Review Article

# Exploring the Relation between Bacterial Infections and Cancer Progression

S. HARAKEH[1*], A. L. BILGRAMI[2], M. MOULAY[3,4], M. M. MAHMOUD[1,4], JAWAHIR A. MOKHTAR[5,6], HANOUF A. NIYAZI[5], HATOON A. NIYAZI[5], M. A. KHORMI[7], KAWTHER A. ZAHER[8], HEND ALRASHEEDI[9], SOAD AL-JAOUNI[10], M. M. ALAMRI[11], HANAA M. ALSAEDI[11], MAYADA H. EZMIRLY[11] AND A. D. TEKLEMARIAM[12]

[*]Yousef Abdul Latif Jameel Scientific Chair of Prophetic Medicine Application, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia. [1]King Fahd Medical Research Center, King Abdulaziz University, Jeddah, 21589, Saudi Arabia, [2]Deanship of Scientific Research, King Abdulaziz University, Jeddah, Saudi Arabia, [3]Stem Cell Research Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, 21589, Saudi Arabia,[4]Department of Medical Laboratory Sciences, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Saudi Arabia, [5]Department of Clinical Microbiology and Immunology, Faculty of Medicine, King Abdulaziz University, Jeddah 21589, Saudi Arabia, [6]Vaccines and Immunotherapy Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah 21589, Saudi Arabia, [7]Department of Biology, College of Science, Jazan University, P.O. Box. 114, Jazan 45142, Kingdom of Saudi Arabia. [8]Immunology Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, 21589, Saudi Arabia,[9]Clinical Pharmacy Department, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia, [10]Department of Hematology/ Pediatric Oncology, and Yousef Abdul Latif Jameel Scientific Chair of Prophetic Medicine Application, King Abdulaziz University Hospital, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia. [11]Department of Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah 21589, Saudi Arabia,[12]Addis Ababa University, College of Veterinary Medicine and Agriculture, Department of MIVP, P. O. Box 34, Addisu Ababa, Ethiopia.



**Cancer has become one of the most devastating diseases which have become major source of morbidity and mortality. So this has put a lot of burden on the society and the general health sector. The causes of cancer can be attributed to heredity, environment, lifestyle/behavior, viruses and other potential carcinogens including bacteria. Several investigations have attempted to establish the relationship between bacterial infections and cancer development, but conclusive evidence remains elusive. Some investigators believe that bacteria can induce the production of potential carcinogens or genotoxins through the process of oxidation of bile acids and carbohydrates, and through the hydrolysis of other mutagenic precursors. Based on this reasoning, it is possible to note that several strains of bacteria can cause human cancers which include *Streptococcus bovis*, *Escherichia coli*, *Bartonella*, *Salmonella typhi*, *Helicobacter pylori*, *Chlamydia pneumoniae*, *Borrelia burgdorferi* and *Clostridia* species belonging to Ruminococcaceae. Current and past findings provide substantial evidence, supporting the etiological role of bacterial pathogens in tumor mutagenesis in humans. Although this area of research is still in its early stages and requires further detailed investigation, this review aims to elucidate various types of cancer associated with these carcinogenic bacterial species and their mutagenic mechanisms.**

**Key words: Bacteria, carcinogenesis, colon cancer, tumor, *Salmonella*, *Helicobacter pylori***

Cancer has become one of the leading causes of death and morbidity in modern society worldwide[1]. It is known that several traits are attributed to the establishment and development of carcinogenesis[2]. Infectious agents are suspected to be among these factors. Infectious agents are the cause of up to 20 % of cancers worldwide, according to the American Cancer Society (ACS)[3]. The mutagenic interaction among different human cancers and many oncogenic viruses such as papillomavirus, hepatitis B virus, Epstein-Barr virus and bacteria such as *Streptococcus*

***Address for correspondence**
E-mail: sharakeh@gmail.com



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*bovis* (*S. bovis*), *Chlamydia pneumonia* (*C. pneumoniae*), *Escherichia coli* (*E. coli*), *Helicobacter pylori* (*H. pylori*), *Bartonella*, *Salmonella typhi* (*S. typhi*), *Borrelia burgdorferi* (*B. burgdorferi*) and *Clostridia* species, belonging to Ruminococcaceae has previously been well documented[4,5].

