KNOWN MODIFIABLE RISK FACTOR OF CANCERS

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ABSTRACT

It was estimated the proportion and number of invasive cancer cases and deaths for 26 cancer types in adults aged 30 years and older in the United States in 2014. In this study was found that these cancers were attributable to modifiable risk factors such as cigarette smoking, second-hand smoke, alcohol intake, physical inactivity, excess body weight, red and processed meat consumption, low consumption of vegetables and fruits, dietary calcium, and ultraviolet radiation 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 in the US present risk factors for cancer, which development in malignancies would ultimately depend on the interaction of environmental and genetic factors.

1. Genetic risk factors of cancer

Studies have shown that genetic factors in pair twins show that only 20% have a concordance rate of being affected with breast cancer and the another 80% is due to environmental causes (Kolonel et al., 2004). Table 1 shows the types of cancer and genes involved in carcinogenesis (Anand et al., 2008).

Table 1. Types of cancer and genes involved.

Cancers	Genes involved
Colorectal cancer	MLH1, MSH2, MSH6, PMS2, APC, DPC4, Bmpr1, PTEN, MYH
Breast	BRCA1 and BRCA2
Nasopharyngeal carcinoma	TLR9
Malignant melanoma	CDKN2

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Chronic myeloid leukaemia	ABL, BCR
Burkitt lymphoma	MYC
Lung cancer	SCLC1
Multiple endocrine neoplasia	MEN1, RET
Gastric cancer	TLR4
Pancreatic cancer	DPC4
Retinoblastoma	RB1
Hemangioblastoma	VHL
Neurofibromatosis	NF2
Ovarian cancer	BRCA1 and BRCA2
Li-Fraumeni syndrome	P53, CHEK2
Prostate cancer	HPC1, TLR1, TLR4, TLR6, TLR9

***The percentage attributed to these genes was not recorded.**

The dysregulated fibroblast growth factor (FGF) signalling pathway regulates immunity, cell fate, angiogenesis and metabolism through its receptors. FGFR1 to FGFR4 cause human cancer, including breast, gastric and lung cancer.

2. 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 (Petros et al., 2012). Some of these cancers include; lung, larynx, head and neck, and bladder. Interestingly, endometrial cancer is less common in women who smoke cigarettes (Kuper et al., 2002).

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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. Activation of cell signalling pathways via NF-κB may play a role. (Zhong et al. 2008) 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 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

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N-nitroso was the most striking among carcinogens of the brain system known in experimental animals. Conversely, several studies indicated an insignificant or null association between smoking and malignant brain tumours. One reported no association (Filippini et al., 2002). However, Zumel-Marne et al., 2019, 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. Pang et al., 2003 investigated self-reported smoking habits in parents of 3838 children with cancer and 7629 control children included in the United Kingdom Childhood Cancer Study (UKCCS). Several cancers were analysed, including lymphoma, leukaemia, central nervous system tumours and others. An increased risk of developing hepatoblastoma was documented in children. Their mothers smoked preconceptionally (OR=2.68, P=0.02) and most robust for both parents smoking (OR=4.74, P=0.003).

Tobacco use is constantly associated with an increased risk of developing many forms of cancer. It has been branded as a predisposing factor for liver cancer by the World Health Organization International Agency for Research on Cancer. 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 (Massarweh & El-Serag, 2017). Nevertheless, this investigation was inconsistently based on clinical data, patient history, and contrast. In another study, population-based smoking increased the odds of intrahepatic cholangiocarcinoma (ICC) by 80% (Massarweh & El-Serag, 2017). Lastly, according to Baecker et al., 2018 tobacco smoking is attributed to a 13% risk for all liver cancer cases worldwide. (Baecker et al., 2018).

3. HIV and Tobacco

HIV may cause lung carcinoma owing to T-lymphocyte depletion (Sigel et al., 2017). Non-small cell lung cancer (NSCLC) represents 86–94% of HIV+ patients with lung cancer, while small cell carcinoma has been reported in only 5–13% (Cooley, 2003). 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 overactivity 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). In addition to dealing with HIV,

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these patients are further burdened by systemic disparities in their treatment. HIV-positive patients tend to have worse outcomes after a lung cancer diagnosis.

4. Alcohol

Over 25-68% of upper aerodigestive cancers are attributable to alcohol consumption, of which over 80% of these cancers can be prevented by alcohol and smoking abstinence (La Vecchia et al., 1997). A 3.5% of global cancer-related deaths can be attributable to alcohol consumption (Boffetta et al., 2006). 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). Studies have also found a dose-dependent increased risk of alcohol consumption and breast cancer likely due to increased oestrogen and androgens (Williams and Horm 1977).

