[1]Department of Paraclinical Sciences. Faculty of Medical Sciences. The University of the West Indies. St. Augustine. Trinidad and Tobago.

Corresponding author: angel.vaillant@sta.uwi.edu

ABSTRACT

In this study was found that these cancers were attributable to modifiable risk factors such as cigarette smoking, alcohol intake, excess body weight, diet, and six cancer-associated infections. Several databases were reviewed including PUBMED, Google scholar, and Web of Science. The facts suggest that a number of individuals present risk factors for cancer, which can be modifiable.

1. Tobacco

Lung cancer is the leading cause of cancer-related mortality worldwide. (Gao et al. 2016). Smoking is the leading risk factor for lung cancer and accounts for 80% of lung cancer in males and 50% in females. While the risk is likely to increase in a dose-dependent relationship, genetic predisposition may play a role in tobacco-related cancers, as evidenced by the familial occurrence of some tobacco-related cancers (Kotnis et al., 2012). Tobacco use has been directly linked to at least 19 cancers. Some of these cancers include; lung, larynx, and head and neck, (Petros et al., 2012).

Tobacco smoke causes oxidative stress via reactive oxygen species that 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 (DCs, macrophages, NK cells) and adaptive (T-cells, B-cells) immune system, weakening the immune response pathologically (Cao et al., 2021). While many carcinogens in tobacco, such as benzopyrene diol epoxide, are directly associated with lung cancer (Rajalakshmi et al., 2015), smoking contributes to cancer and remains fully understood.

The activation of NF-κB is complex and involves stimuli that activate the inhibitor of the κB (IκB), IKappaB Kinase (IKK) complex. This complex contains IKK1, IKK2, and NEMO gene complexes. Once activated, the IKK complex phosphorylates IκB, which leads to its degradation. It leads to free NF-κB dimers that can translocate from the cytoplasm to the nucleus and facilitate gene transcription. Many stimuli lead to the activation of NF-κB. These

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include cytokines such as TNF-a and IL-1. It also includes epidermic growth factors (EGF), bacterial and viral components (lipopolysaccharide), radiation, reactive oxygen species, and DNA damage from intracellular oncogenic stress. (Xia et al., 2014)

It has undoubtedly been reported as the main modifiable factor responsible for the development of lung cancer worldwide: Ding et al., 2021 and Shen et al., 2021 linked cigarette smoking to lung cancer occurrence. Ding et al. 2021 noted an increased likelihood of lung cancer in smokers versus non-smokers. Additionally, Bernatsky et al., 2018 further define this link, remarking, regarding Systemic Lupus erythematosus (SLE) patients who developed lung cancer, that most of the reported lung cancer cases in SLE were ever-smokers. Furthermore, Ding et al., 2021 identified a dose-response relationship between many cigarettes and lung cancer. Kalia and Kwong, 2019 also mention that smoking and exposure to second-hand smoke increase the risk for skin cancers. More specifically, Arafa et al., 2020 suggest that chronic and regular smokers are at a higher risk of developing squamous cell carcinoma but at a decreased risk of developing Basal Cell carcinoma.

Most studies have reported positive associations between paternal smoking during pregnancy and childhood brain tumour risk. However, only one study was statistically significant (Preston-Martin et al., 1982). The authors proposed a hypothesis that brain tumours were related to in utero exposure to N-nitroso compounds in young people as it was well-known that N-nitroso was the most striking among carcinogens of the brain system known in experimental animals. However it was investigated the impact of parental smoking on the development of brain tumours. Smoking during pregnancy posed an increased relative risk for brain tumours in offspring, with increased risk associated with parental exposure to polycyclic aromatic hydrocarbons (Zumel-Marne et al., 2019).

A study compared with non-smokers showed a 51% increase in the risk of hepatocellular carcinoma (HCC) in ongoing smokers and a 12% increase in the risk of developing HCC in prior smokers. Nevertheless, this investigation was inconsistently based on clinical data, and patient history (Massarweh & El-Serag, 2017). The same authors in another study, reported that population-based smoking increased the odds of intrahepatic cholangiocarcinoma (ICC) by 80%. Lastly, according to Baecker et al., 2018 tobacco smoking is attributed to a 13% risk for all liver cancer cases worldwide.

