ACCESS MICROBIOLOGY

INSIGHT REVIEW

Menati Rashno *et al.*, *Access Microbiology* 2021;3:000247

DOI 10.1099/acmi.0.000247

MICROBIOLOGY SOCIETY

OPEN ACCESS

Microbiome in human cancers

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Abstract

A microbiome is defined as the aggregate of all microbiota that reside in human digestive system and other tissues. This microbiota includes viruses, bacteria, fungi that live in various human organs and tissues like stomach, guts, oesophagus, mouth cavity, urinary tract, vagina, lungs, and skin. Almost 20% of malignant cancers worldwide are related to microbial infections including bacteria, parasites, and viruses. The human body is constantly being attacked by microbes during its lifetime and microbial pathogens that have tumorigenic effects in 15–20% of reported cancer cases. Recent scientific advances and the discovery of the effect of microbes on cancer as a pathogen or as a drug have significantly contributed to our understanding of the complex relationship between microbiome and cancer. The aim of this study is to overview some microbiomes that reside in the human body and their roles in cancer.

INTRODUCTION

One of the most lethal diseases around the world, cancer is caused by genetic disorders or environmental impacts and is defined as uncontrollable and abnormal proliferation of cells. In addition to ultraviolet rays in sunlight and chemicals, bacteria and viruses too play important roles in developing cancers [1]. In many cancer cases, secondary tumours are formed due to late diagnosis which is the leading cause of high death rates. Common treatments like chemotherapy or radiotherapy have low viability rates due to drug resistance, tumour development, and low specificity of treatment [2]. New studies suggest that microbiome can be potentially used in treatment of many diseases including cancer.

Human microbiome

The human body is the habitat of many microbial organisms. Genome of this microbiome codes for almost 100 times more genes than the human genome. The largest portion of this microbiome resides in our digestive system. Human newborn babies like all mammals acquire some parts of this microbiomes from their mother during birth, labour methods vaginal or caesarian, and breastfeeding. Our diet has a direct impact on our microbiome, hence the long-term diet has a greater influence than the short-term diet. Changes in our social interactions and lifestyle can impact our microbiome throughout life [3–6]. Having considerable metabolic capacity and serious impact on immune system, the microbiome has an undeniably profound influence on human biology. The symbiosis between microbiome and its human host is complicated and although sometimes can harm our health, is mainly beneficial for us as hosts. On the other hand, our gut's microbiome can positively increase and facilitate nutrients absorption, for example by its abundant carbohydrate metabolizing genes [7, 8].

Microbial pathogens are the culprit for 15–20% of cancers and in comparison with symbiotic microbiome have a lower impact on initiation and development of tumours [9]. Some of the microbial carcinogens are mentioned in the table below (Table 1).

Received 18 September 2020; Accepted 17 June 2021; Published 11 August 2021

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Keywords: cancer; medication; microbiome; pathogen; the human body.

Abbreviations: CCA, Cholangiocarcinoma; CD4, cluster of differentiation 4; CPE, Clostridium perfringens enterotoxin; CR2, complement receptor type 2; CRC, Colorectal cancer; EBNA-1, Epstein-Barr virus Nuclear Antigen 1; EBV, Epstein barr virus; EBVaGC, Epstein-Barr virus (EBV)-associated gastric carcinoma; ELISA, enzyme-linked immunosorbent assay; ESPs, excretory–secretory products; HBV, Hepatitis B virus; HCC, hepatocellular carcinoma; HCV, Hepatitis C virus; HIV, human immunodeficiency viruses; HTLV, Human T lymphotropic virus; HV, Herpes virus; IBD, inflammatory bowel disease; IFN-γ, Interferon gamma; IHC, Immunohistochemistry; IL, Interleukin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK, Natural killer; Oip A, Outer Inflammatory Protein A; PV, Papilloma virus; QPCR, quantitative polymerase chain reaction; ROS, Reactive Oxygen Species; *TGF-β*, transforming growth factor beta; Th1, T helper type 1; TNF, tumour necrosis factor; WEA, wall-extracted antigens; WHO, World Health Organization.

Table 1. Microbes designated as carcinogenic to humans by the International Agency for Research on Cancer (IARC)

Microbe	Site of cancer
Helicobacter pylori	Stomach
Hepatitis B virus (HBV) *Hepatitis C virus (HCV)* *Opisthorchis viverrini* *Clonorchis sinensis*	Liver
Human papillomavirus (HPV)	Cervix Vagina Vulva Anus Penis Oropharynx
Epstein-Barr virus (EBV)	Nasopharynx Non-Hodgkin lymphoma Hodgkin lymphoma

Because of the increasing importance of the microbiome and its contribution to some cancers, microorganisms affecting prevalent cancers are discussed below.

Bacteria and cancer

More than 20% of cancers worldwide are related to infectious agents [10]. Compared to viruses, bacteria and their role in cancer have been underestimated [11–13]. Bacteria can increase cancer development by manipulating host cells signalling pathways, producing metabolites, or causing inflammation [14, 15]. Although chemotherapy is widely and effectively being used for treatment of many cancers and tumours, it can cause irremediable harms to healthy tissues and organs [16]. Bacteria can be successfully and specifically used against cancer through unique mechanisms and various methods. For instance, they can target tumours directly and kill them through controlled cytotoxicity. In recent decades, studies have shown that Salmonella spp. and Clostridium spp. have inhibitory effects on tumour growth [17, 18].