It has traditionally been believed that bacterial infections make up a small percentage of cancer cases. Bacteria, however have been associated with cancer by two cases, chronic inflammation and synthesis of mutagenic by-products[6]. Various studies have demonstrated that some bacterial species facilitate the process of carcinogenesis by the production of toxic by-products resulting from bile acid and carbohydrates metabolism, as well as through the hydrolysis of other carcinogenic precursors[7].

One of the most well-studied bacterial infections linked to cancer is *H. pylori*[8]. According to the International Agency for Research on Cancer (IARC), *H. pylori* is class I human gastric carcinogen. The mechanisms of action of bacterial mediated carcinogenesis are complex and encompass interplay, effecting on the physiology of the host cell, chronic inflammation and alterations in tissue stem cell homeostasis[9].

Gallbladder Cancer (GBC) is relatively infrequent in comparison to more common cancers of the colon, lungs, prostate or breast[10]. Bacterial strains like *S. typhi* are responsible for GBC. However, the detail mechanism of action of how the organism could cause cancer and the cellular interaction between them is still in its initial stage.

According to the research findings, some people are more vulnerable to bacterial infections that lead to cancer development and certain cancers occur at higher incidence in certain populations. For instance, women are more likely to develop GBC than men in all populations[11]. Despite the fact that lung cancer is more prevalent in smokers, only a small percentage of smokers develop this disease[12]. Colon cancer being the 3rd most common cancer in the United States of America (USA), patients with Inflammatory Bowel Disease (IBD) have far higher risk for Colorectal Cancer (CRC) than those without IBD[13]. In addition, relationship between chronic infectious agent and susceptible host and/or its immune response are thought to attribute to the development of cancer[14].

It has been reported that many bacteria are capable of causing persistent infections or producing toxins that disrupt the cell cycle, altering cell proliferation and development[15]. The resulting disturbance in cell growth and Deoxyribonucleic Acid (DNA) damage is identical to the damage caused by other mutagenic agents[16]. Most of these carcinogenic agents may either directly cause mutations (tumor initiators) or accelerating mutations (promoters). As cancer grows, blood flow to the region boosted, consequently results in the proliferation of blood vessels or angiogenesis. The most dangerous outcome of bacterial mediated tumorigenesis than other form of cancer is metastasis which occurs when cells lyse from tumor and disseminate cancer cells at distant sites[17].

This review explores the association between bacterial infection and different types of cancers. Besides, some of the proposed mechanisms of action of bacterial infections in the development of tumors have also been described. The bacterial pathogens which are particularly discussed in relation to cancer include *S. Typhi*, Paratyphi A, Typhimurium, *S. bovis*, *Mycoplasma*, *Fusobacterium nucleatum* (*F. nucleatum*), *Chlamydia pneumonia* and *Bacteroides fragilis* (*B. fragilis*).

## FACTORS CONTRIBUTING TO CARCINOGENESIS

### Bacterial factors:

Several research findings reveal that different bacterial factors such as enzymes, toxins or other metabolic products have been associated with the progression of cancers in humans. According to the report by Luu *et al*.[18] *Clostridia* species is known for producing an estrogen-metabolizing enzyme called Beta (β)-glucuronidases. This enzyme was found play substantial role in the development of breast cancer in humans[18]. Similarly, the Cytolethal Distending Toxin (CDT) produced by *E. coli*[19] and the downregulation of the expression of Cyclin-Dependent Kinase inhibitor 2A (CDKN2A) gene by uropathogenic *E. coli*[20] have been linked with the progression of CRC and prostate cancer in humans[19]. Further, it has been reported that CDT and Lipopolysaccharide (LPS) of *S. typhi* facilitate the development of GBC in humans[19] while lipopeptides, Ribonucleic Acid (RNA) and DNA of *E. coli* contribute to the occurrence of esophageal cancer[21]. Activation of the host immune response and release of specific cytokines are the mechanisms by which LPS affects cancer development. The LPS mediated cytokines such as Interleukin (IL)-1β, IL-10 and Chemokine Receptor 5 (CCR5) induce chronic inflammatory response which can cause somatic mutations accompanied by

higher incidence of carcinogenesis[22]. There are also other bacterial traits that are implicated in causing mutagenesis, including the synthesis of oncogenic bacterial proteins, like the Cytotoxin associated gene A (CagA) protein, encoded by the Cag gene in *H. pylori*, which leads to gastric adenocarcinoma through increased IL-8 production and proliferation of cells[19].