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). This risk of HCC was even more significant with the presence of Hepatitis B or C infections, illustrating a positive synergistic effect with viruses (Yu et al., 2008). 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), as shown in Figure 4. 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).

Like tobacco, alcohol can also stimulate cellular signalling pathways via NF-κB (Szabo et al., 2007). 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

 doi:10.20944/preprints202212.0579.v1

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 higher BMI, potentially increasing the risk of lung squamous cell carcinoma. Ko et al., 2020, which looked at risk factors for lung cancer in non-smokers, perceived alcohol as carcinogenic. Further research is thus required to determine the relationship between alcohol consumption and a consequent manifestation of lung cancer.

Notwithstanding the impact of both smoking and alcohol use on cancer development, it is vital to understand the influence of alcohol consumption independent of smoking behaviours. Heavy alcohol consumption has been identified as a significant risk factor in the aetiology of HCC and ICC (Anand et al., 2008). Genetic variation in HSD17B13 reduces the risk of developing these two liver tumours. The authors concluded that a genotypic/phenotypic risk score could facilitate earlier diagnosis and management of HCC in this population. Consequently, most patients suffer from a chronic liver disease predisposing them to develop primary liver cancer (Stickel et al., 2020). Early studies reveal the association of alcohol use with breast cancer (Willett et al., 1987).

The next most important risk factor for gastric cancer is alcohol consumption. Alcohol consumption increases nitrosamine intake by creating a mechanism that causes chronic inflammation. Alcohol consumption has been reported as a risk factor in 84 studies (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 4% 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).

5. Diet as a risk factor for cancer.

Diet is a well-described lifestyle risk factor for cancer. However, the exact aetiology of diet and carcinogenesis is still to be understood. Over 30% of cancer deaths in the USA have been

 doi:10.20944/preprints202212.0579.v1

linked to diet. It was linked diet to many cancers, including endometrial cancer (50%), larynx, bladder, mouth, pharynx and oesophagus (20%), lung cancer (20%), colorectal cancer (70%), pancreatic cancer (50%), prostate cancer (75%), breast cancer (50%), gastric cancers (35%), gall bladder cancer (50%) and other cancers (10%) (Anand et al., 2008; Willett & MacMahon, 1984).

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, which we discussed in a further chapter (Mentella et al., 2019).

Ultra-processed foods have undergone multiple biological and chemical (for example, the addition of food preservatives) processes to become palatable and affordable (Fiolet et al., 2018). The National Research Council (US) Committee on Diet, Nutrition and Cancer reported that over 2500 chemicals are added to foods to alter flavour, taste, colour and cost.

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). Long-term consumption of nitrate preservatives and azo food dyes (organic compounds such as amaranth, allura red, and tartrazine) has been associated with cancer formation (Sasaki et al., 2002). 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 (Bingham et al., 2002). It may, however, be associated with a decreased risk of lung cancer (Dosil-Díaz et al., 2007). Cooking meats produce carcinogenic heterocyclic amines. In addition, smoking meats produce harmful carbons such as pyrolysates and amino acids (Lauber et al., 2007). A ketogenic diet creates an unfavourable environment for cancer cells by limiting tumour growth and protecting healthy cells from chemotherapy and radiation (Weber et al., 2020). Therefore, this diet may be considered an adjuvant therapy for cancer patients. Caloric restriction is known to decrease the risk of cancers. In rodent studies, caloric restriction has decreased plasma

 doi:10.20944/preprints202212.0579.v1

glucose and IGF-1 and reduced inflammation, which may reduce cellular proliferation. (Longo & Finch. 2003). Lian 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 stomach cancer, whereas a higher food intake of fruits and vegetables decreases this risk (González et al., 2006).

5.1 Fruits and Vegetables

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 (Ranjan et al., 2019; Alok et al., 2019); carotenoids, vitamins, resveratrol, quercetin, silymarin, and indole-3-carbinol (Dandawate et al., 2016) have been identified. They may protect against various cancers by targeting multiple cell-signalling pathways.

Carotenoids are found in many fruits and vegetables, and lycopene has shown anti-cancer properties in vitro and Vivo. The proposed mechanism involves ROS scavenging up-regulation

 doi:10.20944/preprints202212.0579.v1

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)

Resveratrol is found in many fruits, such as grapes, berries, and peanuts. It has anti-cancer properties against many cancers. It includes lymphomas, myelomas, breast cancer, and prostate cancer. The anti-cancer properties are mediated via cell cycle arrest (Dandawate et al., 2016). *Quercetin* is a flavonoid found in many fruits and vegetables. It has antioxidant, anti-inflammatory, and antiproliferative properties. It is known to block NF-κB activation, which may prevent cancer formation (Dandawate et al., 2016).