Clostridium perfringens and colon cancer

Colorectal cancer is the second most common cancer among women and the third among men with the highest prevalence in North America, New Zealand and Australia [19]. Risk factors for colorectal cancer include obesity, lack of physical activity, smoking [20, 21], although there are several treatments such as chemotherapy and radiotherapy, there is a need for more specific treatments like gene therapy [22]. Bacterial toxins have been proven effective candidates in killing cells *in vitro* and *in vivo* and have attracted special attention to *C. perfringens* enterotoxin (CPE) [23]. *C. perfringens* type A is a Gram-positive anaerobe which is mainly detected in food poisoning and attaches claudin-3 and claudin-4 proteins to the target cells [24, 25]. The family of claudin consists of 27 proteins and plays an important role in maintenance of cell polarity and transportation, and are necessary for strong binding of epithelial and endothelial cells [26, 27]. The attachment of CPE to claudins forms a complex of membrane pores that results in the disruption of osmotic equilibrium and rapid cell lysis [28, 29]. Cells which do not express claudin-3 or claudin-4 are not affected by the toxin. Results from studies on increasing the expression of claudin-3 or claudin-4 in epithelial tumours and colon cancer showed that this is an evidence for the selective ability of target cells like tumour with CPE [30, 31]. In a study done by Pahle *et al*. CPE gene therapy was used for selective eradication of colon cancer by expressing claudin-3 and claudin-4. CPE expression in these cells leads to rapid selection and destruction of colon cancer. This study showed that CPE can attach to these cells specifically and CPE gene therapy can be applied for successful treatment of colon cancer [32].

Radiotherapy and chemotherapy induces changes in the diversity of the faecal microbiota and also exhibit marked changes in intestinal microbiota, with most frequently, decrease in *Bifidobacterium*, *Clostridium*, and increase in *Enterobacteriaceae*. These modifications may contribute to the development of mucositis, particularly diarrhoea. Due to the effects of these treatments on the microbiome, we can mention the effect of a chemotherapy drug called cyclophosphamide, that can cause shortening of the intestinal villi and damage to the mucosal barrier [33, 34].

Salmonella typhimurium and prostate cancer

Prostate cancer is very common among men [35]. Prostate cancer is the second most frequent malignancy (after lung cancer) in men worldwide, counting 1276106 new cases and causing 358989 deaths (3.8% of all deaths caused by cancer in men), although only 1 in 350 men under the age of 50 years will be diagnosed with prostate cancer, the incidence rate increases up to 1 in every 52 men for ages 50 to 59 years. The incidence rate is nearly 60% in men over the age of 65 years [36, 37]. As men age, the risk of prostate cancer increases and most cases appear in men aged 50 and older. The chance of treatment is significantly higher when the cancer is limited to the prostate gland, but the development of cancer to other parts such as bones can cause nerve compression, hypercalcemia, and breaks which are life-threatening [38]. Bisphosphonates are medications used for prostate cancers with metastasis to bones, the compounds reduce the cancer growth, relieve pain and strengthen bones. *S. typhimurium* A1-R which is genetically engineered is capable of attacking cancer cells selectively [39]. *S. typhimurium* A1-R is used as a monotherapy in bare mice models and has been capable of inhibition and eradication of primary and metastatic tumours in prostate [40, 41]. As tumours are very sensitive to *S. typhimurium* A1-R and as A1-R can increase vessel destruction in tumours by starter dose it can be an evidence for anti-tumour effects of A1-R [42]. Expression of nestin-driven green fluorescent protein selectively in new vessels of transgenic mice shows the destruction of tumour vessels and inhibition of tumour growth by *S. typhimurium* A1-R [43]. A study by Ming Zhao *et al*. showed the therapeutic effect of *S. typhimurium* A1-R on prostate cancer. In this study, of the ten mice with the PC-3 tumours that were injected weekly with *S. typhimurium* A1-R, four A1-R-treated mice remain

alive and well 6 months after implantation. It took 10 to 12 weekly injections of bacteria to completely cure the mice [44]. Another study by Aisada Uchugonova *et al*. to understand the tumour cell-killing mechanism of *S. typhimurium* A1-R, studied the interaction of *S. typhimurium* A1-R with three different prostate cancer cell lines *in vitro*, the results of this study showed the fatal effect of *S. typhimurium* A1-R on different human prostate cancer cell lines and the time required for *S. typhimurium* A1-R to kill the majority of cancer cells varied from line to line, ranging from 2 hours to 48 hours [45]. In a study by Toneri *et al*. it was shown that A1-R can significantly control the growth of prostate cancer and inhibit its metastasis. The result of this study could be promising for the treatment of prostate cancer [46]. The results of another study also show an increased in the attack of *S. typhimurium* A1 to PC-3 human prostate cancer cells line and the cytopathic effect of this bacterium on PC-3 cell line, understanding the various mechanisms of cancer-cell killing by *S. typhimurium* A1 will be important for its use as a general therapeutic for cancer. PC-3 is a human prostate cancer cell line used in prostate cancer research and drug development. PC-3 cells are useful in investigating biochemical changes in advanced prostate cancer cells and in assessing their response to chemotherapeutic agents. PC-3 cells are also used to study viral infection in mammalian cells that exhibit an immune response [47, 48].