Moreover, it has been reported that micro (mi) RNAs are known to be the major mediators of the inflammatory process that enhance malignance *via* their adverse effect on the proliferation of cells, DNA methylation, mutation of DNA and cell death, causing carcinogenesis through host DNA damage[23]. Altogether, induction of chronic inflammatory response by some bacterial mutagenic agents can facilitate genomic transformation and accelerate the development of cancer.

**Host factors:**

In the last decade, a British microbiologist, proposed the idea that approximately 20 %-25 % of all cancers are caused by bacterial pathogens which arise from chronic inflammatory response associated with persistent infection[24,25].

Regarding factors associated with the host that induces carcinogenesis, it has been realized that constant release of cytokines, growth factors, reactive nitrogen and oxygen species from the inflammatory cells can affect the normal biological activities which eventually lead to genomic instability. The instability of genome in a cell finally results in the development of cancer[26].

The initiation of tumorigenesis by immune cells, inflammatory mediators and Pattern Recognition Receptors (PRRs) like Toll-Like Receptors (TLRs) has globally been reported in which the expression of TLR-1, 2, 3, 6, 7 and 9 in esophageal cancer has enhanced[19]. Besides, raised level of regulatory T cells ($T_{reg}$) and T helper 17 ($T_h17$) cells is encountered in CRC caused by Enterotoxigenic *B. fragilis* (ETBF) infection[27]. It has been also reported that pronounced expression of chemokine genes such as Chemokine Ligand 20 (CCL20) and increased activation of $T_h1$ cells are linked with GBC, while increased synthesis of IL-8 and Prostaglandin E2 (PGE2) are linked with CRC caused by *S. bovis* infection[28].

Another host factor assisting bacterial tumorigenesis is cytokine production by immune cells. In this regard, for instance, cytokines such as Interferon Gamma (INF-γ), IL-6, 8, IL-10 and Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF) have been reported in association with ovarian cancer linked with *Mycoplasma genitalium* (*M. genitalium*) infection[19].

## ASSOCIATION OF BACTERIAL AGENTS IN CANCER

### Bacterial agents (*Salmonella typhi*, Paratyphi A and Typhimurium):

The incidence of GBC varies widely across the globe[29]. It is also highly lethal with only diagnosis[30]. There are some evidences of chronic biliary infection with *S. typhi*, the agent that causes typhoid fever, also accounts to increase the risk of GBC[31]. According to a study published by Axelrod *et al*.[32], an individual with the history of typhoid fever for 30 y was diagnosed with GBC. Later *S. typhi* was isolated from the gallbladder wall and bile as well. Numerous retrospective investigations in Denmark, USA and Scotland have provided evidence that chronic *S. typhi* disease individuals are at higher risk of death associated with GBC compared with the general population[33-35]. According to Saravanan *et al*.[36], Indian subcontinent is the place where the incidence of GBC is amongst the highest in the globe whereby *Salmonella* infection is substantially higher. Currently, numerous studies have stated strong relationship between GBC and *S. typhi*, where both GBC and typhoid fever are endemic. These relationships are not always correlated with *S. typhi* infection. Methods used to detect *S. typhi* in the GBC may not be sensitive enough. The serostatus of Vi antibodies do not necessarily indicate infection with *S. typhi*. Hence, the association between GBC and *S. typhi* remains unknown.

Chronic infection caused by *S. typhi* in GBC is linked with long-term bacteria excretion. Epidemiological investigations conducted in *S. typhi* endemic area, like Bolivia, Chile, Ecuador and some other areas such as Pakistan, India, Japan and Korea, have displayed that around 90 % of chronically sick individuals and this linkage in turn, infers as a predisposing agent for GBC development in humans[37].

GBC is one of the most common Gastrointestinal Tract (GIT) cancers and denotes one of the most prevalent biliary tracts tumorigeneses[38]. The global yearly prevalence of GBC is around 2 time among 100 000 individuals, with marked geographical and ethnic variations[39]. The uppermost prevalence rates were reported among American Indians, South Americans, Indian subcontinent, Korea and Pakistan. GBC is rare in various North American and European countries and

the mortality rate is declining, though comparatively high incidence where mortality rate is still encountered in certain central European regions[38]. The malignancy has been linked with lifestyle and genetics, nevertheless GBC and *S. typhi* infection represent the prominent risk factors (fig. 1)[40]; size of gallstone increases the risk of GBC. When the size of the stones is >3 cm the risk is 10-fold bigger in comparison with smaller gallstones[41]. Robust epidemiological results of the association between GBC and *S. typhi* infection arose from retrospective studies performed in the USA and Europe, suggesting that chronic *S. typhi* infected individuals who were exposed to higher risk of mortality from GBC compared with uninfected people[42].

