groups (35-64) among males in Chennai.

Rectum 3.0
NHL 3.1
Sec.Lymph N 3.2
Larynx 4.9
Hypopharynx 6.5
Esophagus 7.5
Tongue 7.7
Lung 7.9
Mouth 9.6
Stomach 10.4

Figure 5. Leading sites in broad age groups (35-64) among females in Chennai.

Thyroid 1.7
Vagina 1.7
Tongue 1.7
Hypopharynx 1.9
Stomach 2.9
Esophagus 3.3
Ovary 5.2
Mouth 5.6
Breast 23.1
Cervix 34.4
Figure 6. Leading sites in broad age groups (65 and above) among males in Chennai.

- Rectum: 3.1%
- Sec Lymph N: 3.8%
- Prostate: 4.7%
- Larynx: 5%
- Hypopharynx: 8.5%
- Tongue: 7.2%
- Esophagus: 8.5%
- Lung: 8.6%
- Stomach: 9.6%
- Mouth: 10%

Relative proportion %

Figure 7. Leading sites in broad age groups (65 and above) among females in Chennai.

- Thyroid: 2.1%
- Rectum: 2.3%
- Lung: 2.6%
- Tongue: 2.6%
- Ovary: 3.6%
- Stomach: 4.5%
- Esophagus: 7%
- Mouth: 10.3%
- Breast: 18.1%
- Cervix: 23.6%

Relative proportion %
2.5 Anatomy

The UADT involves oral cavity, pharynx and larynx [Figure 8]. The oral cavity includes the lip, floor of the mouth, tongue, alveolar ridge, retromolar trigone, hard palate, and buccal mucosa. The pharynx includes the soft palate, tonsil, posterior and lateral pharyngeal walls, base of the tongue, pyriform fossa, lateral and posterior hypopharyngeal walls, and post cricoid region. The larynx includes the supraglottic, glottic, and subglottic larynx58,59.

2.5.1 Oral cavity

The vermilion border of the lips is the anterior boundary of the oral cavity, while the anterior tonsillar pillars, the posterior aspect of the hard palate, and the circumvallate papillae of the tongue form the posterior boundary. The mucosa of the oral cavity consists of stratified squamous epithelium.

2.5.2 Pharynx

It is divided into nasopharynx, oropharynx and laryngopharynx. Nasopharynx is the superior portion of the pharynx, situated posterior to the nasal cavity and superior to the soft palate. It is lined by pseudostratified ciliated columnar epithelium. The lymphoid tissue in the pharynx forms an incomplete tonsillar ring around the upper part of the pharynx which is aggregated in certain regions to form masses called tonsils. The enlarged pharyngeal tonsils or adenoids are situated in the mucous membrane of the roof and posterior wall of the nasopharynx [Figure 9]. Oropharynx is the middle portion of the pharynx that lies posterior to the oral cavity and extends from the soft palate to the superior border of epiglottis. It is surrounded by soft palate superiorly, the base of the tongue inferiorly, and the palatoglossal and palatopharyngeal arches laterally. The mucosa of the oropharynx consists of nonkeratinized stratified squamous epithelium.
Figure 8. Anatomy of UADT
(Source: www.cetmc.com/head-and-neck.html)

Figure 9. Anatomy of Pharynx
(Source: http://img.tfd.com/dorland/thumbs/pharynx.jpg)

Figure 10. Anatomy of Larynx
(Source: http://www.medicalook.com/systems_images/larynx.jpg)
The laryngopharynx or hypopharynx is the inferior part of the pharynx situated behind the larynx. It extends from superior border of the epiglottis and the pharyngoepiglottic folds to the inferior border of the cricoid cartilage, where it narrows and becomes continuous with the oesophagus. The laryngopharynx is lined by nonkeratinized stratified squamous epithelium with a muscular wall consisting of the middle and inferior constrictor muscles.

2.5.3 Larynx

The larynx is composed of three anatomic subsites. The supraglottic larynx extends from the epiglottis superiorly to the false cords inferiorly. Sites within the supraglottic larynx include the epiglottis (both lingual and laryngeal surfaces), aryepiglottic folds, arytenoids, and false cords. The glottic larynx consists of the true vocal cords (including the anterior commissure) superiorly and tissues within 5 mm of the inferior surface of the true vocal cords inferiorly. The subglottic larynx extends from the glottis superiorly to the inferior border of the cricoid cartilage inferiorly [Figure 10].

2.6 Pathology

The UADT cancers are most commonly squamous cell carcinomas (SCC), originating from the squamous cells that line the upper aerodigestive tract. Other important pathological types are adenocarcinoma, adenoid cystic carcinoma and mucoepidermoid carcinoma. SCC is most often characterized as exophytic or ulcerative or a combination of both. Exophytic lesions are generally less common, slower-growing and less infiltrative than ulcerative lesions. Ulcerative lesions are more common, and often appear as red or grayish ulcers and are deeply infiltrative. SCCs are graded histologically from low-grade tumors that show more extensive keratinization, infrequent mitosis and little nuclear pleomorphism to high-grade tumors showing little keratin, much mitosis and extreme nuclear pleomorphism.
There are several variants of SCC, of which the two most common are basaloid squamous cell carcinoma and verrucous carcinoma. Basaloid SCC, characterized by basaloid cells that are arranged in nests or cords with pseudo-glandular spaces and a high mitotic rate. Verrucous carcinoma that accounts for fewer than 5% of all oral cavity carcinomas are characterized by their whitish, warty, bulky cauliflower like growth, with a broad base.

### 2.6.1 Pathogenesis

Squamous cell carcinomas constitute almost 95% of oral cavity cancers. Macroscopically, there are three different types of oral cancers viz. (a) exophytic growths (b) flat cancers with central ulceration and indurated edges (c) deeply infiltrating ulcers. Among the exophytic lesions, verrucous carcinoma is histologically well differentiated and has a better prognosis than other oral cancers. Cancers of the upper lip metastasize to parotid and submandibular nodes while those of the lower lip metastasize to submental and submandibular nodes, upper and mid jugular nodes. The midline cancers of the lip, the tongue, and the floor of the mouth metastasize to the lymph nodes bilaterally. The site and size of the primary cancer influence the incidence of cervical lymph node involvement from cancers of the oral cavity. Usually the cancers of the oral tongue and the floor of the mouth have a higher incidence of cervical lymph node involvement than the cancers of the lip, hard palate, or buccal mucosa.

Most oropharyngeal cancers which are richly supplied with lymphatics are squamous cell carcinomas and they are less well differentiated than oral cavity cancers. Posterior pharyngeal wall cancers metastasize bilaterally to jugular chain nodes and the retropharyngeal nodes of Ranvier. Cancers of the tonsillar region metastasize primarily to the upper and mid jugular chain nodes and to the submandibular nodes. The overall incidence of cervical lymph node involvement from cancer of the oropharynx is approximately 70%.

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The incidence of poorly differentiated cancer is higher in the hypopharynx than in other regions and over 95% of hypopharyngeal cancers are squamous carcinomas presenting as infiltrating ulcerative lesions. Cancer of the hypopharynx has a high propensity for lymphatic invasion with most patients having cervical lymph node metastasis at the time of initial presentation. Occult cervical lymph node metastasis are also common, causing the overall incidence of cervical lymph node metastasis at presentation to be approximately 75%\(^6\).

Squamous cell carcinoma of the supraglottic larynx accounts for 35% of laryngeal cancers and 50% of these patients will present with cervical lymph node metastasis. Cancer of the glottic larynx tends to be well differentiated with slow growth and late metastasis and accounts for nearly 65% of laryngeal cancers. There is a high incidence of cervical lymph node metastasis with subglottic cancers. The subglottic laryngeal cancers drain into the mid and lower jugular lymph nodes and to the prelaryngeal node with subsequent involvement of the pretracheal and paratracheal lymph nodes\(^{39,60,61}\).

2.6.2. Gross pathological progression of the cancers of UADT

Development of multiple independent premalignant and malignant foci or lesions in the UADT is widely believed to be due to ‘field cancerization’ of the epithelium from prolonged exposure to carcinogens especially from tobacco and alcohol\(^6\). Field cancerization may describe three phenomena: (1) the widespread upper aerodigestive tract mucosa that tends to be affected by pre-malignant disease (2) the frequent occurrence of multiple primary tumors in epithelial mucosa affected by pre-malignant disease and (3) the possibility of distant related primary tumors in the upper aerodigestive tract\(^6\). The clinical appearance of most of the premalignant lesions of the mucosal surfaces of the upper aerodigestive tract include leukoplakic, erythroplakic, or speckled leukoplakia reflecting the presence of a white, red, or mixed white/red lesion, respectively.
Leukoplakia is a chronic whitish patch or plaque that cannot be characterized clinically or pathologically as any other disease and which is not associated with any physical or chemical causative agent except the use of tobacco. Erythroplakia is a chronic red mucosal macule which is commonly associated with microinvasive carcinoma. If left untreated, 60-90% of erythroplakia may turn into cancer in 5-10 years. It is associated with a greater likelihood (4 to 7 times) of malignant transformation compared to leukoplakia. Among these clinical changes, erythroplakic lesions are commonly associated with different histopathologic alterations, including severe dysplasia, carcinoma in situ or invasive carcinoma. In contrast, leukoplakic lesions are not necessarily a premalignant lesion and may demonstrate a spectrum of histopathologic changes ranging from an increased surface keratinization without dysplasia to invasive keratinizing squamous carcinoma. The clinical appearance of a mixed white and red lesion, called speckled leukoplakia, carries an intermediate risk between leukoplakic and erythroplakic lesions for the development of a malignancy [Figures 11-14].

Figure 11. Premalignant lesions

Leukoplakia

Erythroplakia

Figure 12. Various stages of gross pathological progression of oral cancer

SCC of lip

SCC with lymph nodes

Late stage of SCC

Figure 13. SCC of Pharynx

Figure 14. SCC of Larynx
2.6.3. Histopathogenesis

Histologic criteria for the diagnosis of intraepithelial neoplasia of the UADT include both cytomorphologic and maturation abnormalities. These abnormalities include the proliferation of immature cells characterized by a loss of cellular organization or polarity, nuclear pleomorphism with increase in nuclear size relative to the cytoplasm, increase in the nuclear chromatin with irregularity of distribution, and increased mitoses, including atypical forms in all epithelial layers. The dysplastic changes may or may not be associated with keratosis and/or dyskeratosis. These architectural and cytomorphologic changes within the epithelium represent key diagnostic parameters in the assessment of UADT epithelial dysplasia. The oral carcinogenesis in a normal epithelium passes through different stages of dysplasia prior to the onset of invasive cancer\textsuperscript{66,67} [Figure 15].