Helicobacter pylori

Helicobacter pylori is a Gram-negative bacterial pathogen that selectively colonizes the gastric epithelium, *H. pylori* is considered the most common etiologic agent of infection-related cancers, which represent 5.5% of the global cancer burden [49, 50]. *H. pylori* has several pathogenicity factors such as OipA, BabA, VacA, CagA, which are connected to the gastric epithelial cells by the receptor molecules in their surface, and this interaction creates a series of intracellular signalling cascade pathways, causing cell changes and ultimately damage to the cell and the tissues it is hosted by [51]. In a study was conducted in 2018 by Teimoorian *et al*. to investigate the relationship between *H. pylori* and clone cancer by ELISA method, the results of this study indicate a higher prevalence of this bacterium in people with cancer and also in men studied in this study [52].

Helicobacter pylori in stomach cancer and breast cancer

The high prevalence of *H. pylori* is directly connected to the risk of stomach cancer. The growth of stomach cancer varies in different regions [53]. Though anti- *H. pylori* treatments which have been shown to be successful in preventing stomach cancer, the risk of this type of cancer initiated by *H. pylori* would be significantly decreased [54]. Stomach cancer is around the fifth most common cancer in the world and regarding the fatalities it is considered the third most common cause [55].

Cascade changes in stomach mucus starts with acute/chronic inflammation and then to atrophic inflammation associated with intestinal metaplasia that can finally lead to dysplasia and stomach cancer [56]. In 1991 WHO introduced *H. pylori* as class 1 carcinogen for humans [57]. Studies show that from a genetics perspective, this microorganism represents the highest inter-species recombination rates and also represents the highest rates of variation. The high rates of mutations and recombination have enabled *H. pylori* to adapt itself to challenges in the harsh stomach environment leading to its invasiveness and clinical pathogenicity [58, 59]. Studying *H. pylori* shows their capability for sustained and prolonged attachment to stomach mucus and their destructive effects in causing duodenum ulcers, gastritis, and stomach cancer [60]. The complexity of *H. pylori's* pathogenicity can be related to two things. On one hand, some factors from this microorganism can induce apoptosis and on the other hand can induce cell proliferation. Regarding these characteristics, apoptosis inductive factors can be used to destroy the cancer cells directly. As a pathogen, *H. pylori* combined with genetic and biotechnology techniques could be adapted to be used as a treatment against cancer [61]. Breast cancer is one of the most prevalent cancers and a leading cause of deaths among females around the world. Common treatments for this disease mainly focus on using cytotoxic chemotherapies which have many negative side effects. Researchers have always been looking for alternative treatments with less severe side effects and recently bacterial products such as proteins and toxins have captured their interest. *H. pylori* is a Gram-negative bacteria which attaches to the stomach epithelial cells by its surface receptors. Outer Inflammatory Protein A (Oip A) is one the most important outer membrane proteins in *H. pylori* which plays a role in stomach inflammation [62]. Oip A is highly antigenic and causes high levels of interleukin eight in blood [63]. Previous studies have shown that Oip A plays a role in attachment and colonization on *H. pylori* [64]. A study has been done by Soleimani *et al*. which focuses on the toxic effects of recombinant protein Oip A of *H. pylori* on cancerous mouse cells (4T1 cells). Results from this study show that tumour cells viability after encountering Oip A with concentration of 31 $\mu g\ ml^{-1}$ and more, kills at least 50% of the breast cancer cells ($P < 0.001$) and in concentrations of 250 $\mu g\ l^{-1}$ the highest lethality is observed ($P < 0.001$) and this lethal effect is dependent on concentration and time. Western blot test results proved the presence of recombinant protein regarding the specific antibody reaction [65]. According to the results from these studies and the potential of this protein for cancer treatment, this protein can be considered a good choice for further studies in the future [66, 67].

Streptococcus bovis and colorectal cancer

Colorectal cancer (CRC) is the third common cancer in the US and the risk of this cancer increases after 40 [68]. Among microorganisms related to chronic colon infections which contribute to higher risks of colon cancer *E. coli* and several types of *Streptococcus* spp. can be named. Results

Table 2. Summary of previous studies on the association of *T. gondii* infection with brain tumours incidence