In a study conducted in Scotland, chronically infected typhoid and paratyphoid individuals exhibited superior incidence of GBC and some were exposed to colon, rectum, pancreas and lung cancer coupled with other rarely occurring neoplasms[35]. Consequent investigations confirmed these findings, suggesting typhoid infected individuals with enhanced incidence of the hepatobiliary cancer, though not supported by any serological evidence[43]. On the other hand, serological investigations performed in Northern India, indicated that the frequencies of isolation of *S. typhi* from bile, gallstones and gallbladder tissue from GBC infected individuals were significantly higher in comparison to those individuals who were suffering from benign gallbladder cancer[44]. The proportion of people having anti-Vi serum antibody titers were 38.5 %, 13.9 % and 9.2 % for GBC patients, benign gallbladder cancer and healthy individuals, respectively. In a study conducted by Tewari *et al*.[45] hepatobiliary samples from GBC patients contained 67.3 % of *S. typhi* flagellin gene which was detected using a specific nested Polymerase Chain Reaction (PCR) technique. This percentage was significantly lower in individuals among benign gallbladder disease individuals.

Histologically, over 80 % of GBC are associated with gallstones while 10 % are associated with adenocarcinomas[46]. Studies have shown that chronic *S. typhi* carrier status is strongly correlated with the presence of gallstones[47].

Although GBC and *S. typhi* exhibit positive association, the mechanism that facilitate chronic persistence as well as the possible carcinogenic properties of *S. typhi* remain unclear. The production of biofilms may contribute significantly to the colonization and chronic persistence of *S. typhi*. This observation is supported by some findings indicating that a lipid-rich bile with antimicrobial characteristics situated in the gallbladder enhances the synthesis of O-antigen that enables the formation of *S. typhi* biofilm on human gallstones[48]. Hence, gallstones which are embedded with biofilm may represent the most conducive niche for the persistence of bacteria in the gallbladder and may cause recolonization of the intestinal tract and shedding *via* faeces. This phenomenon will lead to the transmission of bacterial agent to a new host.

On the contrary, non-typhoidal *Salmonella* species (*S. choleraesuis* and *S. Typhi*murium) that provoke superior immune response in comparison to the typhoidal species and are associated with systemic sickness which have yet not reported to have any connection with disease of gallbladder or cancer as well[49].

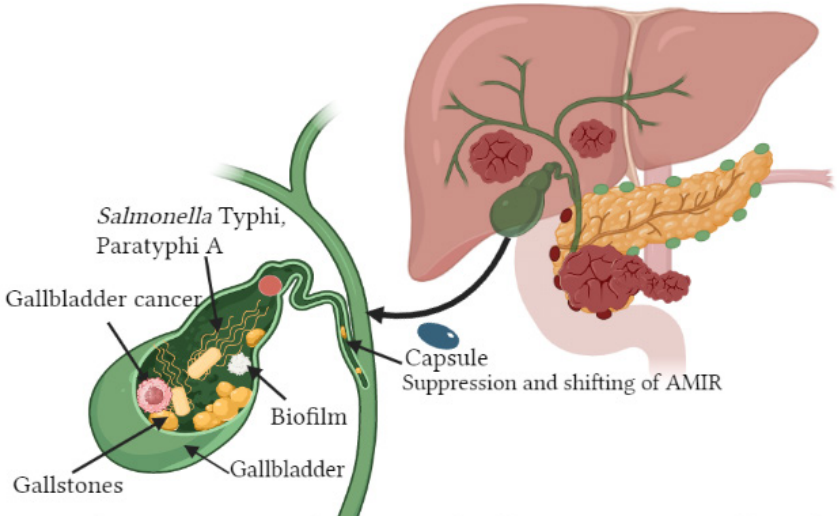


**Fig. 1: Schematic illustration of the most important risk factors (*S. typhi* infection and gallstone disease) of GBC**

***S. bovis*:**

*S. bovis* is presently named *Streptococcus gallolyticus* (*S. gallolyticus*). According to the reports, about 25 %-80 % of the individuals with bacteremia due to *S. gallolyticus*, experience colorectal tumors[50]. It has been reported that *S. bovis* infected individuals have experienced CRC and incidence of colonic neoplasia[51]. It has been reported that 94 % and 18 % of individuals face the issue of bacteremia linked with CRC, was in fact specifically associated with *S. bovis* biotypes I and II, respectively[52].