These dysplastic cells have enlarged nuclei with eosinophilic nucleoli and increased nuclear-cytoplasmic ratio. These cells also appear to be crowded more closely together than normal keratinocytes. There is increased mitotic activity in dysplastic epithelium. Enlarged, tripolar or star-shaped mitotic figures are much more indicative of precancerous changes. Premature production of keratin below the surface layer is another important alteration, but is much more commonly seen in oral carcinomas than in oral premalignancies. This dyskeratosis may be represented by individually keratinized cells or by tight concentric rings of flattened keratinocytes (epithelial pearls). Cellular necrosis and loss of cellular cohesiveness (acantholysis) are major signs of poorly differentiated carcinoma but are extremely rare in the epithelial dysplasia of oral precancer [Figure 16]\textsuperscript{68}. 
The prognosis of patients with squamous cell carcinoma of the upper aerodigestive tract has improved in western countries because of better understanding of disease and advances in treatment. But management in many developing countries remains suboptimal, largely because of economic constraints and lower levels of education, which result in a large proportion of patients presenting late with advanced disease. In Asia, the incidence of oral cavity carcinoma is high because of factors such as poor oral hygiene, chewing betel nuts, smoking and drinking alcohol. In addition, viral infections, dietary and genetic factors have also been found to be responsible for the high incidence of the upper aerodigestive tract cancers.
Figure 15. Stages leading to the clinical progression of oral cancer

Bening squamous hyperplasia  
Dysplasia  
Carcinoma  
Dysplasia  
Carcinoma

Figure 16. Stages leading to the histopathological progression of oral cancer

Normal mucosa  
Hyperplasia  
Dysplasia  
Carcinoma in situ  
Carcinoma
2.7. Risk factors related to UADT cancers

Epidemiologic data have shown considerable variability in determining the trends in the incidence of UADT malignancies worldwide, emphasizing the multifactorial etiologies for these cancers. The regional variations in the development of UADT cancers are strongly related to habitual, cultural and genetic risk factors that are prevalent in each ethnic group. Several studies have established a strong dose-response relationship between the risk factors and the development of these cancers. Since it is a multi-step process, several risk factors may play a synergetic role in the tumorigenesis. In India, the disproportionately higher incidence of carcinoma of the upper aerodigestive tract in regard to other malignancies may be due to the use of tobacco in various forms, consumption of alcohol, low socioeconomic condition related to poor hygiene, nutritional deficiencies, occupational exposure and viral infections. The risk factors that increase the likelihood of developing UADT cancers are described below.

2.7.1. Environmental factors:

The variation in incidence of cancers by subsite of UADT cancers is mostly related to the relative distribution of major environmental risk factors. The field of epidemiology has contributed significantly in identifying tobacco and alcohol as the major risk factors in developing UADT cancers9,70,71. About 80%–90% of squamous cell carcinomas of the UADT are attributable to tobacco and/or alcohol use72,73. Among this, 80% of cancers among men and 61% in women are attributed to smoking and alcohol consumption74. In south Asia, including India, UADT cancer has been associated with smoking and chewing of tobacco alone or together with betel quid (BQ), whereas in western countries cigarette smoking and chronic alcohol consumption are the main environmental factors75. It has been estimated that approximately 75% of all the oral malignancies in the United States of America are attributable to tobacco or alcohol intake or both74.
2.7.1. Tobacco Use: A Global Perspective

According to the World Health Organization (WHO), tobacco is the second major cause of death in the world and it is currently responsible for the death of one in ten adults worldwide. Tobacco consumption remains the most important avoidable cancer risk. It was reported that 25% to 30% of all cancers in developed countries are tobacco-related. It is consumed both in its smoking as well as in smokeless form. According to WHO, the tobacco smoking is practiced worldwide by over one thousand million people. Among them, about 300 million (200 million males and 100 million females) are in the developed countries, and nearly three times as many (800 million- 700 million males and 100 million females), in developing countries. In developed countries, 41% of men and 21% of women are regular smokers. In the developing countries, half the men are smokers, compared with about 8% of women. It has caused about 62 million deaths or 13% of all deaths (20% of deaths in men and 4% in women) in developed countries between 1950 and 2000. It has been estimated that, worldwide, tobacco smoking will cause about 150 million deaths in the first quarter of this century and 300 million in the second quarter.

However, while smoking prevalence has declined in many developed countries, it remains high in developing countries. Men in most populations between one-fifth and two-thirds are prone to smoking habits. The rate of smoking among women varies widely. Smoking has consistently been reported to confer a dose dependant increase in the risk of developing these cancers. In India, smoking of bidi (a type of cigarette) is the most common form of tobacco use, about 6 times more common than cigarette smoking. Bidi contains sun cured shredded tobacco wrapped in rectangular piece of tendu or temburni dried leaf (Diospyros melanoxylon) and tied with cotton thread.

In India, tobacco consumption results in half of all the cancers in men and a quarter of all cancers in women. The country has a long history of tobacco use in a variety of
ways of chewing and smoking. However, the tobacco smoking is the most common form of tobacco consumption in urban male population whereas in rural population, chewing tobacco is more common. The World Health Organization predicted that by 2020 tobacco related deaths in India may exceed 1.5 million annually. India is the third largest producer and consumer of tobacco. In India, the per capita consumption of cigarettes has been increased by 2% over the last decade.

According to International Agency for Research on Cancer (IARC), cigarette smoking is an important cause of lung cancer, esophageal, oral, oropharyngeal, hypopharyngeal, and laryngeal cancers as well as pancreatic cancer, bladder cancer and cancer of the renal pelvis. The carcinogenic compounds in cigarette smoke are thought to be responsible for these cancers. It is known that cigarette smoke is a complex mixture of over 4,000 substances. The IARC has estimated that, more than 60 carcinogens are present in cigarette smoke either in laboratory animals or humans that initiates or promotes tumors. These carcinogenic products belong to various group of chemicals, such as polycyclic aromatic hydrocarbons (PAH), azo-arenes, N-nitrosamines, aromatic amines, heterocyclic amines, aldehydes, volatile hydrocarbons, nitro compounds, miscellaneous organic compounds and metals and other inorganic compounds. The number and relative percentage of specific sites of tobacco related cancers (TRCs) from different registries among males and females were estimated during 2001-2003.

**Males:** In Mumbai, Mouth (27.0%), lung (16.8%) and tongue (15.2%) were the main sites that contributed to overall TRCs. Hypopharynx (21.2%), esophagus (20.6%) and lung (15%) were the three leading sites in Bangalore. In Chennai, mouth (20.0%) was the leading site followed by lung (16.5%) and esophagus (16.1%). Cancer of lung was the leading contributor of TRCs (29.5%) followed by mouth (20.5%) and tongue (12.9%).

**Females:** In Mumbai, Mouth (26.0%), lung (17.0%) and tongue (14.3%) were the main sites that contributed to overall TRCs. Hypopharynx (21.0%), esophagus (21.0%) and lung (14%) were the three leading sites in Bangalore. In Chennai, mouth (20.0%) was the leading site followed by lung (16.5%) and esophagus (16.1%). Cancer of lung was the leading contributor of TRCs (27.5%) followed by mouth (18.0%) and tongue (12.0%).
in Thiruvananthapuram while in Dibrugarh, cancer of the hypopharynx constituted 28.1% of TRCs followed by esophagus (27.5%) and mouth (11.2%) [Table 5].

**Females:** Among TRCs in Mumbai, mouth (31.2%), esophagus (20.9%) and tongue (16.3%) were the leading sites. In Bangalore, mouth (47.7%) was the leading cancer that contributed almost half of the TRCs followed by esophagus (28.1%). Similarly, in Chennai, mouth (36.0%) constituted for most of the TRCs followed by esophagus (22.5%) and hypopharynx (12.6%). In Thiruvananthapuram also mouth (42.6%) was the leading contributor for most of TRCs followed by tongue (19.8%) and lung (15.1%), whereas in Dibrugarh, the esophagus (48.1%) was the major site for TRCs followed by mouth (22.6%) and hypopharynx (8.1%) [Table 6].
### Table 5. Number & relative proportion of tobacco related cancers in males\(^{57}\)

<table>
<thead>
<tr>
<th>Sites of Cancer</th>
<th>Mumbai n</th>
<th>%</th>
<th>Bangalore n</th>
<th>%</th>
<th>Chennai n</th>
<th>%</th>
<th>Thiruvananthapuram n</th>
<th>%</th>
<th>Dibrugarh n</th>
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### Table 6. Number & relative proportion of tobacco related cancers in females\(^{57}\)

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<th>Bangalore n</th>
<th>%</th>
<th>Chennai n</th>
<th>%</th>
<th>Thiruvananthapuram n</th>
<th>%</th>
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<th>%</th>
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<td>1634</td>
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### Important carcinogens identified in cigarette smoke

<table>
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<tr>
<th>Polycyclic aromatic hydrocarbons&lt;sup&gt;69-93&lt;/sup&gt;</th>
<th>Tobacco-specific N-nitrosamines (TSNAs)&lt;sup&gt;92,94-96&lt;/sup&gt;</th>
<th>Aromatic amines&lt;sup&gt;92,93&lt;/sup&gt;</th>
<th>Aza-arenes&lt;sup&gt;93&lt;/sup&gt;</th>
<th>Heterocyclic amines&lt;sup&gt;97&lt;/sup&gt;</th>
<th>Aldehydes&lt;sup&gt;95-100&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Anthanthrene</td>
<td>NNK (4-Methylnitrosoamino)-1-(3-pyridyl)-1-butanone)</td>
<td>4-Aminobiphenyl</td>
<td>Benz(a)acridine</td>
<td>2-amino-1-methyl-6-phenylimidazo [4,5-b]pyridine (PhIP)</td>
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<td>Benz(a)anthracene</td>
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<td>2-Aminophthaline</td>
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<td>o-Toluidine-chromium</td>
<td>Dibenz(a,h)acridine</td>
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<tr>
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<td>2,1-BNT (Benzon(b) naphtha (2,1-d)thiophene</td>
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</table>
Among the PAHs, benzo (a) pyrene (BaP) is the most extensively studied compound. Apart from tobacco smoke, BaP is found in coal tar, automobile exhaust fumes (especially from diesel engines), wood smoke and in charbroiled food. BaP is bioactivated by CYP enzymes to acquire its mutagenic and carcinogenic properties. The first step in the metabolism is the formation of B[a] P-7, 8-epoxide followed by hydrolysis by epoxide hydrolase to the B[a] P-trans-7, 8-dihydrodiol which is further metabolized by CYP enzymes to the ultimate genotoxic (±)-B[a] P-r-7, t-8-dihydrodiol-t-9,10-epoxide (DE2) compound.

