

## **Modifiable Cancer Risk Factors**

**Abstract:** Cancer is the second leading cause of death in Trinidad and Tobago and has created tremendous challenges for healthcare services and expenditures throughout the region. In this study, it was found that cancer could be attributed to risk factors such as cigarette smoking, second-hand smoke exposure, alcohol intake, excess body weights, bad diet, and cancer-associated infections. Manual searching of 4 electronic databases (PubMed, Medline, PMC, and Google Scholar) from September 2021 – August 2022 was done. The facts suggest that a large number of individuals have risk factors for cancer that may be modifiable or controllable.

**Keywords:** Carcinogenesis, lifestyle, diet, cancer risk factors.

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### **1. Introduction**

Cancer is the second leading cause of death in Trinidad and Tobago and has caused pressure to healthcare in the region [1]. Warner et al. (2018) stated "The population of Trinidad and Tobago (TT) in 2010 was 1,328,019 with a diversity of ancestral groups including African (34.2%), East Indian (35.4%), mixed (22.8%), unknown (6.2%), and all other ethnic groups (Chinese, White, and Syrian/Lebanese) totaling 1.4%" [2].

According to the World Health Organization (WHO), cancer incidence will increase by 58%, from 84,703 cases in 2015 to 133,937 cases in 2035. Cancer mortality will increase by 67% during this period, from 52,282 to 87,430 deaths [3]. Nationals of African ancestry exhibited the highest rates of the cancer incidence rate of 243 per 100,000 per year and mortality rate of 156 per 100,000 per year compared to their counterparts of Indian ancestry (incidence rate of 125 per 100,000 per year; and mortality rate of 66 per 100,000 per year) or mixed ancestry (incidence of 119 per 100,000 per year; and mortality: 66 per 100,000 per year) [1].

Certain factors globally known can influence the incidence and mortality of cancer in Trinidad and Tobago, which has a population of 1.3 million inhabitants. Regarding ancestry, African descendants had the highest incidence and mortality rates than others as Indian descendants and mixed race. It was found that the cancers that were most common among men were cases of prostate [2], lung, colon, stomach, and hematologic cancers [1]. In contrast, among women, the most prevalent cancers were breast, cervical, endometrial, colon, and ovarian [1].

Our aim in this review is to discuss cancer modifiable or controllable risk factors that affect too many individuals worldwide, including tobacco, alcohol, bad diet, physical inactivity and exercise, and cancer-related infectious organisms.

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## 2. Modifiable Cancer Risk factors

### 2.1 Tobacco

Lung cancer is the leading cause of cancer-related mortality worldwide. Smoking is the leading risk factor for lung cancer, accounting for 80% of lung cancer cases in men and 50% in women. While the risk is likely to increase in a dose-dependent manner, genetic predisposition may play a role in tobacco-related cancer, as evidenced by the regular occurrence of such cancer [4]. Tobacco use has been directly linked to at least 19 types of cancer, including lung, larynx, head and neck cancers [5].

Tobacco causes oxidative stress via reactive oxygen species, which affect many cell types, including fibroblasts (the primary cell type of tumour stroma) and adjacent epithelial cells. It results in cancerous properties such as cell growth, adaptation, and survival. Tobacco smoke also negatively affects the innate immune system (DCs, macrophages, and NK cells) and adaptive immune system (T cells and B cells), pathologically weakening the immune response [6]. Many carcinogens in tobacco, such as benzopyrene diol epoxide, are directly associated with lung cancer [7], and the contribution of smoking to cancer is fully understood.

The activation of NF- $\kappa$ B is complex and involves stimuli that activate the inhibitor of the  $\kappa$ B (I $\kappa$ B) kinase (IKK) complex. This complex contains IKK1, IKK2, and NEMO gene complexes. Once activated, the IKK complex phosphorylates I $\kappa$ B, which leads to its degradation. This then leads to free NF- $\kappa$ B dimer that can translocate from the cytoplasm to the nucleus and facilitate gene transcription. Many stimuli lead to the activation of NF- $\kappa$ B, including cytokines such as TNF- $\alpha$  and IL-1, as well as epidermal growth factor (EGF), bacterial and viral components (lipopolysaccharides), radiation, reactive oxygen species, and DNA damage from intracellular oncogenic stress [8].