Year	Country	Tumour type	Methods	Results	Reference
1963–1964	USA	Glioma, Meningioma	Sabin-Feldman dye-test	Tumour patients (*n*=126): 56.3% Healthy controls (*n*=126): 41.3%	Schuman *et al.* [82]
1987–1990	Australia	Glioma, Meningioma	ELISA (IgG)	Tumour patients (*n*=53): 47.0% Healthy controls (*n*=348): 31.0%	Ryan *et al.* [187]
1979–2007	France	Brain tumour	Database	Brain tumour mortality rates increase with *T. gondii* seroprevalence in France.	Vittecoq *et al.* [86]
2008	37countries	Brain tumour	Database	Infection with *T. gondii* was associated with a 1.8-fold increase in the risk of brain tumours.	Thomas *et al.* [87]
2012–2014	China	Brain tumour	ELISA (IgG)	Tumour patients (*n*=900): 35.6% Healthy controls (*n*=900): 17.4%	Cong *et al.* [188]

from several studies have shown that *S. bovis* or antigens extracted from its cell wall (WEA) could develop cancer in rats [69, 70]. Recent studies also confirm the relationship between *S. bovis* and CRC [71]. These studies show a correlation of 18–62% between *S. bovis* infection and CRC [72]. *S. bovis* resides in human digestive system and can cause several complications including endocarditis and urinary tract infections [73]. A study conducted by Tsai *et al*. in 2016 showed that between 25 and 80% of patients with *S. bovis* bacteremia have concomitant colorectal tumours. In this study that, a total of 107 patients with *S. bovis* bacteremia were identified, were investigated with colonoscopy; 15 of these patients (30.6%) had colorectal adenocarcinoma [74]. Another study conducted by Gold *et al*. in 2004, the results showed that *S. bovis* bacteremia is associated with both colonic neoplasia and extracolonic malignancy. In this study, colorectal adenomas or adenocarcinomas were diagnosed in 16 patients with *S. bovis* bacteremia and neoplasia was associated with *S. bovis* bacteremia in 26 (58%) of the 45 patients [75]. We believe that physicians caring for patients with *S. bovis* need to be alert to the possibility of malignancy.

Parasites and cancer

Parasites can cause chronic inflammation in tissues which can lead to cancer [76]. Since chronic infections are important contributors to inflammation related cancers, all forms of microbial infections can initiate an inflammatory immune response which can in toxic environmental conditions encourages the growth of tumour cells. Microbial infections like those by parasites are responsible for 17.8% of known cancers worldwide, and prevention and proper treatment of these infections in developing countries can cut this type of infections down to 26.3% [77]. Infections by single cell parasites are prominent health issues in developing countries [78]. Almost 20% of malignant cancers worldwide are related to microbial infections including bacteria, parasites, and viruses [79]. These microbes can disrupt a host cell's processes such as cell cycle and DNA repair mechanisms and cause disorders in the body's immune system and chronic inflammation [80]. Some of the parasites related to human cancers are mentioned below.

Toxoplasma gondii and brain cancer

This parasite is an obligate intracellular parasite which infects human and other mammals. Up to 80% of the population may be infected, depending on eating habits and exposure to cats [81]. This parasite attacks the central nervous system and causes chronic infection [82]. This is one of the most common infections in the world and it is estimated that almost one third of the population is the carrier of this parasite [83]. Studies show a relationship between brain cancer and antibodies against *Toxoplasma gondii*, which means this infection can increase the risk of brain cancers in humans. After entering the nervous system cells and reproduction, the parasite can generate cysts in brain tissue which can remain latent by not initiating the immune response, this explains regulations on gene expression and cell signalling pathways induced by the parasite. *Toxoplasma* infection additionally controls several cellular pathways to establish an anti-apoptotic environment, and subverts immune cells as a conduit for dissemination [84]. Studies by Thirugnanam *et al.* showed that *Toxoplasma* gains control of host cell functions including proliferation and apoptosis by channelizing parasite proteins into the cell cytoplasm and some of the proteins are targeted to the host nucleus. *Toxoplasma* significantly reduces Fas/CD95-triggered apoptosis by impairing activation of the initiator caspase eight in cell. Also, *Toxoplasma* targets activation of the pro-apoptotic Bak and Bax to inhibit the apoptogenic function of mitochondria. *Toxoplasma* infection has been shown to promote the expression of anti-apoptotic proteins: Bcl-w, Bfl1, Mcl-1, Bcl-Xl, Bcl2, Bax and Bad in host cells. *Toxoplasma* also modulates several cell signalling pathways including AKT and phosphoinositide 3-kinases (PI3Ks) pathways. Interestingly, recent studies showed that miRNAs, which are important regulators of gene expression, are manipulated by *Toxoplasma* to interfere with the host cell functioning. Thus the possibility that *Toxoplamsa* infection can alter expression of several other miRNAs in different of host cells cannot be ruled out [85].

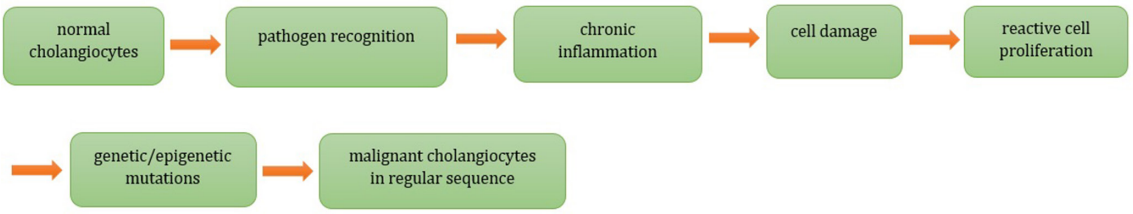

Fig. 1. Proposed mechanisms leading to transformation of normal biliary cells into malignant cholangiocytes. Cholangiocarcinoma cells express altered molecular mechanisms, which enhance cell proliferation, decrease apoptosis, and increase the capacity of tissue invasion, stromal proliferation, and angiogenesis.