Apart from PAH, another major carcinogenic chemical found in cigarette smoke is the tobacco-specific-nitrosamines (TSNA). Of the seven TSNA found in the tobacco, N'-nitrosonornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) are considered the most carcinogenic. In 1970s, it was proven that NNN induces malignant tumors in the upper aero digestive tract of rats.

In India and other Asian countries, oral neoplasia has been associated with chewing of tobacco with BQ. The Indian cancer registries have confirmed a high incidence of oral cancer. Case control and cohort studies have established that the high incidence is due to widespread habits of tobacco chewing and smoking. The oral use of smokeless tobacco is widely prevalent in India; the different methods of consumption include chewing, sucking and applying tobacco preparations to the teeth and gums. The chewing of tobacco with BQ results in exposure to carcinogenic tobacco specific nitrosamines to about 1000 µg/day, compared with approximately 20 µg/day in smokers as well as nitrosamines derived from areca nut alkaloids. It has also reported that chewing of BQ generates high amount of reactive oxygen species (ROS) in mouth, which have been implicated in multistage carcinogenesis. Thus TSNA and ROS are the major genotoxic agents involved in chewing related UADT cancers. The use of BQ,
containing both areca nut and tobacco, is associated with a relative risk of oral cancer, between 8-15 times as compared to that of 1-4 times, when using the betel quid, without tobacco\textsuperscript{112}. Among the rural population of Maharastra, India, the development of oral cancer was significantly associated with the synergistic effects of all the three or even two of the risk factors, i.e., oral tobacco use, smoking and alcohol consumption\textsuperscript{113}.

In the United States of America, a high incidence of upper aerodigestive tract cancers has been reported among women using oral snuff\textsuperscript{114}. A southern Sweden based study confirmed that both tobacco smoking and alcohol consumption are the risk factors for oral and oropharyngeal squamous cell carcinoma whereas the moist snuff was not associated with the disease risk\textsuperscript{115}. Tobacco intake in the form of inverse smoking conferred a 5.19 times increased risk for oral precancerous lesions than tobacco chewing\textsuperscript{116}.

2.7.2. Alcohol

Chronic alcohol consumption is implicated as one of the risk factors in the etiology of UADT cancers, worldwide. Development of UADT cancers and the consumption of alcohol are strongly linked, predominantly when there is concurrent tobacco use. Alcohol synergizes with tobacco as a risk factor for all the upper aerodigestive tract SCCs.

There are several mechanisms that are involved in alcohol-associated cancer development which include the effect of acetaldehyde (AA), the first metabolite of ethanol metabolism, the induction of CYP2E1 leading to the generation of ROS, and enhanced procarcinogens activation and nutritional deficiencies\textsuperscript{117}.

Acetaldehyde, the first metabolite of ethanol oxidation is responsible for the co-carcinogenic effect of alcohol\textsuperscript{118}. The highly toxic, mutagenic and carcinogenic acetaldehyde is generated in the gastrointestinal tract through mucosal and/or bacterial
alcohol dehydrogenase. It interferes at many sites with DNA synthesis and repair and result in tumour development. Acetaldehyde produced by the oral bacteria was detected in significant amounts in the saliva of healthy volunteers after ingestion of a moderate dose of alcohol. These levels were ten to twenty times higher than those in systemic blood, even at a higher alcohol intake.

In India, different alcoholic beverages that are commonly consumed are toddy, arrack and foreign liquor. Toddy is a locally fermented palm sap; arrack is locally brewed liquor with almost 40% ethanol content while the foreign liquor consist of wine, whisky, beer, brandy, gin and rum.

Polymorphisms in the gene coding for the enzymes responsible for acetaldehyde generation and detoxification, results in increased cancer risk. In Asian countries, a high percentage of individuals have a mutation of the acetaldehyde dehydrogenase (ALDH) 2 gene. Furthermore, the polymorphisms in alcohol dehydrogenase 2 (ADH2) and alcohol dehydrogenase 3 (ADH3) modulates cancer risk. In addition, chronic alcohol consumption leads to an induction of CYP2E1, the enzyme that metabolizes ethanol to acetaldehyde. The induced enzyme generates ROS and substrate derived free radicals which can mediate lipid peroxidation, protein inactivation and DNA damage. The enzyme is also involved in the metabolism of various low-molecular-weight compounds into reactive intermediates.

The increase in oral cavity cancer in the western countries had been related to increased consumption of alcohol. It has been estimated that 25–68% of UADT cancers are attributed to alcohol and that up to 80% of these malignancies can be prevented by abstaining from alcohol and tobacco smoking.
The relative risk of both oral and pharyngeal cancer elevates with the level of alcohol consumption. A meta-analysis of oral and pharyngeal cancers found that consumption of 25, 50 or 100g pure alcohol/day was associated with relative risk of 1.75, 2.85, and 6.01 respectively. The risk associated with laryngeal cancer was 1.38 (1.32-1.45), 1.94 (1.78-2.11) and 3.95 (3.43-4.75) respectively among 25, 50, or 100g pure alcohol/day\textsuperscript{122}. A study found that drinking is directly associated with the risk of laryngeal cancer in people who do not smoke, with risk increasing with the level of alcohol consumption\textsuperscript{124}.

Alcohol enhances the penetration of carcinogenic compounds by facilitating the uptake of environmental carcinogens especially from tobacco smoke through the mucosal membranes that are damaged by the direct effect of alcohol\textsuperscript{120}. In chronic alcoholics, the entire nutritional status is disturbed due to primary and secondary malnutrition. Various deficiencies of vitamins (vitamin A) and trace elements (zinc and selenium) that occur in chronic alcoholics may contribute to alcohol related carcinogenesis.

\textbf{2.7.2. Occupational risk}

In central and eastern Europe, an association between coal dust exposure and risk of cancer of the larynx and hypopharynx had been demonstrated\textsuperscript{125}. Among Brazilians, the occupation as vehicle repair worker or employment in vehicle maintenance shops increased the risk for oral cancer, independent to smoking and alcohol. The risk was further increased with prolonged exposure\textsuperscript{126}.

\textbf{2.7.3. Dietary factors}

The role of diet in the etiology of UADT cancers remains unresolved. The most consistent results show decreased risk associated with the consumption of fruits and vegetables\textsuperscript{127}, but available evidence is still inconsistent for other dietary components.
Nutritional deficiencies and immune suppression have also been associated with the cancers of head and neck. The nutritional deficiencies often occur in heavy alcohol consumption and may be equally responsible for alcohol's increased risk. Malnutrition as well as dietary deficiencies in some vitamins such as riboflavin, vitamin B derivatives, vitamin A and retinoids may also play a significant role. Diets that are low in certain micronutrients and some aspects of oral hygiene are likely cofactors.

Excessive consumption of processed meats and red meat were associated with increased rates of cancer of the head and neck, while consumption of raw and cooked vegetables seemed to be protective. In a Brazilian study, the low consumption of fruits and vegetables was associated with increased risk of oral cancer, whereas the traditional Brazilian diet which consists of rice and beans plus moderate amounts of meat was associated with decreased risk of oral cancer.

An Indian study reported a reduced risk for oral cancer among vegetarians when a comparison between non-vegetarian and vegetarian diets and alcohol and tobacco use was considered. The Italian studies have found that the fiber intake may have a protective role on oral, pharyngeal and esophageal cancers while the fruits and vegetables with more of micronutrients showed a protective effect against oral cancer.

A 2.4 fold increased risk associated with UADT cancer with red meat intake was observed, while vegetables, fruits and legumes were associated with negative risk. Salted meat, a source of nitrosamines, was also associated with a 60% increased risk for esophageal cancer. The potential benefit of increasing fruits and vegetables consumption which protects against risk of cancers of the UADT was supported by a prospective European investigation into cancer and nutrition study.
2.7.4. Family History

In Sweden, a study related to family history of cancer using data on medically verified diagnosis did not find a significant risk for upper aerodigestive tract cancers among the offsprings of parents having concordant cancer\textsuperscript{134}. Studies from Kerala, a south Indian state, revealed a familial association in 0.94 percent of the total oral cancers accrued from January to July 1995, consistent with autosomal inheritance\textsuperscript{135}.

2.7.5. Orodental factors

Poor oral hygiene, faulty restorations, sharp teeth and irritation caused by ill-fitting dentures have also been implicated as etiological factors for oral cancer. The studies done earlier suggested that poor oral hygiene is a contributory factor in the causation of oral cancer\textsuperscript{136,137}. Tumors in the floor of mouth could be due to the mechanical irritation from dentures with an improper fit. In western countries, the mechanical irritation from the studs that many young people wear in their tongues could affect the incidence of tongue cancer\textsuperscript{138}.

A study conducted in three areas in southern India (Bangalore, Chennai and Thiruvananthapuram) observed that in men, 35% of oral cancer is due to the combination of smoking and alcohol drinking and 49% to pan tobacco chewing; whereas in women, 95% of oral cancer was attributed to tobacco chewing and poor oral hygiene\textsuperscript{139}. In addition to both smoking tobacco and alcohol consumption, the independent risk factors identified are poor oral hygiene, inadequate dental status and malfunctioning of the complete dentures\textsuperscript{140}.