**Cigarette**  
Smoking has been reported as the main modifiable factor responsible for the development of lung cancer worldwide. Studies by Ding et al. (2021) [9] and Shen et al. (2021) [10] reported a link between cigarette smoking and lung cancer occurrence. It was noted an increased likelihood of lung cancer in smokers versus non-smokers [9]. It was further defined this link, noting that among systemic lupus erythematosus (SLE) patients who developed lung cancer, most of them were ever-smokers [11]. Furthermore, it was identified a dose-response relationship between cigarettes and lung cancer [9]. It was also noted that smoking and exposure to second-hand smoke increase the risk of skin cancer [12]. More specifically, Arafa et al. (2020) [13] suggested that chronic and regular smokers are at higher risk of developing squamous cell carcinoma but at decreased risk of developing basal cell carcinoma.

Most studies have reported a positive association between parental smoking during pregnancy and childhood brain tumour risk. However, only one study reported statistically significant data [14]. The authors proposed a hypothesis that brain tumours in children are related to in utero exposure to *N*-nitroso compounds, as it is well known that *N*-nitroso is the most notable among carcinogens of the brain system in experimental animals. The impact of parental smoking on the development of brain tumours was also investigated. Smoking during pregnancy posed an increased relative risk of brain tumours in the offspring, associated with parental exposure to polycyclic aromatic hydrocarbons [15].

A study comparing smokers with non-smokers showed a 51% increase in the risk of developing hepatocellular carcinoma (HCC) for ongoing smokers and a 12% increase for prior smokers [16]. The same authors reported in another study, population-based smoking increased the odds of developing

intrahepatic cholangiocarcinoma (ICC) by 80% [16]. Finally, according to Baecker et al. (2018), a 13% risk for all liver cancers worldwide can be attributed to tobacco smoking [17].

#### *HIV and Tobacco*

HIV can cause lung carcinoma due to T lymphocyte depletion. There is evidence that chronic HIV infection can contribute to the development of lung cancer through HIV-specific mechanisms. HIV is associated with a greater risk of developing chronic obstructive pulmonary disease (COPD), which may be due to the higher smoking rates in this population and an inappropriate immune response resulting from CD8+ T cell overactivity within the lungs, which contributes to more significant amounts of inflammation. Recurrent infections can become compound. These factors contribute to an increased risk of COPD [18].

## 2.2 Alcohol

Alcohol consumption is a risk factor for cancers of the upper aerodigestive tract, including the oral cavity, pharynx, hypopharynx, oesophagus, and the gastrointestinal organs, including the liver, pancreas, colon, and rectum. On the contrary, moderate alcohol intake (less than 30 g daily) may protect against kidney cancer [19]. Consumption of more than 30 g increases the risk of liver cirrhosis, while intake of more than 60 g daily is associated with a linearly increased risk of developing hepatocellular carcinoma (HCC). The risk of HCC is increased 3- to 10-fold with alcohol abuse. Ethanol has been classified as a Group 1 carcinogen by the International Agency for Research on Cancer [20]. Ethanol and its metabolite, acetaldehyde, are carcinogenic. While the exact aetiology of alcohol consumption and cancer formation is not fully understood [21], it is known that ethanol is digested via acetaldehyde dehydrogenase into acetaldehyde. This leads to free radicals, which bind to DNA proteins, destroying folate and resulting in hyperproliferation. Free radicals can also be formed via alcohol-induced oxidative stress (activating cytochrome P450 2E1 (CYP2E1) and lipid peroxidation [22,23]. Increased oestrogen and metabolism leading to decreased folate and retinoids due to alcohol use may play a role in cancer development [24].