Results from a study in France shows a direct relationship between seru-prevalence of *Toxoplasma gondii* and brain cancer mortality rate particularly in people of 55 years of age and older [86]. Analysing data obtained from a study from 37 different countries showed that the risk of brain cancer in adults infected by *T. gondii* is almost double than the healthy adults [87]. Table 2 summarizes previous studies about the relationship between *T. gondii* infection and brain cancer.

Clonorchis sinensis and cholangiocarcinoma

Clonorchis sinensis is prevalent in areas where it can be transmitted through raw food especially raw fish. *C. Sinensis'* life cycle includes three alternative sexual and asexual reproductions in three hosts such as fish, mammals, and snails. Most infected people do not show any significant symptoms. If not cured, the parasite can live up to 25–30 years in the person's body and can cause severe symptoms. The diagnosis is by identifying parasite eggs in stool samples. Safe and efficient medications are available for the disease. Treating foods like fish by methods such as freezing and enough cooking will destroy the parasite. Most infected cases show no signs but one of the physical symptoms of clonorchiasis infection is jaundice [88, 89]. Cholangiocarcinoma (CCA) is a fatal liver cancer which causes malignant tumours in bile ducts epithelium [90]. CAA is usually diagnosed in developed stages of the disease and the survival chance for the patient is less than 24 months. The only possible treatment is surgery or liver transplant [91]. The prevalence of this type of cancer in areas in Asia like north-eastern Thailand where *C. Sinensis* is common, is higher [92]. Although clonorchiasis is known as the major risk factor for CAA, chronic viral infections like B and C hepatitis are also known to be contributors to the disease [93].

The severity of these changes exhibits a tendency to correlate with the duration of infection and the susceptibility of the host. Pathological changes to the liver can be caused by a bacterial infection or formation of liver stones in which case liver excretes some highly immunogenic metabolic products (so-called ESPs) which can be either toxic or initiate inflammation, encourage reproduction, and suppress apoptosis in bile ducts epithelium [94, 95]. Although the molecular mechanisms involved in CCA development are not clearly understood, it is possible to simply explain a multi-step process [96, Fig. 1]:

Cryptosporidium parvum and colorectal cancer

Colorectal cancer (CRC) is the third most common cancer in the world. Overall, the lifetime risk of developing colorectal cancer is: about 1 in 23 (4.3%) for men and 1 in 25 (4.0%) for women [97]. CRC is the consequence of accumulation of genetic and epigenetic changes and rather than genetic causes, factors like lack of physical activity, smoking, diet, and age are other contributors. In total, 99% of CRC cases happen at ages over 40 which proves age as a risk factor in this type of cancer [98, 99]. New findings reveal the role that microbes play in CRC. *Cryptosporidium* is a single-cell intracellular obligate parasite and its most common genus in the world is *C. parvum*. This parasite infects human digestive tract's epithelium and is one of the major causes of diarrhoea in humans [100, 101]. The infection with *C. parvum* in healthy people usually has no signs. This parasite is known to be opportunistic and is transmitted mainly through contaminated food and water and rarely through direct contact with infected human or animals. Chemotherapy for the CRC patients is an option, but severe diarrhoea, electrolyte imbalance, and malabsorption in severe cases can cause death [102]. This infection is a fast spreading cause of cancer in the world [103]. Many studies have proved this parasite and its infection in patients with CRC. Many intracellular proteins of *C. parvum* which are known to be able to induce apoptosis inhibition can play a key role in developing malignancies [104, 105]. Inflammation is the immune system's primary response against *C. parvum* and when re-infection occurs which is followed by immune system's inactivity against tumour cells, tumours will form. Induction of cell proliferation and the instability of genetic processes can also be consequences of infection. Many of these disorders can cause oncogenic mutations in epithelial cells [106]. When an intestine's epithelial cells are infected, the body's defensive mechanism activates NF-kB and this activation can act as a potential regulator for CRC formation in the long term. Risk of CRC in people who suffer from inflammatory bowel disease (IBD) following the infection with *C. parvum* is higher. Inflammation will increase secretion of Interleukin-1 (IL-1), (IL-17), TNF-α and other cytokines affecting the tumour formation and ultimately induce NF-kB

activity. Modulation of IL-6/STAT3 signalling in response to inflammatory signals can cause uncontrolled cell proliferation which is the initiator of cancer [107, 108]. Results from a study shows a 12.6% infection of *C. parvum* in CRC patients [109]. Another study done on mice with combined immunodeficiency Dex-treated showed the ability of *C. parvum* in inducing neoplasia and tumour formation in intestines [110]. The results of various studies show that *Cryptosporidium* is strongly associated with human colon cancer being maybe a potential etiological agent of this disease. Because *Cryptosporidium* is an opportunistic agent that causes significant morbidity and mortality in patients, it is possible that individuals with malignancies have a higher risk of developing an infection with this parasite. In addition, the World Health Organization acknowledges that nowadays 20% of cancers are due to infectious agents, and some authors have hypothesized that within 2050 the great majority of cancers will be considered to have an infectious origin. More research is needed to find links between clinical, epidemiological data, molecular factors, parasites, and cancer development.