2.7.6. Genetic factors

Molecular epidemiological studies have now provided evidence that an individual's susceptibility to cancer is mediated mainly by the combined effects of genetic and environmental factors. Cancers can be classified into two, based on the difference in the
involvement of genetic factors as hereditary or sporadic\textsuperscript{38,141}. Hereditary cancers, which account for approximately 2\% of all cancers, are caused by germline mutations of distinct genes inherited in an autosomal dominant or recessive manner. The genes responsible for hereditary cancers are tumor suppressor genes, oncogenes and DNA repair genes. Sporadic cancers are characterized by the occurrence of spontaneous mutations and constitute remaining 98\% of all the cancers. Recent epidemiological data indicate that the susceptibility to sporadic cancers in humans is influenced considerably by multiple polymorphic host genes with relatively weak effects. This indicates that in addition to hereditary cancers, the sporadic cancers are also under strong genetic control\textsuperscript{141}. Therefore, cancer genes can be classified mainly as gatekeeper genes and caretaker genes characterized by their control of net cellular proliferation or maintenance of genomic integrity. While the gatekeeper genes affect cell cycle control and DNA replication, the caretaker genes affect DNA repair, metabolic activation and detoxification of carcinogens\textsuperscript{12}.

2.7.6.1. Cell cycle control and DNA replication genes
Progression of eukaryotic cells through major cell cycle transitions is mediated by the activation and inactivation of a family of serine-threonine protein kinases, the cyclin dependent kinases (CDK). The balance between CDK activation and inactivation determines whether cells proceed through $G_1$ into $S$ phase and from $G_2$ to $M$, through regulatory mechanisms. Cell cycle control and replication affects many aspects of development especially it can be deregulated in cancer and the 'pRb pathway' has been implicated in multistep oncogenesis of possibly all human tumor types eg. p53 tumour suppressor gene. The p53 protein senses DNA damage and arrests the progression of the cell cycle in $G_1$ (by blocking the activity of CDK2) thereby acts as transducers of negative growth signals\textsuperscript{142,143}. 
2.7.6.2. DNA repair genes

The human DNA repair systems are essential for the maintenance of genomic integrity. The DNA repair enzymes monitor chromosomes to correct damaged nucleotide residues generated by exposure to carcinogens and cytotoxic compounds. The damage can be caused by environmental agents such as ultraviolet light from the sun, inhaled cigarette smoke, or incompletely defined dietary factors. In order to maintain genome integrity, the co-ordinated action of surveillance and repair pathways are required. Any disregulation of repair genes is expected to be associated with significant, detrimental health effects, which can include an increased prevalence of birth defects, an enhancement of cancer risk and an accelerated rate of aging.

2.7.6.3. Metabolic activation and detoxification genes

Enzymes that are involved in the metabolic activation and detoxification of carcinogens belong to functionalization (phase I) and conjugation (phase II) group of drug metabolizing enzymes respectively. Functionalization reactions consist of oxidation, reduction and hydrolysis. These reactions usually lead to metabolites that are more polar than the parent compound by introducing an oxygen atom into the substrate molecules. In the conjugation reaction, an endogenous hydrophilic moiety is conjugated to a target molecule, producing a metabolite that is more water-soluble than the parent compound which in turn render the reactive intermediates harmless. These enzymes are a diverse group of proteins that are responsible for metabolizing a vast array of compounds, including endobiotics, such as steroids, bile acids, fatty acids, prostaglandins, leukotrienes and xenobiotics, including most of the therapeutic drugs and environmental pollutants. The phase I and phase II group of drug metabolizing enzymes often exhibit genetic polymorphisms, which may alter the enzyme activity and consequently have an influence on the risk of various cancers. In addition to phase I and II, the phase III transporter system consists of antiporter activity that is associated with P-gp. The excretion of parent drugs, metabolites and xenobiotics from the cell via
transmembrane efflux pump is the main activity that occurs during phase III elimination\textsuperscript{16,17}. The genetic polymorphism in drug transporters that are involved in the transmembrane efflux of xenobiotics may also result in susceptibility of normal tissues to neoplastic transformation by various carcinogens\textsuperscript{151}. Therefore, the genetic polymorphisms in genes encoding phase I, phase II enzymes as well as phase III are important to understand the high degree of individual variability in cancer susceptibility.

Xenobiotics are molecules that are not produced \textit{in vivo}, but which are introduced into the body from the environment and subsequently biotransformed in the body. Drug or xenobiotic metabolizing enzymes play a dual role in the chemical carcinogenesis. They transform lipophilic compounds to more polar metabolites and thus enhance their excretion through bile or urine. On the other hand, some of the reactive intermediates especially from the environmental pollutants that arise during the process interact with DNA to form DNA adducts thus becoming genotoxic. Hence, the coordinated expression and regulation of all the three phases and their metabolic balance between activation and detoxification of potential carcinogens is therefore an important determinant of its carcinogenic potency.

The phase I enzymes constitute the cytochrome P450 multigene family and epoxide hydroxylases while phase II enzymes are mainly UDP-glycosyltransferases (UGTs), glutathione transferase (GST), sulphotransferase (SULT) and N-acetyltransferase (NAT)\textsuperscript{17}. Phase III system that consists of P-glycoprotein is an energy dependent efflux pump that reduces the intracellular accumulation of a wide range of xenobiotics is encoded by the multidrug transporter gene, \textit{ABCB1}\textsuperscript{18}.

Chemical carcinogens require metabolic activation to react with cellular macromolecules. Various steps involved in carcinogenesis are: (a) metabolic activation of a carcinogen by xenobiotic metabolizing enzymes, (b) binding of the activated
metabolite to DNA to produce a DNA adduct or DNA-binding intermediate (c) faulty repair of the DNA adduct to produce a gene mutation (d) cell replication to fix the mutation to the genome and (e) progression to neoplasm of the replicating cell containing the mutated genes. Therefore, individual variations in activities of the phase I, phase II enzymes and phase III transporter protein regulate the clearance of xenobiotics, their DNA toxic metabolites or activated intermediates from the body. The excretion of the toxic metabolites prevents the DNA adduct formation which may otherwise lead to cell death or carcinogenesis [Figure 17].

Cytochrome P450 enzymes encompass a highly diverse superfamily of hemoproteins which was first discovered in 1955 in rat liver microsomes. The first report on the existence of a CYP enzyme or a microsomal carbon monoxide-binding pigment as known previously, was published in 1958. This enzyme gave a unique 450-nm optical absorption peak in the presence of carbon monoxide, and when its hemoprotein nature was recognized, it was given the name cytochrome P450. These enzymes, particularly those corresponding to the CYP1, CYP2 and CYP3 families, are involved in the metabolism of drugs, and other exogenous and endogenous substances. Among these families, the most relevant enzymes that participate in the metabolic activation of procarcinogens are CYP1A1, CYP1A2, CYP1B1, CYP2E1, CYP3A4 and CYP3A5. The genes that encode these enzymes which are largely responsible for the metabolic activation of many different chemical carcinogens in the environment are polymorphic. The mutations can cause absence, reduced, altered or increased enzyme activity, because of gene deletions, single nucleotide polymorphisms and gene duplications.
Among the xenobiotic metabolizing cytochrome P450 enzymes, the most extensively studied are CYP1A1 and CYP2E1.

**Cytochrome P-450 1A1 (CYP1A1)**

In humans, CYP1A1 is transcriptionally controlled by the aryl hydrocarbon receptor-aryl hydrocarbon receptor nuclear translocator (AHR-ARNT) pathway that regulates gene expression. CYP1A1 is a key enzyme, which catalyzes oxidative reactions and activates xenobiotics to carcinogenic reactive metabolites. The human exposure to environmental pollutants that include polycyclic aromatic hydrocarbons (PAHs) is unavoidable. As most of these compounds are human carcinogens, elevated cancer rates may occur in individuals subjected to PAH exposures through tobacco smoking, occupational factors, polluted air, food consumption and medications.

The enzyme contributes remarkably to the toxicity of many carcinogens, especially PAHs, since it is the principal enzyme activating them into DNA-binding forms. The CYP1A1 encodes an aromatic hydrocarbon hydroxylase enzyme that catalyzes the oxidation of PAHs to their phenolic metabolite or diol epoxide [e.g. BaP to
Benzo(a)pyrene-Diol-Epoxide (BPDE). High levels of CYP1A1 mRNA, protein, and enzyme activity are detectable following the induction by PAHs. It is also involved in the bioactivation of several other tobacco related procarcinogens such as nitrosamines and aromatic amines into carcinogenic products. CYP1A1 is expressed in many epithelial tissues especially in buccal mucosa, suggesting the in situ activation of tobacco carcinogens. Because of the significance of CYP1A1 in the activation of procarcinogens, it is rational to link the polymorphisms of the CYP1A1 gene with the individual susceptibility to chemically induced cancers, especially the upper aerodigestive cancers.

The CYP1A1 gene is located on the chromosome 15 (15q22-q24). There are four important genetic polymorphisms described for CYP1A1 gene. Among these, two polymorphisms are associated with increased enzymatic activity. The first is a T→C transition in the 3'-noncoding region creating an Msp I restriction enzyme cleavage site (CYP1A1*2A); the second is A→G transition in the heme-binding region of exon 7 resulting in substitution of isoleucine/valine (CYP1A1*2C) [Figure 18].

Studies of CYP1A1 in cultured human lymphocytes showed significantly elevated levels of inducible enzyme activity among individuals carrying CYP1A1*2C mutant genotypes. Another study reported that CYP1A1*2C mutant alleles were associated with increased CYP1A1 inducibility at the mRNA level, and a threefold elevation in AHH enzyme activity. The CYP1A1*2A mutant gene also encodes an inducible form of CYP1A1. These two polymorphisms are associated with increased risk for various smoking related cancers of lung, head, neck and esophagus in various populations, and have been widely investigated.
Previous studies have shown inconclusive findings on the associations between CYP1A1 gene polymorphisms and cancer susceptibility. Studies have been conducted in various population to determine the risk associated with CYP1A1*2A and CYP1A1*2C gene polymorphisms and risk of UADT cancers. In Germans, neither a significant association for CYP1A1*2A and CYP1A1*2C genotypes nor interactions between genotypes and smoking or alcohol consumption was observed for cancers of UADT. These findings were in agreement with another German study where they did not find an association between CYP1A1*2C genotypes and oral cavity cancer.