Silymarin is another flavonoid commonly found in the milk thistle plant *Silybum marianum*. It also is an antioxidant that is believed to have anti-cancer properties by inhibiting NF-κB activation (Russo. 2007). *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).

5.2 Vitamins

Vitamins play a critical role against cancer. A study showed that high vitamin C concentration in plasma correlated with cancer-related mortality. Vitamin C is an antioxidant that inhibits inflammation and gap junction intercellular communication, which may have anti-cancer properties. The American Institute for Cancer Research estimates that Vitamin C can reduce the risk of many cancers (Lee et al., 2003). Vitamin D plays a role in nuclear transcription, including apoptosis, and may have protective anti-cancer effects (Ingraham et al., 2008).

6. Obesity

The positive energy balance seen in obesity causes metabolic alterations in the pathogenesis of many disease states, including tumorigenesis. There is no one explanation for how obesity leads to an increased risk of cancer, as it is likely a consequence of multiple neurohormones and cell signalling pathways. The Insulin and Insulin-like growth factor-1 (IGF-1) axis, cytokines (for example, leptin and adiponectin, TNF and IL-1), chronic inflammation, and sex steroids seen in obese patients are among the significant hormonal pathways that lead to cancer development (Anand et al., 2008).

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Nimptsch and Pischon. (2016) proposed that activation of NF-kB may link obesity and cancer. Tang et al., 2007 documented that hyperglycemia, a common association with obesity and metabolic syndrome, is also known to activate NF-kB. The clinical implications of inhibitors of these neurohormones and cell signal pathways toward preventing or even treating obesity-related cancers remain unanswered.

6.1 *Insulin/ Insulin-like growth factor-1 (IGF-1)*

Hyperinsulinemia and Insulin resistance are characteristic of obesity, increasing the risk of cancer development, progression, and mortality (Renehan et al., 2008). The Insulin and IGF-1 belong to a receptor tyrosine kinase family. When 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 (Hua et al., 2020). It is further supported by the overexpression of the mitogenic insulin receptor isoform A (IR-A). In addition, the insulin-like growth factor receptor (IGF-1R) in cancer cells (Belfiore et al., 2018).

6.2 *Adipokines*

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 (Zhang et al., 2005). *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

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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).

6.3 *Other aspects of obesity as risk factors*

Nindrea et al., 2017 found that BMI indicative of overweight/obese (>25 kg/m2) exhibits 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 (Ligibel et al., 2019) but also worsens prognosis from increased recurrence and morbidity. Obesity also introduces physical and social barriers to mammographic screening, an essential strategy for early detection and intervention of breast cancers.

7. 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).

8. 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.

 doi:10.20944/preprints202212.0579.v1

(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 2.

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).

Almost all infection-related cancers have implicated NF-kB as a vital link toward carcinogenesis (Pisani et al., 1997; Guan et al., 2008). *H. pylori* also induces inflammation that can produce free radicals and N-nitroso compounds which induce cell proliferation and cancer (Parsonnet. 1995). HPV accounts for 90% of cervical cancers, while Hepatitis B and C account for 80% of hepatocellular carcinomas (van Elsland and Neefjes. 2018). The latency period between initial infection and cancer development ranges between 15-40 years and is not an acute consequence (except for EBV-induced acute lymphoproliferative disease) (zur Hausen. 2009). HPV is the most common infection-related cause of cancer in women, while cancers from infections other than HPV are more common in men.

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Table 2. Link between infections and respective cancers. (van Elsland and Neefjes. 2018*).

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 heamatobium	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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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).

9. Radiation

Radiation, both ionising (for example, radon, x-rays, gamma rays) and non-ionising (for example, UV radiation and pulsed electromagnetic fields), are a risk factor for cancer and accounts for 11% of solid cancers (Gilbert, 2009). Ionising radiation exposure is most commonly due to radon and radon decay products at home or workplaces such as radon mines. Another source of ionising radiation is the medical use of x-rays (Hill & Ullrich, 2021), a risk factor for breast cancer in women and pubertal girls during their rapid breast development

 doi:10.20944/preprints202212.0579.v1

(Andrieu et al., 2006). While the risk factor between radiation and cancer is primarily dose-dependent, other factors such as patient age, physiological state, genetic susceptibility, and synergism between radiation and carcinogens may play an integral role.

Non-ionising radiation exposure is mainly from UV rays. UV radiation is the most common modifiable risk factor for skin cancers such as basal cell carcinoma, squamous cell carcinoma, and melanoma (Watson et al., 2016). UV rays' exposure is also increased due to the depletion of the ozone layer. UV rays from cosmetic tanning may account for an increasing incidence of melanoma (Narayanan et al., 2010). Contrary to this, UV radiation may protect against cancer via its activation of Vitamin D, which has many cellular functions, including regulation of cell proliferation and differentiation (Krause et al., 2006).

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