It is also suggested an association between smoking behaviour and alcohol intake, thus accounting for lung cancer in smokers with heavy alcohol intake [9,25]. It was indicated that establishments where alcohol is consumed can be presumed to be environments with second-hand smoke exposure, which can be related to lung cancer development [25]. However, it was denied that alcohol intake is a direct risk factor for non-smokers but noted that increased alcohol consumption is linked to higher BMI, potentially increasing the risk of squamous cell lung carcinoma [9]. Koetal. (2020) looked at risk factors for lung cancer in non-smokers and determined that alcohol was carcinogenic [25].

Alcohol consumption is the second most important risk factor for gastric cancer, by increasing nitrosamine levels and creating a mechanism that causes chronic inflammation [26]. Alcohol has many adverse effects on the liver, and the amount and rate of alcohol intake can affect the amount of fat deposition. This can cause fatty liver disease, alcoholic hepatitis, and cirrhosis, previously reported as risk factors. Approximately 13 to 23% of HCC cases are due to alcohol-related illnesses, with a higher risk for men, whites, blacks, and Hispanics [16]. The relationship between ICC and alcohol consumption have yet to be studied. A meta-analysis of 19 studies conducted by the World Cancer Research Fund reported a substantially increased risk per 10 g of alcohol intake per day [27]. Another study showed that over 150,000 cases of HCC were attributed to alcohol consumption, accounting for 26% of the total worldwide [17].

## 2.3 Diet as a Risk Factor for Cancer

The traditional diet in Mediterranean countries is characterised primarily by high consumption of vegetables and olive oil and moderate consumption of protein. This diet is thought to confer health benefits that can reduce the risk of many cancers, including oesophageal, colorectal, uterine, kidney, liver, thyroid, and many others, which are discussed in another study [19].

Ultra-processed foods undergo multiple biological and chemical processes (for example, the addition of food preservatives) to become palatable and affordable [28]. The use of food additives or cooking can introduce carcinogens such as nitrates, nitrosamines, pesticides, and dioxins, which are then consumed; nitrates occur naturally in soil and water and are frequently used as preservatives in processed meats [29]. Food packaging is also associated with cancer. Plastic food containers contain carcinogenic compounds such as bisphenol that can be incorporated into the food products and increase cancer risk [30].

The consumption of red meat is also associated with an increased risk of cancer [31]. A ketogenic diet creates an unfavourable environment for cancer cells by limiting tumour growth and protecting healthy cells from chemotherapy and radiation [32]. It was reported that the consumption of fish reduces the risk of brain cancers by activating neuroprotective mechanisms. In addition, adequate vegetables and antioxidants (such as vitamins C and A) in the diet may have a protective effect [33]. In contrast, no correlation with glioma incidence has been shown with other factors, according to Bielecka and Markiewicz-Zukowska (2020) [34].

A study conducted by Yamamura et al. (2013) examined the relationship between dietary factors and de novo acute myeloid leukaemia in adults. The study revealed a notable increase in risk for individuals who frequently consumed significant amounts of red meat compared to those who mainly consumed dark green vegetables, seafood, and nuts [35]. Furthermore, it was reported an increased risk of lung cancer for persons  $\geq 70$  years of age who consumed a meat-based diet [25], while it was found no connection between meat intake and lung cancer by Shen et al., 2021 [10]. The risk may be attributed to the increased production of nitrosamines, phenols, and hydroquinones from the consumption of red meat [25]. On the other hand, the same authors indicate that fruits and vegetables contain compounds that may have anticarcinogenic properties, such as lycopene, flavonoids, and folic acid [10,25]. Many studies have linked high salt intake to an increased risk of stomach cancer. According to these studies, the OR for salt intake is a critical risk factor [26]. Inadequate intake of fresh fruits and vegetables is another risk factor for cancer, whereas a higher intake of fruits and vegetables decreases the risk [36].

The fact that 90–95% of cancers are due to environmental and lifestyle factors provides significant opportunities for prevention even if there is a genetic predisposition. Diet, obesity, and metabolic syndrome account for 30–35% of cancer cases, highlighting that cancer-related mortality can be significantly reduced by modifying the related lifestyle factors. More than 25,000 phytochemicals have been identified as being protective against cancer, including lycopene, catechins, and capsaicin [37].