Among the American Caucasians, the individuals carrying CYP1A1*2C polymorphic genotypes were at an increased 2.6-fold risk for oral cancer. The risk observed was not influenced by differences in exposure to tobacco smoke and alcohol consumption. However, another study in Americans did not reveal a significant risk for head and neck cancers among carriers of CYP1A1 polymorphic genotypes. In a Japanese population, a 4-fold risk was observed for head and neck squamous cell carcinoma among individuals homozygous for CYP1A1 Val/Val (CYP1A1*2C) genotype. The risk was increased in pharyngeal cancer patients carrying the homozygous mutant genotype suggesting that different sites may be responsive to different chemicals from the environment. In another Japanese study, the CYP1A1*2A rare mutant genotype, was associated with increased risk for oral squamous cell carcinoma, in particular, at low cigarette dose levels and the susceptibility varied between the subsites of the oral cavity. A Korean study demonstrated a significantly increased risk for the oral cancer which was associated with the CYP1A1*2A homozygous mutant genotype, despite the smoking history.

Sato et al. reported that individuals carrying CYP1A1*2A homozygous mutant genotype as well as GSTM1 null genotype had a genetically high risk for oral carcinogenesis especially at a low dose level of cigarette smoking. Later, when the investigators
analysed the genetic risk associated with oral SCC and CYP1A1*2C genotype, the Val/Val genotype had a 4-fold risk of developing cancer compared with the Ile/Ile genotype. Furthermore, Individuals with a combined genotype of Val/Val and GSTM1 null genotype were at an increased risk for oral SCC in particular, at a low dose level of cigarette smoking\textsuperscript{182}. A Brazilian study did not demonstrate a significant association between CYP1A1*2C variant genotypes and oral cancer risk\textsuperscript{183}, while another study in the same population found a 2.4-fold increased risk for head and neck cancers associated with polymorphic CYP1A1*2A and GSTM1 null genotypes, eventhough a significant risk was not observed with CYP1A1*2A genotype alone\textsuperscript{184}. A study conducted in Italy did not find a significant role of polymorphic CYP1A1*2A genotypes in the head and neck cancer risk and also any associated gene-gene and gene-environment interactions\textsuperscript{185}.

An Indian study had found a significant risk associated with the combined genotypes of CYP1A1*2A homozygous variant and GSTM1 null in the susceptibility to oral cancer in tobacco users\textsuperscript{186}. Another study conducted in Keralite population of south India demonstrated a positive association between CYP1A1*2C polymorphism and oral cancer\textsuperscript{187}, whereas a study done in eastern part of India indicated a negative correlation between CYP1A1*2A polymorphism and oral squamous cell carcinoma\textsuperscript{188}. Another Kolkata based study did not find a significant risk associated with leukoplakia among the tobacco users carrying the CYP1A1*2A and CYP1A1*2C genotypes\textsuperscript{189} [Table 7]. Hence, there are conflicting results regarding the association between CYP1A1*2A and CYP1A1*2C genotypes and the risk to UADT cancers in various ethnic groups.
Table 7: Summary of the studies on CYP1A1 genotypes in the risk of UADT cancers

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>No. of Cases/Controls</th>
<th>Genotypes</th>
<th>Tumor site</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park et al, 1997176</td>
<td>America</td>
<td>135/135</td>
<td>CYP1A1*2C</td>
<td>Oral cancer</td>
<td>S</td>
</tr>
<tr>
<td>Matthias et al, 1998174</td>
<td>Germany</td>
<td>398/219</td>
<td>CYP1A1<em>2A &amp; CYP1A1</em>2C</td>
<td>UADT</td>
<td>NS</td>
</tr>
<tr>
<td>Monta et al, 1999178</td>
<td>Japan</td>
<td>145/164</td>
<td>CYP1A1*2C</td>
<td>Head &amp; neck</td>
<td>S</td>
</tr>
<tr>
<td>Tanimoto et al, 1999179</td>
<td>Japan</td>
<td>100/100</td>
<td>CYP1A1*2A</td>
<td>Oral cancer</td>
<td>S</td>
</tr>
<tr>
<td>Sato et al, 1999181</td>
<td>Japan</td>
<td>142/142</td>
<td>CYP1A1*2A</td>
<td>Oral cancer</td>
<td>S</td>
</tr>
<tr>
<td>Sato et al, 2000182</td>
<td>Japan</td>
<td>142/142</td>
<td>CYP1A1*2C</td>
<td>Oral cancer</td>
<td>S</td>
</tr>
<tr>
<td>Olshan et al, 2000177</td>
<td>America</td>
<td>182/202</td>
<td>CYP1A1*2C</td>
<td>Head &amp; neck</td>
<td>NS</td>
</tr>
<tr>
<td>Sreelekha et al, 2001187</td>
<td>India</td>
<td>98/60</td>
<td>CYP1A1*2C</td>
<td>Oral cancer</td>
<td>S</td>
</tr>
<tr>
<td>Hahn et al, 2002176</td>
<td>Germany</td>
<td>94/92</td>
<td>CYP1A1*2C</td>
<td>Oral cancer</td>
<td>NS</td>
</tr>
<tr>
<td>Sikdar et al, 2003188</td>
<td>India</td>
<td>99/227</td>
<td>CYP1A1<em>2A &amp; CYP1A1</em>2C</td>
<td>Leukoplakia</td>
<td>NS</td>
</tr>
<tr>
<td>Sikdar et al, 2005188</td>
<td>India</td>
<td>80/67</td>
<td>CYP1A1*2A</td>
<td>Oral cancer</td>
<td>NS</td>
</tr>
<tr>
<td>Gattas et al, 2006184</td>
<td>Brazil</td>
<td>103/102</td>
<td>CYP1A1*2A &amp; GSTM1 null</td>
<td>Oral cancer</td>
<td>S</td>
</tr>
<tr>
<td>Leichsenring etal, 2006183</td>
<td>Brazil</td>
<td>72/80</td>
<td>CYP1A1*2C</td>
<td>Oral cancer</td>
<td>NS</td>
</tr>
<tr>
<td>Cha et al, 2007186</td>
<td>Korea</td>
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<td>CYP1A1*2A</td>
<td>Oral cancer</td>
<td>S</td>
</tr>
<tr>
<td>Anantharaman et al, 2007188</td>
<td>India</td>
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<td>CYP1A1*2A &amp; GSTM1 null</td>
<td>Oral cancer</td>
<td>S</td>
</tr>
<tr>
<td>Boccia et al, 2008188</td>
<td>Italy</td>
<td>210/245</td>
<td>CYP1A1*2A</td>
<td>Head &amp; neck</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant (P>0.05); S, significant (P<0.05).
Cytochrome P-450 2E1 (CYP2E1)

CYP2E1, well known as the ethanol-inducible form of cytochrome P-450, is of particular interest to the industrial and environmental field\textsuperscript{196}. CYP2E1 is responsible for the metabolic activation of procarcinogens such as N-nitrosamines (N-nitrosodimethylamine and the tobacco-specific nitrosamine N-nitrosornornicotine), benzene, urethane, styrene and various other low-molecular-weight compounds into reactive intermediates that play an essential role in chemical carcinogenesis\textsuperscript{22,23}. In addition, various halogenated anesthetics and drugs have been identified as substrates for CYP2E1\textsuperscript{197}. Thus, CYP2E1 may be an important determinant of human susceptibility to toxicity and carcinogenicity of industrial and environmental chemicals. Inherited differences in metabolic capacity play an important role in individual responses to occupational and environmental toxicants\textsuperscript{166,192}.

Several mechanisms have been implicated in the regulation of CYP2E1 expression, including transcription, translation and posttranslational regulation\textsuperscript{193}. The level of CYP2E1 can be elevated in response to its exposure to ethanol and acetone\textsuperscript{194}. In addition, different pathophysiologic conditions such as diabetes\textsuperscript{195}, fasting\textsuperscript{196}, obesity\textsuperscript{197} and chronic alcohol consumption\textsuperscript{198} have been found to induce or alter the expression of CYP2E1. The induced enzyme has the high capability to generate reactive oxygen species and substrate derived radicals which can mediate lipid peroxidation, protein inactivation and DNA damage\textsuperscript{199}.

CYP2E1 gene is mapped in the region of 10q24. Several genetic polymorphisms in CYP2E1 have been reported but majority of these occur in either upstream sequences or introns. The most frequently studied genetic polymorphism is CYP2E1*5B that constitutes Rsa I (-1053C>T) and Pst I (-1293G>C) in the 5' promoter region of the gene that affects the transcriptional regulation of the gene. The polymorphism results from a mutation, losing the restriction site to Rsa I and creating a site for the enzyme Pst I.
These two polymorphisms are in complete linkage disequilibrium\textsuperscript{200,201}. Another commonly studied polymorphism is CYP2E1*6 or Dra I polymorphism located in intron 6 with a base change at 7632T>A\textsuperscript{202}. Several studies have reported that the variant c2 and C alleles of the Rsa I/Pst I and Dra I sites respectively are associated with enhanced enzyme activity\textsuperscript{203}. There are also studies that report the reduced enzyme activities associated with CYP2E1*5B and CYP2E1*6 polymorphisms\textsuperscript{204}. The discrepancy in the CYP2E1 enzyme activities could be explained based on its enhanced activity found in Asians while reduced in Caucasians, thereby modulating the susceptibility towards cancers\textsuperscript{205}. CYP2E1*1B or Taq I polymorphism located in intron 7 with a base change at 9896C>G\textsuperscript{206}, has not been yet investigated in the Asian population. This polymorphism results in enhanced activity of CYP2E1 enzyme \textit{in vivo}\textsuperscript{207} [Figure 19].

Polymorphisms of CYP2E1 gene have shown variations in the prevalence between different ethnic and racial groups\textsuperscript{208}. The genotype frequencies of CYP2E1*1B, CYP2E1*6, CYP2E1*5B have been documented in Tamilian population of south India. The CYP2E1*1B A2A2 and A2A1 genotypes were significantly different from Caucasians. The frequency of CYP2E1*5B c1c2 genotype was lower than Caucasians and Taiwanese while CYP2E1*6 genotypes lie between these two populations. A similar distribution of CYP2E1*5B and CYP2E1*6 genotypes was noticed among south and north Indian populations\textsuperscript{33}.