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HIV may cause lung carcinoma owing 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 being diagnosed with COPD, which may be due to the higher smoking rates in this population and inappropriate immune responses resulting from CD8+ T cell over-activity within the lungs, all of which contribute to more significant amounts of inflammation. Recurrent infections can be compound. These factors contribute to an increased risk of COPD (Sigel et al., 2017).

2. Alcohol

Alcohol consumption is a risk factor for cancers of the upper aerodigestive tract. It includes the oral cavity, pharynx, hypopharynx, oesophagus and other gastrointestinal tract organs, liver, pancreas, colon, and rectum. Contrary to this, moderate alcohol intake (less than 30g daily) may protect against kidney cancer (Mentella et al., 2019). Consumption of more than 30g increases the risk of liver cirrhosis, while intake of more significant than 60g of alcohol daily has a linear increased risk of developing hepatocellular carcinoma (HCC). The risk of HCC is increased 3- to 10-fold in alcohol abuse. Ethanol has been classified as a Group 1 carcinogen by the International Agency for Research on Cancer (Matsushita and Takaki. 2019). Ethanol and its metabolite, acetaldehyde, are carcinogenic. While the exact aetiology of alcohol consumption and cancer formation is not fully understood (Xu & Luo, 2017). Ethanol is digested via acetaldehyde dehydrogenase into acetaldehyde. It leads to free radicals, which bind onto DNA proteins, destroying folate and resulting in hyperproliferation. Free radicals may also be formed via alcohol-induced oxidative stress (activating cytochrome P450 2E1, CYP2E1) as well as lipid peroxidation (Rumgay et al., 2021; Gianni et al., 2014). Increased oestrogen and metabolism leading to decreased folate and retinoids due to alcohol use may play a role in cancer development (Ratna and Mandrekar. 2017).

Moreover, Ding et al., 2021 and Ko et al., 2020 also suggest an association between smoking behaviour and alcohol intake behaviour, thus accounting for lung cancer in smokers with heavy alcohol intake. Ko et al., 2020 indicate that establishments where alcohol is consumed, can pose as presumed environments for second-hand smoke exposure, which can be related to lung cancer development. However, Ding et al., 2021, deny alcohol intake as a direct risk factor in non-smokers but note that increased alcohol consumption is linked to a

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which looked at risk factors for lung cancer in non-smokers, perceived alcohol as carcinogenic.

The next most important risk factor for gastric cancer is alcohol consumption by increasing nitrosamine intake and creating a mechanism that causes chronic inflammation (Poorolajal et al., 2020). Alcohol has many adverse effects on the liver because of the amount and rate at which one drink can cause fat deposition. This deposition 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 in males, whites, blacks, and Hispanics (Massarweh & El-Serag, 2017). The relationship between ICC and alcohol consumption has yet to be studied at the current moment. A meta-analysis of 19 studies conducted by the World Cancer Research Fund reported a substantial increased risk per 10 g alcohol intake per day (Yang et al., 2019). Another study showed that over 150,000 cases of HCC were attributed to alcohol consumption, which accounted for 26% of the worldwide total (Baecker et al., 2018).

3. Diet as a risk factor for cancer.

A Mediterranean diet, a traditional diet in Mediterranean countries, is characterised primarily by high consumption of vegetables and olive oil and moderate protein consumption. Moreover, thought to confer health benefits that can reduce the risk of many cancers including oesophageal carcinoma, colorectal, uterine, kidney, liver, thyroid and many others cancers (Mentella et al., 2019).

Ultra-processed foods have undergone multiple biological and chemical processes (for example, the addition of food preservatives) to become palatable and affordable (Fiolet et al., 2018). The use of food additives or cooking can introduce many carcinogens such as nitrates, nitrosamines, pesticides, and dioxins, that are then consumed; nitrates occur naturally in soil and water but are frequently used as food preservatives in processed meats (Chazelas et al., 2021). The packaging of food is also associated with cancer. Plastic food containers contain carcinogenic compounds, such as bisphenol, that can be incorporated into food products and may increase cancer risk (Muncke, 2021).

Consumption of red meat is also associated with an increased risk of cancer (Wie et al., 2014). A ketogenic diet creates an unfavourable environment for cancer cells by limiting tumour

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et al., 2017 fish intake reduces the risk of brain cancers since they exhibit neuroprotective mechanisms when consumed. As well, adequate vegetables and antioxidants (such as vitamins C and A) provided with a diet could have a protective effect. In contrast, other factors have shown no correlation with the glioma incidence, according to Bielecka & Markiewicz-Zukowska. 2020.