Carotenoids are found in many fruits and vegetables, and lycopene has been shown to have anti-cancer properties *in vitro* and *in vivo*. The proposed mechanism involves ROS scavenging, upregulation of detoxification systems, interference with cell proliferation, induction of gap-junction review, inhibition of cell-cycle progression, and modulation of signal transduction pathway [38].

Quercetin is a flavonoid found in many fruits and vegetables that has antioxidant, anti-inflammatory, and anti-proliferative properties. It is known to block  $NF-\kappa B$  activation, which may prevent cancer formation. Sulforaphane is a compound found

in vegetables, especially broccoli, and in vitro and in vivo studies have found that it has chemopreventive effects. Sulforaphane inhibits many mechanisms in cell signalling, including blocking NF- $\kappa$ B activation, like most other phytochemicals [39].

Hua et al. (2020) [40] and Belfiore et al. (2018) [41] reported that stimulation of insulin and IGF-1 leads to signalling via the PI3K and mitogen-activated protein kinase (MAPK) transduction pathways, resulting in cell growth, proliferation, differentiation, metabolism, and apoptosis. Aberrant signalling from the insulin and IGF-1 axis may lead to malignant cell transformation and progression. This is further supported by the overexpression of mitogenic insulin receptor isoform A (IR-A) and insulin-like growth factor receptor (IGF-1R) in cancer cells. It was proposed that activation of NF- $\kappa$ B may be a link between obesity and cancer [42].

#### Adipokines

are cytokines secreted by adipose tissue that affect satiety, metabolism, signalling pathways, and inflammation [43]. Leptin is an adipokine responsible for energy intake, homeostasis, and immune response. Leptin is a tumorigenic adipokine that activates multiple signalling transduction pathways, including the Janus kinase/signal transducers and activators of transcription (JAK/STAT), MAPK, and PI3K pathways [44].

Leptin can bind to its receptor (ObR), leading to the leptin/ObR axis, which is involved in hallmark cancer features such as cellular survival, metabolism, angiogenesis, and metastasis. Leptin can also interact with other pathways such as those of sex hormones (e.g., oestrogen) and induce inflammation via the production of cytokines, including IL-6, which can lead to further stimulation of cellular signal transduction pathways [45].

Adiponectin counteracts many of the pro-tumorigenic effects of leptin. The activation of adenosine monophosphate-activated protein kinase (AMPK) by adiponectin leads to cell cycle arrest, inhibits mammalian target of rapamycin (mTOR) activity. As a result, adiponectin is anti-diabetogenic; it is also an anti-atherogenic, anti-inflammatory, and anti-cancer adipokine [44]. Obesity not only increases the risk of breast cancer by 1.5 to 2 times among post-menopausal women, but also worsens the prognosis from increased recurrence and morbidity [46].

## 2.4 Physical Inactivity and Exercise

An estimated 40% of cancers can be prevented by lifestyle modifications [47]. In American adults, increased BMI (>40) is associated with increased death from all cancers for men and women compared to lower BMI (<24.9) [48]. Exercise leads to multifactorial bodily changes such as changed body composition and increased and decreased hormone levels, decreased inflammation, and improved cellular immunity, which improves outcomes for patients diagnosed with cancer. Oxidative stress is known to affect DNA and increase cancer risk. Regular physical exercise induces cellular responses that augment the antioxidant response [49].

While a lack of exercise is linked to obesity and higher BMI, it is vital to understand the impact of this factor individually. Physical activity reduces breast cancer risk independent of BMI, smoking, and hormone therapy. The WHO recommends 10 minutes of working out daily to markedly reduce risk. Physical activity delays breast cancer development even in carriers of the BRCA genetic mutation. The mechanisms that facilitate risk reduction remain elusive but involve desirable decreases in oestrogen and inflammation and regulation of metabolic function and body composition. Therefore, physical activity, diet modification, and weight control are key management strategies for these patients [46].

## 2.5 Infectious Agents

Gastric cancers are responsible for ~780,000 deaths annually. It is the third-most prevalent type of cancer mortality globally. Epstein–Barr virus-associated is associated with this common type of malignancy [50]. Viruses account for most infection-mediated cancers, while other microorganisms, including parasites such as *Opisthorchis viverrini* and *Schistosoma haematobium* and bacteria such as *Helicobacter pylori* can also cause cancer, as shown in Table 1 [51].