Viruses and cancer

In late 19th century viruses were classified as small infectious particles that can pass through the filter membranes [111]. Viruses contribute to 10–15% of human cancers globally [112]. International Agency for Research on Cancer has introduced several viruses that can cause cancer including: Hepatitis B virus (HBV), Herpes virus (HV), Hepatitis C virus (HCV), Papilloma virus (PV), Epstein-Barr virus (EBV) [113]. Studying intercellular systems and cell signalling mechanisms between cells and adoption of these systems by viruses for replication, have introduced some ways of detecting and curing some viral diseases as well as cancers [114]. Scientists now believe that studying cancer without considering the role of viruses would not be comprehensive. Studying cancer viruses and their tumorigenic mechanisms can help us in preventing and curing these diseases.

Epstein-Barr virus and Burkitt's lymphoma

The first human virus proved to be carcinogen is Epstein-Barr virus (EBV). This virus belongs to family Herpesviridae and so far has been detected from several tumours. EBV contains a double stranded linear DNA genome and is enclosed by capsid proteins [115, 116]. The prevalence of this virus in serum of adults is more than 90% and in the young that infection happens at early ages the rate is 50% [117]. This virus is able to infect epithelial cells as well as B cells [118]. In patients with immune deficiency, a strong relationship between Epstein-Barr virus and Burkitt's lymphoma has been observed [119]. Furthermore, the relationship between EBV and stomach and breast carcinoma has been confirmed [120]. Burkitt's lymphoma- a non-Hodgkin lymphoma- is related to Epstein-Barr virus and according to its epidemiologic and clinical characteristics is classified in three groups including HIV associated Burkitt's lymphoma, endemic Burkitt's lymphoma, and sporadic Burkitt's lymphoma [121]. Endemic Burkitt's lymphoma engages jaw and face bones and sporadic Burkitt's lymphoma engages upper respiratory tract and intestines, both leading to tumours in those areas [122]. Studies show that the interactions between the virus and B cells prepares the ground for the development of Burkitt's lymphoma and the key factor in tumorigenicity of Burkitt's lymphoma is the activation of C-myc oncogene through its transfer into the immunoglobulin region.

Epstein-Barr Virus (EBV) and gastric cancer

EBV has oncogenic activity in humans. Its genome was detected in samples from patients with stomach cancer using PCR techniques in 1990 [123]. Findings from around the world have shown that about 10% of gastric cancers are related to *EBV* (EBVaGC) [124]. Since in stomach cancer the proliferation happens in single infected cells *EBV* infection is possibly involved in the first stages of the cancer [125]. In most EBVaGC cases rather than methylation of viral genes, methylation of host cell DNA also happens [126–128] and hypermethylation of tumour related gene promoters leads to reduction in their gene expression [129]. Also target gene silencing by viral miRNAs in *EBV* infected cells has been reported [130]. Both aforementioned mechanisms can increase the tumour development in EBVaGC. Most studies show no correlation between age and EBVaGC and but it has a higher prevalence in men. Endoscopy is the best diagnosis method. Endoscopy shows EBVaGC as superficial ulcers on the stomach's upper parts [131]. Prevalence in China with 4.3% and the US and Germany with 16–18% have the smallest and largest distributions [132].

EBV penetrates human epithelial and B lymphocytes using different mechanisms. This virus has a high affinity for surface receptors on B cells such as CD21 or human complement receptor type 2 (CR2) and enters these cells through endocytic pathways [133, 134]. At last the interaction between BMRF2 protein, integrins present on polar epithelial cells, and EBV-encoded membrane protein are suggested as patterns for *EBV* adhesion to cell surfaces. Studies show *EBV's* high capacity in infecting epithelial cells and B cells [135, 136]. Studies shows that *EBV* infection in epithelial cells mainly appears through cell-to-cell contact. This rate of infection is 103 times more than transmission without mediator cell which is a B cell that keeps the virus on its surface and transfers it to epithelial cells [137, 138].