A study conducted by Yamamura et al., 2013 examined the relationship between dietary factors and adult de novo acute myeloid leukaemia. It revealed a notable increase in risk in individuals who consumed significant amounts of red meat often instead of those who mainly consumed dark green vegetables, seafood and nuts. Furthermore, Ko et al., 2020 also describe an increased risk for lung cancer in persons ≥ 70 who consume a meat-based diet, while Shen et al., 2021 found no connection between meat intake and lung cancer. It may be attributed to red meat, which leads to increased production of nitrosamines, phenols, and hydroquinones. At the same time, fruits and vegetables contain compounds that may have anticarcinogenic properties like lycopene, flavonoids and folic acid, as indicated by the same authors.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 (Poorolajal et al., 2020). Inadequate fresh fruits and vegetable intake is another risk factor for cancer, whereas a higher food intake of fruits and vegetables decreases this risk (Peltzer & Phaswana-Mafuya. 2012).

The fact that 90–95% of cancers are due to environment and lifestyle provides significant opportunities for preventing cancer even if there is a genetic predisposition. Diet, obesity and metabolic syndrome account for 30-35% of cancer incidence, emphasising that there can be a significant reduction in cancer-related mortality by modifying these lifestyle factors. More than 25 000 phytochemicals have been identified as protectors against cancer. Include lycopene, catechins, capsaicin (Alok et al., 2019).

Carotenoids are found in many fruits and vegetables, and lycopene has shown anti-cancerproperties in vitro and Vivo. The proposed mechanism involves ROS scavenging up-regulation of detoxification systems, interference with cell proliferation, induction of gap-junctional communication, inhibition of cell-cycle progression, and modulation of signal transduction pathway (Ranjan et al., 2019).

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inflammatory, and antiproliferative properties. It is known to block NF-κB activation, which may prevent cancer formation. Sulforaphane is a compound found in vegetables, especially broccoli. In vitro and in vivo studies have found chemopreventive effects. There are many mechanisms in cell signalling that Sulforaphane inhibits, which like most other phytochemicals, includes blocking NF-κB activation (Dandawate et al., 2016).

Hua et al., 2020 reported that insulin and IGF-1 are stimulated, they lead to signalling via the PI3K and Mitogen-Activated Protein Kinase (MAPK) transduction pathways, resulting in cellular growth, proliferation, differentiation, metabolism, and apoptosis. Aberrant signalling from the Insulin and IGF-1 axis may lead to malignant cell transformation and progression. It is further supported by the overexpression of the mitogenic insulin receptor isoform A (IR-A), and in addition, the insulin-like growth factor receptor (IGF-1R) in cancer cells (Belfiore et al., 2018). Nimptsch and Pischon. (2016) proposed that activation of NF-kB may link obesity and cancer.

Adipokines are cytokines secreted by adipose tissue that affect satiety, metabolism, signalling pathways, and inflammation (Hursting et al., 2012). Leptin is an adipokine responsible for energy intake, homeostasis, and immune response. Leptin is a tumorigenic adipokine. It activates multiple signalling transduction pathways, including Janus kinase/signal transducers and activators of transcription (JAK/STAT), MAPK, and PI3K pathways (Hopkins et al., 2016).

Leptin can bind to its receptor (ObR), leading to a leptin/ObR axis involved in hallmark cancer features such as cellular survival, metabolism, angiogenesis, and metastasis. Leptin can also interact with other pathways such as sex hormones, such as oestrogen, and induce inflammation via cytokine production, for example, IL-6, which can lead to further stimulation of cellular signal transduction pathways (Barone and Giordano. 2021).

Adiponectin is sometimes referred to as the 'guarding angel adipocytokine'. It counteracts many of the pro-tumorigenic effects of leptin. By activating adenosine monophosphate-activated protein kinase (AMPK), adiponectin leads to cell cycle arrest. It inhibits the mammalian target of rapamycin (mTOR) activity. It results in adiponectin being an anti-diabetogenic. In addition, it is anti-atherogenic, anti-inflammatory, and anti-cancer adipokine (Hopkins et al., 2016).

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tremendous odds for breast cancer development second to nulliparity. Obesity not only increases the risk of breast cancer by 1.5 to 2 times among post-menopausal women but also worsens prognosis from increased recurrence and morbidity (Ligibel et al., 2019).