**Table 1.** Links between infection and cancer.

| Infectious agent                       | Type of Microorganism        | Cancer type   |
|--|------------------------------|---|
| Epstein-Barr virus                     | Virus                        | Nasopharyngeal carcinoma, Burkitt lymphoma, immunosuppression-related non-Hodgkin lymphoma, Hodgkin lymphoma, extranodal natural killer/Hell lymphoma (nasal type) [52] |
| Hepatitis B virus                      | Virus                        | Hepatocellular carcinoma [53]   |
| Hepatitis C virus                      | Virus                        | Hepatocellular carcinoma, non-Hodgkin lymphoma [54]   |
| Kaposi sarcoma herpesvirus             | Virus                        | Kaposi sarcoma, primary effusion lymphoma [55]  |
| Human immunodeficiency virus 1         | Virus                        | Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, carcinoma of the cervix, anus, conjunctiva [56]   |
| Human papillomavirus type 16           | Virus                        | Carcinoma of the cervix, vulva, vagina, penis, anus, oral cavity, and oropharynx and tonsil [57]  |
| Human T-cell lymphotropic virus type 1 | Virus                        | Adult T-cell leukaemia and lymphoma [58]  |
| Merkel cell polyomavirus               | Virus                        | Merkel cell carcinoma [59]  |
| <i>Opisthorchis viverrini</i>          | Trematode                    | Cholangiocarcinoma [60]   |
| <i>Clonorchis sinensis</i>             | Helminth                     | Cholangiocarcinoma [61]   |
| <i>Schistosoma haematobium</i>         | Trematode                    | Urinary bladder cancer [62]   |
| <i>Helicobacter pylori</i>             | Bacterium                    | Non-cardia gastric carcinoma, low-grade B-cell MALT gastric lymphoma [63]   |
| Alfatoxin (BI)                         | Mould ( <i>Aspergillus</i> ) | Liver cancer [64]   |

|                        |           |  |
|------------------------|-----------|--|
| Salmonella Typhi       | Bacterium | Gallbladder carcinoma [65]   |
| Salmonella Enteritidis | Bacterium | Colorectal carcinoma in the ascending and transverse parts of the colon [66] |
| Chlamydia trachomatis  | Bacterium | Carcinoma of the cervix and ovaries [67,68]                                  |

\* Table extracted from an open access article distributed under the terms and conditions of the Creative Commons attribution license [51].

The aetiology of infection-related cancer is complex and likely involves multiple pathways. The infectious agent may possess oncogenes or tumour-suppressing genes that can lead to cancer formation. Infectious agents implicated in this pathway include HPV, EBV, HHV-8, and HTLV-1 [69]. Infectious agents can also indirectly lead to cancer through chronic inflammation, which can produce metabolites harmful to host cells and DNA and alter the normal progression of the cell cycle. This is the proposed mechanism of *H. pylori* and parasite-related cancers. Additionally, infectious agents can suppress the host immune response, leading to cancer formation. However, this is likely a result of chronic inflammation, which severely overlaps in infection-related cancers [70]. HPV accounts for 90% of cervical cancers, while hepatitis B and C account for 80% of hepatocellular carcinomas [51]. Human papillomavirus is associated with mutations that integrate its DNA into the host cells, resulting in premalignant and malignant changes in gynaecological tissue. HPV has been designated the most important risk factor for cervical cancer worldwide. Thus, HPV vaccination and procedures such as Papsmears, aimed at early detection of HPV infection, may aid in the prevention of such cancer [71].

### 3. Conclusion

We conclude that the facts suggest that a number of individuals have risk factors for cancer that are modifiable. This brings new insights in the field of preventive medicine. Especially for our country, The Republic of Trinidad and Tobago, is very significant that the health system emphasises about how to minimise cancer risk factors as tobacco, alcohol drinking, diet, infectious diseases including HIV/AIDS, and others, which are very prevalent in the country and the region.

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