Epstein-Barr Virus (EBV) and breast cancer

Breast cancer is one of the most common cancers among women in the world [139] and one of its main risk factors is lifestyle [140]. According to the International Agency for Research on cancer, 18–20% of cancers can be related to infections [141]. Recently scientists have confirmed that viruses can be role players in different stages of diseases [142]. One of breast cancer's risk factors is contracting viral infections such as *EBV* and for the first time in 1995, Labrecque *et al*. confirmed the presence of *EBV* genome in breast cancer [143]. Studies show the disrupting impact of virus on telomere function which can be a proof for the effect of virus in cancer development [144, 145]. Contact

Table 3. Previous published studies which evaluated EBNA-1 by IHC on breast cancer specimens

Studies	EBNA-1 positive	Total	References
Bonnet *et al.* 1999 [189]	9	9*	Bonnet *et al.* 1999 [189]
Brink *et al.* 2000 [190]	1	5*	Brink *et al.* 2000 [190]
Chu *et al.* 2001 [191]	12	48	Chu *et al.* 2001 [191]
Grinstein *et al.* 2002 [192]	14	33	Grinstein *et al.* 2002 [192]
Ribeiro-Silva *et al.* 2004 [193]	29	73	Ribeiro-Silva *et al.* 2004 [193]
Preciado *et al.* 2005 [194]	24	69	Preciado *et al.* 2005 [194]
Fawzy S *et al.* 2008 [195]	10	40	Fawzy S *et al.* 2008 [195]

*IHC was done on *EBV*-DNA PCR positive samples only.

between lymphoblastoid cell lines infected with *EBV* and breast epithelial cells can lead to their infection which subsequently leads to *EBV* DNA transfer and stimulation of milk secreting cuboidal cells which are evidence for the impact of *EBV* on breast cancer [146, 147]. PCR and IHC are among methods used for detecting *EBV* in cancerous tissues. Analysis of genomic DNA from cancerous samples using *EBV* specific primers done by Salahshournia *et al.* showed that from 40 cancerous breast tissues, 20 of them (50%) and from 40 healthy samples, under study five of them (12.5%) were positive [148], Richardson *et al.* showed that 24 (34%) of tumour samples and nine (13%) control samples were *EBV* positive. They used QPCR technique on 70 tumour and control samples [149]. In another study by Joshi *et al.* using ELISA and IHC cancerous and healthy control samples were studied. Results from ELISA showed 50 (90.9%) of cancerous samples and 27 (81.8%) of control samples were positive for anti-EBNA-1 (Epstein-Barr virus Nuclear Antigen 1) IgG and there was a meaningful correlation between the increasing rate of infection in cancer proteins in comparison with control group. Also IHC for EBNA1 in cancer group showed 28 (54.9%) positive cases while none was confirmed positive for control group [150]. Table 3 summarizes other-previous ICH assessments for detection of EBNA-1 in patients with breast cancer.

Hepatitis C virus (HCV) and liver cancer

Hepatitis C virus belongs to family *Flaviviridae* and is a RNA virus. Its genome is a single strand RNA and contains 9.6 Kbp. Since its genome is not able to integrate itself into the host cell's genome, its proteins interacts with host cell's proteins and potentially contribute to cells malignant transformation [151]. Hepatitis C infection increases the risk of hepatocellular carcinoma (HCC) by worsening the inflammation and liver fibrosis. In addition to this, factors such as obesity, diabetes and alcohol can increase the risk of development of liver cirrhosis to HCC two to four times [152]. Although epidemiologic studies show a close relationship between HCC and hepatitis C infection, the prevalence of hepatitis C in patients with HCC significantly varies in different geographical regions [153, 154].

Hepatitis B virus and liver cancer

Hepatitis B virus is the smallest DNA virus that infects humans. Epidemiologic studies show a direct relationship between hepatitis B virus and primary liver cancer [155]. In human populations the number of chronic hepatitis B carriers amongst patients with liver cancer is higher. Development of liver tumours is significantly higher in these patients and liver inflammations play the main role in the process of cancer development. Genetic instabilities also play an important role in cancer development. In 80% of HCC related to hepatitis B virus, DNA sequences from the virus is integrated. These sequences are incomplete fragments and can not serve as a template for viral replication, Protein X from hepatitis B virus which is a 154 amino acid protein, by interfering with the cell cycle and combining with the host cell genome, ultimately activates the replication and several signalling cascades. Protein X is highly functional and is capable of inhibiting apoptosis induction in cancer cells by P53, TNF, Fas, TGF-β, and induction of apoptosis in normal cells by increasing the production of Reactive Oxygen Species (ROS), activating caspase 8, removing mitochondrial membrane potential, and release of cytochrome C [156–158]. The expression of Protein X in cytoplasm of HBV infected liver cells is higher and on the contrary the expression of this protein in the nucleus of these cells is low [159–161].

Papilloma virus and cervical cancer

Almost 12% of all cancers in females is cervical cancer which is caused by Human *Papilloma Virus* (*HPV*) infections [162]. This virus has been introduced as one of the most dangerous viruses for humans. Reports from Meisels *et al.* proved that in smears from cervix, in addition to presence of koilocytes, *papilloma virus* infection is also present [163]. In cells from cervical cancer, the expression of specific papilloma virus genes like E6 and E7 has been confirmed. Continuous expression of these proteins in malignant tissues and limited expression of these genes leads to proliferation and development of infected cells [164].

Fungi and cancer

Although fungal infections have less prevalence compared to bacterial and viral infections, in recent decades they are responsible for a significant increase in the incidence of the disease. In studies done in the US during 1979 to 2000 a 207% increase in fungal infections was recorded [165]. Recent scientific advancements and discovering the effect of microbes on cancers both as pathogens and as medications, has emphasized the role of the microbiome in the onset of cancers. Hereby we discuss some fungal species and their role in cancers.