There are studies that described significant associations between CYP2E1 polymorphisms and the incidences of colorectal cancer\textsuperscript{24}, lung cancer\textsuperscript{25} and nasopharyngeal carcinoma\textsuperscript{26} in different populations. On the contrary, there are also studies that showed lack of association between CYP2E1 genotypes and disease susceptibility\textsuperscript{209-212}. There are inconsistent reports on the susceptibility to the cancers of UADT among different ethnic groups. In a Caucasian study, patients carrying rare
alleles of CYP2E1*5B and CYP2E1*6 had significantly increased risk for oral cavity/pharyngeal cancers among the heaviest drinkers (>80 g/day). However, another German based Caucasian study observed neither an association between upper aerodigestive tract cancers and CYP2E1*5B and CYP2E1*6 risk genotypes nor an interaction between these genotypes and smoking and alcohol consumption. A Brazilian study found an increased risk for oral cancer associated with CYP2E1 Pst I polymorphism. No significant differences were observed for the genotypes or haplotypes distributions among Italian head and neck cancer patients carrying homozygous variant forms of CYP2E1*5B and CYP2E1*6 genotypes. There was also no evidence of gene-gene and gene-environment interactions.

A Chinese study showed a significantly increased oral cancer risk for CYP2E1 c1/c2 and c2/c2 genotypes compared with the c1/c1 genotype among those who did not chew betel quid. A Japanese study found a significant interaction among smokers carrying CYP2E1*5B and CYP2E1*6 polymorphic genotypes in causing oral squamous cell carcinoma. However, an interaction was not observed with alcohol consumption and the polymorphic genotypes. An Indian study done in Kolkata population did not find a positive association between Pst I site of CYP2E1 and oral squamous cell carcinoma risk. Another Kolkata based study found that, homozygous rare allele of CYP2E1*6 enhanced the susceptibility to leukoplakia among the tobacco users. But, a positive association was not found among CYP2E1*5B genotype carriers [Table 8].
Table 8. Summary of the studies on CYP2E1 genotypes in the risk of UADT cancers

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>No. of Cases / Controls</th>
<th>Genotypes</th>
<th>Tumor site</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hung et al, 1997¹⁴</td>
<td>China</td>
<td>41/123</td>
<td>CYP2E1*5B</td>
<td>Oral cancer</td>
<td>S</td>
</tr>
<tr>
<td>Matthias et al, 1998¹⁷⁴</td>
<td>Germany</td>
<td>398/219</td>
<td>CYP2E1<em>5B &amp; CYP2E1</em>6</td>
<td>UADT</td>
<td>NS</td>
</tr>
<tr>
<td>Bouchardy et al, 2000²¹³</td>
<td>Switzerland</td>
<td>250/172</td>
<td>CYP2E1<em>5B &amp; CYP2E1</em>6</td>
<td>UADT</td>
<td>S</td>
</tr>
<tr>
<td>Sikdar et al, 2003¹⁸⁸</td>
<td>India</td>
<td>99/227</td>
<td>CYP2E1*6</td>
<td>Leukoplakia</td>
<td>S</td>
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<td>Sikdar et al, 2005¹⁸⁸</td>
<td>India</td>
<td>80/67</td>
<td>CYP2E1*5B</td>
<td>Oral cancer</td>
<td>NS</td>
</tr>
<tr>
<td>Gattas et al, 2006¹⁴⁴</td>
<td>Brazil</td>
<td>103/102</td>
<td>CYP2E1*5B</td>
<td>Oral cancer</td>
<td>S</td>
</tr>
<tr>
<td>Sugimura et al, 2006²¹⁵</td>
<td>Japan</td>
<td>122/241</td>
<td>CYP2E1<em>5B &amp; CYP2E1</em>6</td>
<td>Oral cancer</td>
<td>S</td>
</tr>
<tr>
<td>Boccia et al, 2006¹⁸⁵</td>
<td>Italy</td>
<td>210/245</td>
<td>CYP2E1<em>5B &amp; CYP2E1</em>6</td>
<td>Head &amp; neck</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant (P>0.05); S, significant (P<0.05).
Figure 18. Location of CYP1A1 genotypes

Figure 19. Location of CYP2E1 genotypes
Glutathione S-transferase (GST)
Environmental exposures to genotoxic agents play an important role in causing human cancers. There is a cellular system for detoxification which protects the cells from DNA damage caused by various reactive substances. Glutathione S-transferases are a multigenic family of phase II detoxification enzymes. These enzymes play a central role in the detoxification of many endogenous and exogenous substrates through conjugation to glutathione, a tripeptide consisting of glycine, glutamic acid, cysteine to electrophilic compounds, resulting in less reactive and more easily excretable glutathione conjugates. Among the 3 mammalian GSTs, (mitochondrial, cytosolic and microsomal) cytosolic GSTs represent the largest family and exhibits significant genetic polymorphism. Cytosolic GST isoenzymes can be classified by their substrate specificities, isoelectric points and amino acid sequence homologies into major classes which are encoded by a superfamily of genes located at different loci. The different isoenzymes of cytosolic GSTs are Mu, Theta, Pi, Sigma, Omega, Alpha and Zeta. It has been reported that the deficient genotypes or polymorphisms in GST Mu (M1), Theta (T1), and Pi (P1) contribute to increased susceptibility to various diseases. Among the isoenzymes, GSTP1 is also of particular interest because it is widely expressed in a variety of tumors. The efficacy and toxicity of anticancer agents differ greatly among patients based on their GSTP1 genotypes as the enzyme is involved in the metabolism of certain chemotherapeutics.

The detoxification of genotoxins including aromatic hydrocarbon epoxides and products of oxidative stress such as DNA hydroperoxides is catalyzed by GSTM1. The detoxification of constituents of cigarette smoke such as alkyl halides and cigarette smoke derived chemicals such as benzo (a) pyrene diol epoxide and acrolein are catalyzed by GSTT1. These carcinogens and toxins are found to be associated with increased susceptibility to UADT cancers. The GSTP1 enzyme is widely expressed in
tumour cells and is responsible for the detoxification of benzo (a) pyrene diol epoxide and acrolein present in cigarette smoke\textsuperscript{28}.

The genes that code for GST isoenzymes, involved in the metabolic activation or detoxification of carcinogens, exhibit polymorphisms. Some of these polymorphisms have been found to affect the enzyme activity thereby influencing the individual cancer risk\textsuperscript{225}. Among the GSTs, GSTM1 null, GSTT1 null and the GSTP1 313 A/G substitution polymorphisms are widely investigated in diverse ethnic groups\textsuperscript{216}. The functional consequence of the deficient GSTM1 and GSTT1 genotypes are related to complete loss of enzyme activity. The GSTP1 polymorphism at codon 105 where an adenine to guanine (A>G) transition at nucleotide position 313 causes an isoleucine to valine substitution (I105V) that leads to decreased enzyme activity\textsuperscript{226} [Figure 21].

The genotype frequencies of GSTM1, GSTT1 and GSTP1 genes have been documented in south India. The frequency of GSTM1 null and GSTT1 null was found to be 30.0% and 16.8% respectively whereas the frequency of both the GSTM1 null and GSTT1 null genotypes was found to be 4.6%\textsuperscript{34}. In Tamilian population, the genotype distribution of GSTP1 were 44.0%, 47.0% and 9.0 % for Ile/Ile, Ile/Val and Val/Val respectively\textsuperscript{33}. The frequency of GSTM1 null in south Indians was significantly lower than that in Caucasians and the frequencies of both GSTM1 and GSTT1 null genotypes were significantly lower than in Japanese\textsuperscript{34}. The genotype distribution of GSTP1 Ile/Ile and Ile/Val in Tamilian population varied significantly from Chinese Orientals but it was not significantly different from the Caucasians\textsuperscript{33}.

Polymorphisms of genes that code for these carcinogen detoxifying enzymes have shown variations in the prevalence between different ethnic and racial groups. About 10-65\%\textsuperscript{227} of individuals from different ethnic groups have been reported to possess null genotypes for GSTM1 and GSTT1. When the GSTT1 polymorphism alone was studied
in different ethnic groups, it was found that the prevalence of the null genotype was highest among Chinese (64.0%), followed by Koreans (60.0%), African-Americans (22.0%) and Caucasians (20.0%), whereas the prevalence was lowest among Mexican-Americans (10%)²⁸.

The incidence of cancer mortality induced by smoking in African-American men was found to be higher compared to Caucasian men in US population. It was reported that African-Americans smoke fewer cigarettes than Caucasians, hence, higher rate of UADT cancers in African-Americans cannot be entirely attributed to smoking²²³. This indicates that genetic factors like GST polymorphism may also influence the susceptibility to UADT cancers. There are several studies where association between GSTM1 and GSTT1 null genotypes (single gene or combined gene effect) and susceptibility to UADT cancers have been reported¹⁸¹,²²⁹,²³⁰. Two German studies have reported negative associations between GSTM1 null and GSTT1 null genotypes and UADT cancer risk. One of the studies had also found that the GSTM1 A/B genotype confers a protective role in the UADT cancer susceptibility¹⁷⁴,¹⁷⁵. GSTP1 polymorphisms have also been found to influence susceptibility to oral, pharyngeal and laryngeal carcinomas in a study done in Germans²⁸. A Brazilian study did not find a significant role of GSTP1 genotypes in the risk of oral cancer, while another study observed an increased risk for head and neck cancers associated with GSTM1 null genotype¹⁸³,¹⁸⁴. The American based studies did not find any associations between GSTM1 null, GSTT1 null and GSTP1 genotypes in the head and neck cancer risk. No gene-environment interactions were also observed for these genotypes, except for the smokers carrying GSTT1 null genotype¹⁷⁶,¹⁷⁷. The Chinese study reported that null genotypes of GSTM1 and/or GSTT1 had a significantly increased oral cancer risk compared with those who had both GSTM1 and GSTT1 non-null genotypes²¹⁴. In a Japanese study, the combined genotypes of GSTM1 null and CYP1A1*2A rare mutant have showed a significantly higher risk in the susceptibility to oral cancer, especially, at the low cigarette dose levels¹⁷⁸.
Table 9. Summary of the studies on GST genotypes in the risk of UADT cancers