The occurrence of CRC differs from country to country and it has been considered as one of the major public health concerns in the world. In the USA and United Kingdom (UK), this type of cancer is the 2nd most common cancer after lung or prostate cancer for men and breast cancer for women[53].

In a study conducted by Boleij *et al*.[54], indicated that *S. gallolyticus*, particularly their cell wall antigens, were found to increase the synthesis of inflammatory cytokines in rat's colonic mucosa, suggesting direct association between colonic mucosal cells and *S. bovis* infection which is believed to be responsible for the development of CRC. Wide variety of interaction between CRC and *S. gallolyticus* might be attributed to different ethnic groups and geographical location.

Various bacterial species have been associated with chronic colon infections and predispose patients for colon cancer including *E. coli*[55] and streptococci[56]. *S. bovis* is a normal resident of the human GIT which can cause bacteremia, urinary tract infection and endocarditis, etc. Though *S. bovis* is the 2nd utmost cause of streptococcal endocarditis[51], it is commonly linked with GIT lesions, particularly colon carcinoma. Remarkably, neoplasia of the colon may later develop into bacteremia or septic endocarditis.

A study indicated that there is direct association between CRC and bacteremia[57]. In a different study, the release of *S. bovis*/*gallolyticus* mediated inflammatory cytokines such as Tumor Necrosis Factor-Alpha (TNF-α), IL-1β, 6 and 8 is found to facilitate the normal host defense mechanisms leading to the production of free radicals, nitric oxide, peroxynitrites, superoxide, alkylperoxy and hydroxyl radicals[58]. The mutagenicity and neoplastic processes of these molecular species is mainly caused by modifying cellular DNA. On the contrary, formation of *S. bovis*/*gallolyticus* antigens triggered angiogenic modulators in colonic mucosa, such as IL-8 may also facilitate the process of colon carcinogenesis (fig. 2)[59].

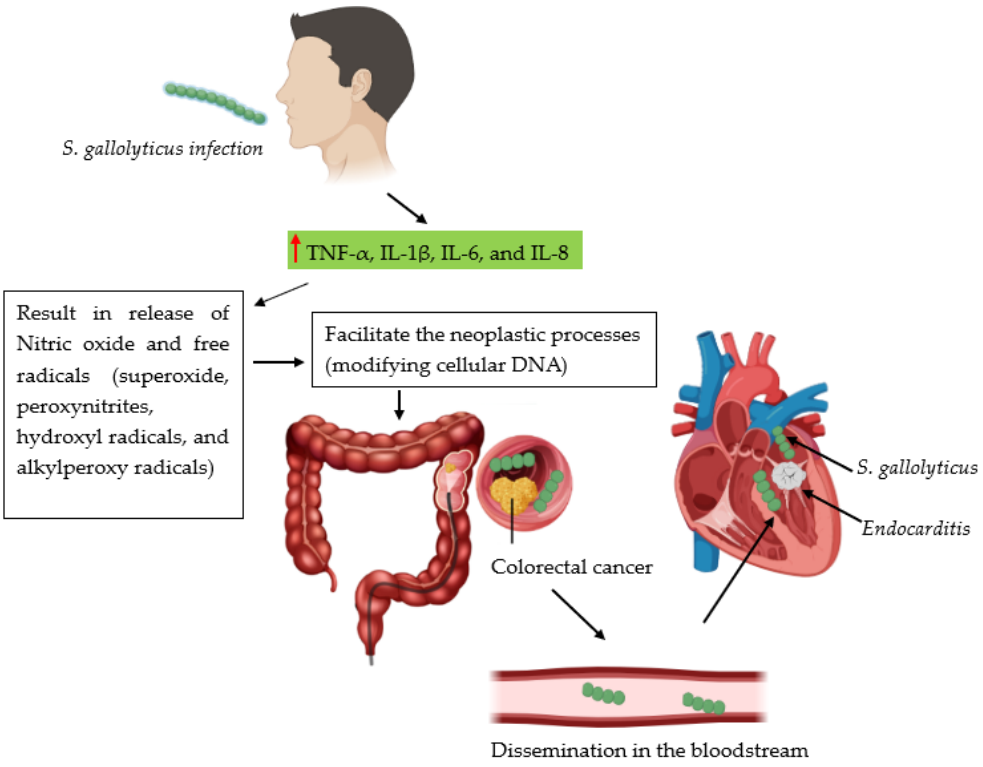


**Fig. 2: Schematic representation of *S. gallolyticus* linked carcinogenesis where *S. gallolyticus* enters the intestine *via* oral cavity which is outcompeted by resident normal flora and exits *via* fecal excretion**