Candida albicans and breast cancer

Candidiasis is a common fungal infection which is caused by opportunistic species of candida like *C. albicans*. This species

is a natural flora of the human body and rarely infects healthy people. Death rate of candida infection is much higher compared to similar bacterial infections and is estimated to be 38–80% [166, 167]. Candida species are considered the fourth cause of septicemia in hospitalized patients and in the US have caused the mortality of 40% of patients [168]. The risk of candida infection in patients with cancer is increased because of prolonged intensive care stays. The dominance of *C. albicans* in more than 50% of candidiasis cases has attracted attentions to this type of fungal infections [169]. Chemotherapy for treatment of breast cancer leads to the damaging of immune cells and makes the patients susceptible to opportunistic infections like *C. albicans* which triggers the immune response in these patients [170]. Results from different studies show the immune suppressing impact of *C. albicans*. Presence of *C. albicans* structural antigens prohibits production of IL-12 [171]. Production of INF8 by T-lymphocytes also decreases significantly under the influence of these structural antigens, signs which show these mechanisms are adopted by *C. albicans* to suppress the immune system [172]. Furthermore, dead *C. albicans* inhibit INF-8 production by NK cells [173]. Production of anion superoxide in neutrophils is also inhibited by *C. albicans* through the release of several soluble factors [174, 175]. In a study done by Holakuyee *et al*. the effects of *C. albicans* infection on survival and size of the tumour in mice with breast cancer was researched. Analysis of the results showed that candidiasis caused by live *C. albicans* and its structural proteins has caused the suppression of lymphocytes proliferation responses in comparison with a control group. Examining the tumour mice which had received structural and secretory proteins through intravenous injection or had contracted *C. albicans* showed that this group had an increase in tumour growth compared to the control group. Also the survival of the infected mice has been reduced. In this study by using flow cytometry technique it was shown that the ratio of T (CD4/CD8) cells penetrated to the tumour in injected mice and also directly infected mice was reduced [176].

Aspergillus fumigatus and breast cancer

A. fumigatus (*Aspergillus fumigatus*) is an important genus of its family. It is saprophytic and can survive different environmental conditions. This fungus will not infect people with a healthy immune system, but attacks those with immune deficiencies, and can be dangerous and even deadly [177, 178]. Previous studies show that cytokines released by helper T-cells fight against *A. fumigatus* infections [179, 180]. Culturing phagocytic cells in adjacency to Th1 cytokines like IFN-γ can increase these cells fungicidal properties while their adjacency with Th2 cytokines (like IL-4 and IL-10) has a reverse effect in fungicidal activity [181, 182]. Cytokines play an important role in sensitivity to and resistance against *A. fumigatus* infection. Many studies show that Th1 cytokines by induction of protective responses and Th2 cytokines by induction of non-protective responses work toward an *A. fumigatus* infection [183]. IFN-γ is an important cytokine which stimulates the body's immune response when faced with *A. fumigatus* infection and inhibition of IFN-γ secretion worsens the disease [184, 185]. Assessing the different cytokines production in mice with breast cancer which were infected by *A. fumigatus* was done by Sohrabi *et al*. and yielded some notable results. These results represented alteration and destruction of protective immune responses in the mice in a way that by increasing the cytokine responses from Th2 cells (like IL-4) and vice-versa resulted in slight reduction in IFN-γ levels in animals. This can be a sign of inhibition of responses initiated by Th-1 cells. These results can confirm the hypothesis that *A. fumigatus* infection in mice with tumours can cause disruption of immune responses. These results can pave the way for developing new treatment methods for patients with tumours who have also contracted invasive fungal infections such as *A. fumigatus* [186].

CONCLUSION

Regarding the significant advancement in techniques for detecting and investigating the factors contributing to cancers such as microbes, the need for more research on the environmental factors causing cancer is being felt more than ever. In-time diagnosis of cancer can be made possible by having more knowledge about microbes and their carcinogenic mechanisms. Environmental factors have significant effects on the human microbiome and therefore on the immune system, metabolism, and biology of the body. Regardless of the detrimental effects of the microbiome on the body, such as contributing to cancers, it can be used as a powerful tool in treating cancer and other diseases since bacterial proteins and toxins, for example, show less severe side effects and more efficiency compared to cytotoxic drugs. Common cancer treatments like chemotherapy which are widely used today can cause irreversible damages to the healthy tissues and organs, thus by harnessing the potential benefits of microbial pathogens through biotechnology and genetic engineering techniques it is possible to fight against cancers more efficiently.

Funding information
The authors received no specific grant from any funding agency.

Author contributions
M.M.R., wrote and edited the manuscript, provided the feedback, drew the tables and searched papers. H.M. and M.R., wrote and translated the manuscript. B.N., collected the related literature and reviewed the manuscript. All authors read and approved the final manuscript.

Conflicts of interest
The authors declare that there are no conflicts of interest.

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