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>No. of Cases / Controls</th>
<th>Genotypes</th>
<th>Tumor site</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hung <em>et al</em>, 1997</td>
<td>China</td>
<td>41/123</td>
<td>GSTM1 null &amp; GSTT1 null</td>
<td>Oral cancer</td>
<td>S</td>
</tr>
<tr>
<td>Park <em>et al</em>, 1997</td>
<td>America</td>
<td>135/135</td>
<td>GSTM1 null</td>
<td>Oral cancer</td>
<td>NS</td>
</tr>
<tr>
<td>Matthias <em>et al</em>, 1998</td>
<td>Germany</td>
<td>398/219</td>
<td>GSTM1 A/B GSTT1 null</td>
<td>UADT</td>
<td>GSTM1-Protective GSTT1-NS</td>
</tr>
<tr>
<td>Matthias <em>et al</em>, 1998</td>
<td>Germany</td>
<td>380/180</td>
<td>GSTP1</td>
<td>UADT</td>
<td>S</td>
</tr>
<tr>
<td>Sato <em>et al</em>, 1999</td>
<td>Japan</td>
<td>142/142</td>
<td>GSTM1 null</td>
<td>Oral cancer</td>
<td>S</td>
</tr>
<tr>
<td>Cheng <em>et al</em>, 1999</td>
<td>America</td>
<td>162/315</td>
<td>GSTM1 null &amp; GSTT1 null</td>
<td>Head &amp; neck</td>
<td>S</td>
</tr>
<tr>
<td>Tanimoto <em>et al</em>, 1999</td>
<td>Japan</td>
<td>100/100</td>
<td>GSTM1 null &amp; CYPIA1*2A</td>
<td>Oral cancer</td>
<td>S</td>
</tr>
<tr>
<td>Olshan <em>et al</em>, 2000</td>
<td>America</td>
<td>182/202</td>
<td>GSTM1 null GSTT1 null &amp; GSTP1</td>
<td>Head &amp; neck</td>
<td>NS</td>
</tr>
<tr>
<td>Sreelekhha <em>et al</em>, 2001</td>
<td>India</td>
<td>98/60</td>
<td>GSTM1 null &amp; GSTT1 null</td>
<td>Oral cancer</td>
<td>NS</td>
</tr>
<tr>
<td>Buch <em>et al</em>, 2002</td>
<td>India</td>
<td>297/450</td>
<td>GSTM1 null</td>
<td>Oral cancer</td>
<td>S</td>
</tr>
<tr>
<td>Hahn <em>et al</em>, 2002</td>
<td>Germany</td>
<td>94/92</td>
<td>GSTM1 null</td>
<td>Oral cancer</td>
<td>NS</td>
</tr>
<tr>
<td>Sikdar <em>et al</em>, 2005</td>
<td>India</td>
<td>80/87</td>
<td>GSTM1 null</td>
<td>Oral cancer</td>
<td>S</td>
</tr>
<tr>
<td>Gattas <em>et al</em>, 2006</td>
<td>Brazil</td>
<td>103/102</td>
<td>GSTM1 null</td>
<td>Head &amp; neck</td>
<td>S</td>
</tr>
<tr>
<td>Sharma <em>et al</em>, 2006</td>
<td>India</td>
<td>40/87</td>
<td>GSTT1 null</td>
<td>Oral cancer</td>
<td>S</td>
</tr>
<tr>
<td>Leichsenring <em>et al</em>, 2006</td>
<td>Brazil</td>
<td>72/60</td>
<td>GSTP1</td>
<td>Oral cancer</td>
<td>NS</td>
</tr>
<tr>
<td>Cha <em>et al</em>, 2007</td>
<td>Korea</td>
<td>72/221</td>
<td>GSTM1 null &amp; CYPIA1*2A</td>
<td>Oral cancer</td>
<td>S</td>
</tr>
<tr>
<td>Ananthararman <em>et al</em>, 2007</td>
<td>India</td>
<td>458/729</td>
<td>GSTM1 null</td>
<td>Oral cancer</td>
<td>S</td>
</tr>
<tr>
<td>Singh <em>et al</em>, 2008</td>
<td>India</td>
<td>175/200</td>
<td>GSTM1 null &amp; GSTT1 null</td>
<td>Head &amp; neck</td>
<td>S</td>
</tr>
<tr>
<td>Boccia <em>et al</em>, 2008</td>
<td>Italy</td>
<td>210/245</td>
<td>GSTM1 null &amp; GSTT1 null</td>
<td>Head &amp; neck</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant (P>0.05); S, significant (P<0.05).

*Significant risk with crude odds ratio, but non-significant with adjusted odds ratio
The Korean subjects carrying GSTM1 null and CYP1A1*2A homozygous mutant genotypes were highly susceptible for the oral cancer, eventhough a significant risk was not observed with deficient GSTM1 gene alone\textsuperscript{186}. An Italian study did not find deficient GSTM1 and GSTT1 genes as significant risk factors in the susceptibility to head and neck cancers. The study had also reported the absence of the gene-gene and gene-environment interactions associated with the cancer in the population\textsuperscript{185}. The different studies conducted in eastern and western parts of India showed GSTM1 null genotype as a risk factor in the oral cancer\textsuperscript{186,188,231}, whereas another Indian study reported the role of GSTT1 null genotype in the risk of oral cancer\textsuperscript{232}. However, a study done in southern part of India did not find a significant association either with GSTM1 null or GSTT1 null in the susceptibility to oral cavity carcinoma\textsuperscript{187}. Another Indian study had reported an increased risk for head and neck cancer patients carrying the GSTM1 and GSTT1 null genotypes, though the risk was not significant when analysed by multivariate logistic regression model. The wild type genotype of GSTP1 in combination with GSTM1 null or GSTT1 null genotype increased the susceptibility for the cancers. The risk was further increased when the combinations of GSTM1 null, GSTT1 null and wild type genotype of GSTP1 was analysed. Gene-environment interactions were also noted with GSTM1 null and GSTT1 null genotypes among tobacco chewers and alcoholics\textsuperscript{233} [Table 9].

**Adenosine triphosphate binding cassette B1 (ABCB1)**

Apart from the drug metabolizing enzymes, drug transporters are energy-dependent efflux pumps, which expel xenobiotics out of a cell, thereby decreasing the intracellular concentration of xenobiotics\textsuperscript{234}. Drug transporters are otherwise called membrane-bound proteins that control the uptake and excretion of xenobiotics. The ABC transporter family comprises of 49 members, many of which are implicated in various disease conditions\textsuperscript{235}. These include ABCB1 or MDR1 (multidrug resistance) and several multidrug-resistance-associated proteins (MRPs). In humans, 2 members of the
ABC gene family (ABCB1 and ABCB3) are present, while 3 genes (abc1a, abc1b, and abc2) exist in rodents. The ABCB1 gene encodes P-gp, an energy dependent efflux pump that is expressed at relatively high levels not only in tumor cells, but also in many normal tissues, such as intestine, liver, kidney, blood-brain barrier, and placenta. P-gp functions as a transmembrane efflux pump, thereby extruding xenobiotics from the intracellular to the extracellular domain [Figure 20]. P-gp mediated efflux transport of substrates can occur at the level of the plasma membrane or from the intracellular compartment which reduces the intracellular accumulation of a wide range of xenobiotics.

Figure 20. Function of P-glycoprotein

(ATP-Adenosine triphosphate; ADP-adenosine diphosphate; PI- inorganic phosphate)

P-gp may have a role in the cellular defense to carcinogens. PAHs are highly toxic compounds present in the environment. Studies in Drosophila melanogaster have shown that P-gp is involved in the transmembrane efflux of PAHs. BaP, a PAH found in tobacco smoke, is a major carcinogen. Studies in mice revealed that 3-
methylcholanthrene (3-MC) is a chemical carcinogen which can induce lung tumours\textsuperscript{239}. Hepatocyte cell culture studies have shown that BaP and 3-MC are substrates for the \textit{ABCB1} efflux pump\textsuperscript{240}. A food-derived carcinogen 2-amino-1-methyl-6-phenylimidazo [4, 5-b] pyridine (PhIP) is a heterocyclic amine formed abundantly during cooking, frying and grilling\textsuperscript{241}. \textit{In vitro} studies in human intestinal Caco-2 cell monolayer revealed significantly higher transport of PhIP towards the apical direction in \textit{ABCB1} transduced cells compared with the untransduced cells. Further, pre-incubation of these cells with verapamil, a P-gp inhibitor stimulated the influx and reduced the efflux of PhIP. This indicates that \textit{ABCB1} play a role in PhIP transport\textsuperscript{242}. Based upon the results of \textit{in vitro} studies in human breast cancer MCF-7 cells, it was concluded that expression of P-gp and the modulation of its function may affect the susceptibility of normal tissues to neoplastic transformation by carcinogens\textsuperscript{32}.

The genetic polymorphisms of phase I enzymes like CYP1A1, CYP2A6, CYP2E1, CYP2D6, ADH2, ADH3 and phase II enzymes like GSTs, NATs are associated with altered risk for SCC of upper aerodigestive tract\textsuperscript{165}. The \textit{ABCB1} gene that belongs to phase III transporter system, also exhibit polymorphism resulting in interindividual variations in the activity of P-gp\textsuperscript{18}. There are 25 SNPs located in the exonic regions of \textit{ABCB1} gene\textsuperscript{243}. In exon 26, at position 3435, a synonymous SNP is found to be associated with altered protein expression\textsuperscript{18} [\textbf{Figure 22}]. Among numerous polymorphisms in human \textit{ABCB1}, the 3435C>T SNP has been associated with decreased mRNA and protein levels which may be due to the reduced mRNA expression in the liver by varying its mRNA stability\textsuperscript{244}.

In a German population, when the P-gp expression in duodenum was assessed by western blot analysis and quantitative immunohistochemistry, individuals homozygous for C allele had a 2-fold higher level of P-gp expression compared with individuals homozygous for T allele\textsuperscript{245}. In a renal cell carcinoma study, patients were reported to...
have higher frequency of 3435TT genotype compared to control subjects, which was correlated with reduced renal P-gp expression\textsuperscript{246}. A Turkish study demonstrated 1.5-fold increased risk for developing breast cancer among carriers of T allele\textsuperscript{247}. In a study conducted to determine the genetic susceptibility of \textit{ABCB1} gene 3435C>T polymorphism to adult acute myeloid leukemia (AML), no association between 3435C>T polymorphism and susceptibility to AML was observed\textsuperscript{248}. On the contrary, in a study conducted in Japanese subjects, 3435TT genotype was reported to have increased P-gp activity\textsuperscript{249}. Further studies need to be performed to verify these conflicting results showing the relationship between \textit{ABCB1} 3435C>T genetic polymorphisms and P-gp expression.