***C. pneumoniae*:**

*C. pneumoniae*, which is a gram-negative, obligate intracellular bacterium, has been identified in 1989, which frequently occurs as a respiratory pathogen resulting in chronic and persistent respiratory infections among humans[60]. *C. pneumoniae* infection is not limited to respiratory infections such as pharyngitis, pneumonia, sinusitis and bronchitis but it is also linked with chronic obstructive pulmonary disease, asthma and lung cancer[61]. *C. pneumoniae* is transmitted *via* aerosols[62]. Similar to all the other *Chlamydia* species, *C. pneumoniae* tends to persist in the tissue[63]. *C. pneumoniae* respiratory infections vary among countries and populations. It is hypothesized that *C. pneumoniae* is linked with other acute and chronic pulmonary diseases such as chronic obstructive respiratory disease, lung cancer and asthma[64]; additionally, it is also related with atherosclerotic cardiovascular diseases depicting several evidences[64].

Lung cancer is one of the main health problems which causes deadly illness in humans[65]. Research findings indicated that around 6 of 10 people with pulmonary cancer die within 1 y after diagnosis. Lung cancer is responsible for 2 093 876 (11.6 %) new cases and 18.4 % of deaths in 2018[10]. The dramatic increase in the prevalence of lung cancer is mainly facilitated by increased smoking among males and females, contributed to 90 % of lung cancer.

Laurila *et al*.[66] firstly discovered that *C. pneumoniae* infection could be an independent causative agent for lung carcinoma in 1997. Since then, the role of *C. pneumoniae* in the development of lung cancer has been intensely investigated[67], nevertheless the reports have been inconsistent. Presently, the mechanism of action by which the causal relationship between chronic *C. pneumoniae* infection and lung cancer is not clearly investigated. According to Chebak *et al*.[68], smoking may accelerate *C. pneumoniae* to colonize the lung whereby superoxide oxygen radicals, IL-1β, TNF-α and IL-8 play vital role, attributing to DNA and lung tissue damage ultimately causing carcinogenesis. Besides, the infection, *C. pneumoniae* may result in irregular apoptosis in lung tissues which leads to cancer.

Research into the interaction between lung cancer and *C. pneumoniae* risk is still in its initial stage. As per the previous studies, *C. pneumoniae* might be involved in the development of lung cancer. Carcinogenesis caused by this organism could be associated with chronic pulmonary diseases such as chronic bronchitis and asthma[66].

***H. pylori*:**

*H. pylori* which is the inhabitant of the human stomach, was 1st identified from peptic ulcer diseased individuals by Marshall *et al*.[69]. The occurrence of *H. pylori* infection remains higher in most countries all over the globe. According to a study, there were 4.4 billion *H. pylori* infected individuals globally in 2015 where Africa continent had the highest rate (70.1 %)[70].

*H. pylori* is a gram-negative helical-shaped bacterium and the ammonia production by *H. pylori* using urease enzyme counteracts the acidity of stomach, making it conducive niche for the bacterium. Moreover, the helical shape of *H. pylori* allows it to hideaway into the mucus layer[71].

*H. pylori* is the most frequent cause of peptic ulcers in the GIT of humans, which has also been linked to several other malignant and benign GIT disorders, most notably gastric cancer[72]. *H. pylori* is now a major cause of duodenal and gastric ulcers, gastric Mucosa Assisted Lymphoid Tissue (MALT) lymphoma and *Nocardia* gastric adenocarcinoma[73]. Besides, epidemiologic investigations have explored the interaction between *H. pylori* and other GIT tumors, including CRC, pancreatic cancer[74,75] and esophageal tumors. A study indicated that CagA positive strains found to be of superior risk factor for cancer than CagA-negative strains[76]. A meta-analysis of 16 studies performed around the world revealed that CagA-positive *H. pylori* infected individuals experienced twice the risk of *Nocardia* gastric cancer than CagA-negative *H. pylori* infected individuals[77]. On the contrary, in Sweden, a study indicated that CagA-positive *H. pylori* infected patients experienced significantly lower risk of esophageal adenocarcinoma[78]. Likewise, in USA, another study displayed that unlike CagA-negative strains, CagA-positive *H. pylori* infection was linked with lowered risk of gastric cardia cancer and/or esophageal adenocarcinoma[79].