4. Physical Inactivity and Exercise

An estimated 40% of cancers can be prevented through lifestyle modifications (Friedenreich et al., 2021). In American adults, increased BMI>40 is associated with increased death rates in all cancers for males and females compared to patients with a lower BMI< 24.9 (Brown et al., 2012). Exercise leads to multifactorial bodily changes such as changes in body composition, hormone levels, decreased inflammation, and improved cellular immunity improving outcomes in patients diagnosed with cancer. Oxidative stress is known to affect DNA and negatively increase cancer risk. Regular physical exercise induces cellular responses that augment an antioxidant response (Idorn & thor Straten., 2017).

While a lack of exercise is linked to obesity and a 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 recommended that 10 minutes workout markedly reduces risk. Physical activity even delays breast cancer development in the BRCA-

genetic mutation carriers. Mechanisms facilitating risk reduction remain elusive but involve desirable falls 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 (Ligibel et al., 2019).

5. Infectious agents

An estimated 17.8% of neoplasms worldwide are associated with infections. In developing countries, infections-related cancers are as high as 22% and 6% in developed countries. (Pappas. 2009). Specifically, viruses account for most infection-mediated cancers, while other microorganisms such as parasites, for example, *Opisthorchis viverrini* or *Schistosoma haematobium* and bacteria, for example, *Helicobacter Pylori* (*H. pylori*) are also caused of cancer as shown in Table 1 (van Elsland and Neefjes. 2018).

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Table 1. Link between infections and respective cancers.

Infectious agent	Type of micro-organism	Cancer type
Epstein–Barr virus	Virus	Nasopharyngeal carcinoma, Burkitt lymphoma, immune suppression-related non-Hodgkin lymphoma, Hodgkin lymphoma, extranodal natural killer/T-cell lymphoma (nasal type) [102]
Hepatitis B virus	Virus	Hepatocellular carcinoma [102]
Hepatitis C virus	Virus	Hepatocellular carcinoma, non-Hodgkin lymphoma [102]
Kaposi sarcoma herpesvirus	Virus	Kaposi sarcoma, primary effusion lymphoma [102]
Human immunodeficiency virus 1	Virus	Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, carcinoma of the cervix, anus, conjunctiva [102]
Human papillomavirus type 16	Virus	Carcinoma of the cervix, vulva, vagina, penis, anus, oral cavity, and oropharynx and tonsil [102]
Human T-cell lymphotropic virus type 1	Virus	Adult T-cell leukaemia and lymphoma [102]
Merkel cell polyomavirus	Virus	Merkel cell carcinoma [103]
Opisthorchis viverrini	Trematode	Cholangiocarcinoma [102]
Clonorchis sinensis	Helminth	Cholangiocarcinoma [102]
Schistosoma haematobium	Trematode	Urinary bladder cancer [102]
Helicobacter pylori	Bacterium	Non-cardia gastric carcinoma, low-grade B-cell MALT gastric lymphoma [102]
Alfatoxin (B1)	Mould (Aspergillus flavus)	Liver cancer [102]
Salmonella Typhi	Bacterium	Gallbladder carcinoma [13]
Salmonella Enteritidis	Bacterium	Colon carcinoma in the ascending and transverse parts of the colon [14]
Chlamydia trachomatis	Bacterium	Carcinoma of the cervix and ovaries [104,105]

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The aetiology of infection-related cancers is complex and likely involves multiple pathways. The infectious agent can 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 (Islami et al., 2018). Infectious agents can also indirectly lead to cancers via chronic inflammation that can produce metabolites harmful to host cells and DNA and alter the normal progression of the cell cycle. It is the proposed mechanism of *H. pylori* and parasitic-related cancers. Additionally, infectious agents can suppress the host immune response, leading to cancer formation. It, however, is likely a result of chronic inflammation, which shows severe overlap in infection-related cancers (Pappas, 2009). HPV accounts for 90% of cervical cancers, while Hepatitis B and C account for 80% of hepatocellular carcinomas (van Elsland and Neefjes. 2018). . Human papillomaviruses are associated with mutations that integrate the HPV DNA into the host cells. It results in premalignant and malignant changes in gynaecological tissue. HPV has been named the most important risk factor worldwide for cervical cancer. Thus, HPV vaccination and procedures such as pap smears aimed at early detection of HPV infection may aid in the prevention of these cancers (Viarisio et al., 2017). We conclude that the facts suggest that a number of individuals present risk factors for cancer, which can be modifiable.

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