The associations between \textit{ABCB1} polymorphism and susceptibility to renal cell carcinoma\textsuperscript{246}, colorectal cancers\textsuperscript{250} and ulcerative colitis\textsuperscript{251} have been studied. Since, \textit{ABCB1} 3435C>T gene polymorphism may alter disease susceptibility, it is hypothesized that the polymorphism may lead to increased susceptibility to UADT cancers caused by carcinogens like PAHs, BaP, 3-MC and PhIP which are substrates for \textit{ABCB1} gene encoded P-gp efflux pump. Although the differential expression of \textit{ABCB1} gene between early and advanced stages of head and neck cancer have been reported\textsuperscript{252}, the role of \textit{ABCB1} polymorphisms on the risk for UADT cancers have not been described so far.
Figure 21. Location of GST genes

GSTM1-1P13.3

GSTT1-22q11.2

GSTP1-11q13

313A>G = Ile105Val

Figure 22. Location of ABCB1 gene

3435 C>T = ABCB1 3435 C>T
2.7.6.4. Gene-gene interaction

In a complex polygenic disease such as cancer, it is likely that genetic risk is dependent on several gene polymorphisms operating in concert. Polymorphisms in individual gene may impart only to a small extent to the risk of cancer, and it is likely that the cumulative effect of many polymorphisms will be important in its pathogenesis. These interactions might determine the functional outcomes over the independent effects of any single susceptibility gene or its genetic polymorphism. Generally, the inconsistencies among the SNP studies could be due to the fact that each individual SNP alters the function of only single gene of many, which are involved in carcinogenesis. The biological events associated with cancer risk that are modestly affected by a SNP may be more greatly affected by a SNP in combination with additional SNPs\(^ {37,253}\). Hence, these studies could have benefited from examining interactions between polymorphisms in distinct genes that may contribute to cancer risk.

2.7.6.5. Gene-environment interaction

Gene-environment interaction implies a specific relationship between genetic traits and environmental exposures. The molecular epidemiological studies have shown that development of the cancer is not only due to endogenous or exogenous carcinogens, but their interactions with genes that are involved in the activation or detoxification of these carcinogens. An inherited difference in the effectiveness of the bioactivation or detoxification of carcinogens further determines the host susceptibility. After exposure to carcinogens, progression of cancer is facilitated by a cumulative effect of mutations or polymorphisms in these genes\(^ {38}\). Hence, it was presumed that incidence of these cancers may require both exogenous exposure and genetic predisposition\(^ {10,11}\).

Most of the diseases are thought to be the result of interactions between several genes and environmental factors\(^ {254}\). Therefore gene-environment interaction represents two
dichotomous factors (e.g., presence or absence of a genotype and presence or absence of an environmental risk factor). The interaction takes into account the various ways in which genetic effects can be modified by environmental exposures at the various levels of these exposures.

Genetic predisposition can be inferred from family history, phenotype or direct genotype analysis. Environmental and lifestyle factors are measured in epidemiological studies using self-reported information; this can be obtained by interview/questionnaire, previous records or biomarker-based inference on environmental exposures\textsuperscript{255}.

Gene-environment interactions have been associated with numerous tobacco-related cancer risk\textsuperscript{256}. The commonest site of occurrence of oral cancer is cheek mucosa, (34.28%) followed by floor of mouth (17.85%). However, the buccal mucosa is the commonest site of oral squamous cell carcinoma in countries where oral use of tobacco is more common such as India, Malaysia and New Guinea\textsuperscript{257}. This is probably due to the fact that location of cancer in oral cavity is directly associated with the type of tobacco use, the majority of the lesions corresponding with the site of maximum exposure to betel quid and also to other related habits\textsuperscript{113}. Most procarcinogens entering the human body require metabolic activation \textit{in vivo} to trigger the development of cancer. The polymorphisms in genes encoding phase I, phase II enzymes as well as phase III drug transporter protein in combination with environmental exposure may confer a differential risk to cancers of UADT among individuals carrying these genetic variants.
Rationale for the gene-environment interaction studies

a) By estimating the combined interactions of genetic and environmental risk factors, a better estimate of the population-attributable disease risk can be obtained.

b) By determining the genetic and environmental risk factors in genetically susceptible individuals, the associations between environmental factors and diseases can be strengthened.

c) Help to appreciate the disease mechanisms in humans by using information on susceptibility or resistant genes to focus on the biological pathways that are most relevant to particular disease, and the environmental factors that are most relevant to the pathways.

d) The information on biological pathways helps to design new preventive and therapeutic strategies.

e) To determine the complex mixtures of compounds that is responsible in disease development on human exposure.

f) By identifying the polymorphisms of genes, the information can be used to intend life style modifications in genetically predisposed high risk individuals.

2.8. Tumour Outcome parameters

In UADT cancers, the important outcome parameters include initial tumour extension (T1-T4), lymph-node involvement and histologic differentiation (G1-G3).

2.8.1. TNM staging

The tumor-node-metastasis (TNM) staging system was first reported by Pierre Denoix in the 1940s. In oncology, TNM staging is one of the fundamental systems which had been in existence for more than 50 years. It is a worldwide benchmark for reporting the extent of malignant disease by classifying the patients with cancer into prognostically similar groups. It is also a major factor in predicting the outcome of the disease. This
facilitates an accurate description of the location and size of the primary cancer, the status of the cervical lymph nodes, and the presence or absence of distant metastasis. The system was developed and is maintained by the International Union Against Cancer (UICC) and American Joint Committee on Cancer (AJCC).

Objectives of the TNM Classification\(^{260}\)

- An aid for the clinician to characterize the disease before selecting treatment
- Assist in evaluating the results of treatment
- Suggestive on disease prognosis
- Facilitates the exchange of information between treatment centers
- To continue investigations on human malignancies

TNM classification is based on the assessment of three components\(^{261}\):

- **T**- the extent of the primary tumour
- **N**- the absence or presence and extent of regional lymph node metastasis
- **M**- the absence or presence of distant metastasis

The 'T' designation varies with each site, while the N and M stages are constant for the UADT sites. The addition of numbers to these components specifies the progressive extent of the malignancies [Table 10]. In general, T1 and T2 stages are considered early cancers while T3 and T4 stages are advanced cancers. The 'N' or node category describes the movement of the disease into the cervical lymphatics. The 'M' indicates the distant dissemination of tumour via the lymphatics or venous system. The vital information needed for the management and reporting of results are presenting site, histologic type, and the anatomic extent of disease. The TNM staging system allows a consistent assessment of prognosis, standardized treatment options and provides uniformity in reporting in the literature. Among these, the stage I cancers are the least advanced and often have a better prognosis. Higher stage cancers are often more advanced, but in many cases can still be treated successfully\(^ {262}\).
Table 10. General definitions of primary tumor (T), regional lymph node (N) and distant metastasis (M)

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>describes the original (primary) tumor</td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumor cannot be evaluated</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1-T4</td>
<td>Extent of the primary tumor</td>
</tr>
<tr>
<td>N</td>
<td>describes absence or presence and extent of regional lymph node metastasis</td>
</tr>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be evaluated</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node involvement (no cancer found in the lymph nodes)</td>
</tr>
<tr>
<td>N1-N3</td>
<td>Involvement of regional lymph nodes</td>
</tr>
<tr>
<td>M</td>
<td>describes the absence or presence of distant metastasis</td>
</tr>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be evaluated</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

### 2.8.2. Histopathologic differentiation and grading

Histopathological classification is based on the pattern of cell differentiation. The differentiation denotes the extent to which parenchymal cells resemble comparable normal cells both morphologically and functionally. Based on the cell differentiation, it can be graded into a) well differentiated (G1) b) moderately differentiated (G2) and c) poorly differentiated (G3). The well differentiated tumor cells resemble the mature normal cells of the original tumor tissue. The poorly differentiated or undifferentiated tumors are usually primitive appearing, unspecialized cells that possess large number of mitoses, which show the higher proliferative activity of the parenchymal cells. The moderately differentiated tumors lie in between well differentiated and poorly differentiated tumors.
2.9. Cancer remission and recurrence

A cancer is considered to be in remission, when the cancer cells are not detected in the body following the treatment. Complete remission refers to the situation where the disease disappears completely with the treatment. Partial remission refers to the situation where the disease shrinks but does not disappear completely with the treatment.

When cancer returns after a period of remission, it is considered as cancer recurrence. This happens because undetected cancer cells can sometimes remain in the body after treatment. These cancer cells may remain dormant for a period of time, but eventually they continue to multiply, and grow large enough to be recognized and diagnosed resulting in the reappearance of the cancer. Cancer can recur in the same place as the original cancer or it can migrate to other parts of the body. Recurrence can happen in weeks, months or years after the original cancer was treated.

Cancer recurrence is divided into three categories based on the site it reappears:

**Local recurrence:** This cancer reappears in the same place it was first found, or very close by. The cancer has not spread to the lymph nodes or to other parts of the body.

**Regional recurrence:** A regional recurrence occurs in the lymph nodes and tissues located in the vicinity of the original cancer.

**Distant recurrence:** This refers to cancer that has spread (metastasized) to areas farther away from where the cancer was first located.
2.10. Tamilian population

Tamilians are an ethnic group of Indian origin from south Asia and they are ethnically, linguistically and culturally related to the other Dravidian population. The oldest Tamil communities are present in southern India and northeastern Sri Lanka. Tamilnadu is on the east coast of southern India with an estimated 70 million Tamilians around the world. They differ markedly from north Indians who are Aryan descendents.

Although the incidence of UADT cancers is highest among the malignancies in India, there is only limited information available on the association between genetic polymorphisms and the risk of UADT cancers among Indians till date with majority of studies having a smaller sample size. In addition, the potential gene-environment and gene-gene interactions, tumor outcome measures and remission and recurrence in association with genotypes have not been looked at together. In the face of this lacuna, this study was planned to analyze a set of genes that are involved in xenobiotic biotransformation and transport, which have been found to be important in UADT carcinogenesis with the aim of pinpointing the possible role of these variables in the disease progression and prognosis.