Bacterial and host factors play an important role in the onset of gastric cancer in *H. pylori* infected individuals. Bacterial virulence factors such as CagA and Vacuolating cytotoxin A (VacA) of *H. pylori* play vital role in instability of cellular DNA and its damage. *H. pylori* tumorigenesis may be also driven by abnormal immune response (blockage of the normal immune response or overexpression of the immune cells) and dysregulation of apoptosis following infection[80] (fig. 3). According to Larussa *et al*.[81] arginase, CagA, VacA and other metabolic products of *H. pylori* alter T cell

activation, proliferation and apoptosis. Recently, it has been reported that the semaphorin 5A-mediated pathway of *H. pylori* enhances the expression of matrix metalloproteinase 9 in gastric cancer cells and facilitate subsequent tumorigenesis process[82].

### *F. nucleatum*:

*F. nucleatum* is non-spore forming, gram-negative oral anaerobe. It is one of among the most prominent species localized in the oral environment[83]. *F. nucleatum* and the *Fusobacterium* adhesin gene A (FadA), are found to be abundant in stool samples of CRC diseased individuals[84]. CRC is the most prominent cause of mortality in humans worldwide[85]. Fusobacterial galactose adhesion hemagglutinin, Fap2, has been shown to intermediate *F. nucleatum* inhabitant of cells by attaching to the tumor induced host receptor D-Galactose and N-Acetyl-D-Galactosamine (Gal-GalNAc)[86].

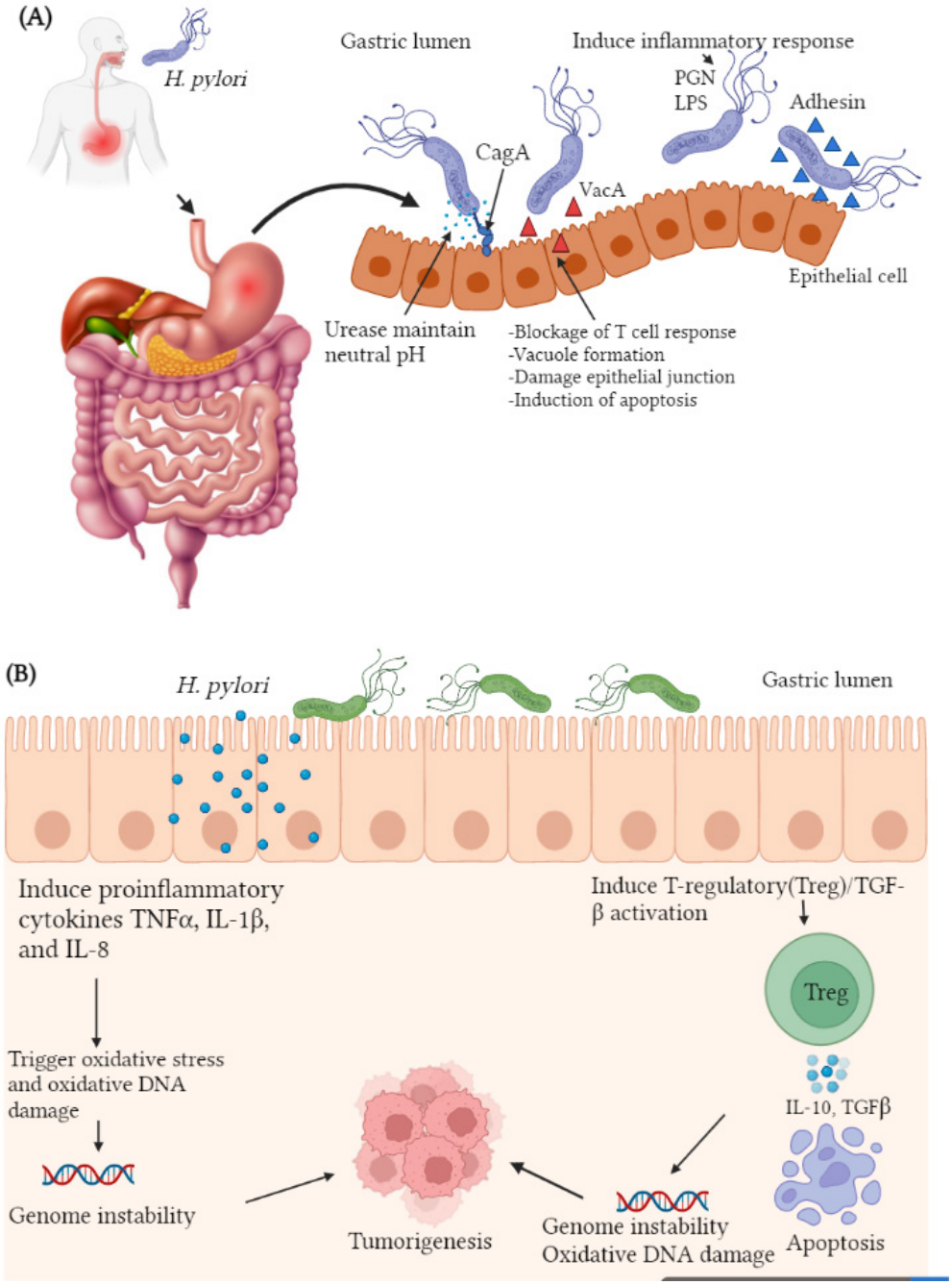


**Fig. 3: Schematic overview of *H. pylori* mediated tumorigenesis pathways, (A): Bacterial factors and (B): Major host response following *H. pylori* infection**

Moreover, purified recombinant protein FadA has been identified to bind and colonize host cells, provoking the development of CRC cells. Interestingly, under disease and stress conditions, amyloid-like FadA might support acid resistance and further facilitate the internalization of the bacterial agent into the GIT, resulting in invasion of *F. nucleatum*. FadA has been recognized to bind to Epithelial-cadherin (E-cadherin) for attachment of the host epithelial cell[87]. This interaction led to the activation of the β-catenin/Wingless-related integration (Wnt) pathway, thus stimulating oncogenic and inflammatory responses[88]. Research findings exhibited that *F. nucleatum* might facilitate carcinogenesis by provoking, metabolism and proliferation of CRC cells[89]. *F. nucleatum* LPS might activate β-catenin *via* TLR4/Phosphor-p21-Activated Kinase 1 (PAK1) cascade in CRC cells[90]. LPS also facilitates TLR4 signalling to Myeloid Differentiation primary response 88 (MYD88), leading to the stimulation of Nuclear Factor Kappa B (NF-κB) and boosting miRNA-21 expression. Moreover, the oncogene miRNA-21 participated in colitis-linked CRC diminishes the expression of Rat Sarcoma p21 protein Activator 1 (RASA1) and stimulates the RAS-Mitogen-Activated Protein Kinase (MAPK) pathway, consequently leading to the accumulation of Synthesis phase (S phase) and enhances CRC cell proliferation[90,91].

Most cancer cells generate energy for the growth of tumor *via* aerobic glycolysis, which is also called as Warburg effect. It has been recognized that *F. nucleatum* infection triggers carcinogenesis and glycolysis by provoking H3K27ac-targeting of the genes Angiopoietin-Like Protein 4 (ANGPTL4) and Enolase 1 (ENO1) in CRC cells (fig. 4)[92].

### *Mycoplasma* species:

The role of *Mycoplasma* and its oncogenic potential in the development of cancer has been explored since the 1950s. *Mycoplasmas* were 1st identified in leukemia diseased individuals, since then, several investigations displayed its presence either directly by PCR or indirectly by assessing the level of antibody in diseased individuals[93].

*Mycoplasma* species particularly *M. genitalium*, *Mycoplasma hominis* (*M. hominis*) and *Ureaplasma urealyticum*, have been identified in individuals from different countries such as Turkey, Australia, Russia, Japan and Iran[94]. Huang *et al*.[95], have documented exciting results depicting that *Mycoplasma* infection might be associated with the occurrence of cancer in various organs such as colon, prostate, breast, cervix, GIT, ovaries, esophagus and brain (fig. 5).

Recent research findings conducted by Klein *et al*.[96] indicated that *Mycoplasmas* have been identified in women who were positive for cervical cancer. Some of these species included *M. genitalium*, *M. hominis* and *Mycoplasma penetrans* (*M. penetrans*). The association between *Mycoplasma fermentans* (*M. fermentans*) infection, lymphatic system and renal cancer has also been studied[97]. Over 80 % of the DNA of *Mycoplasmas* have been found in tissues of cancer diseased individuals. Such fascinating results encouraged the investigators to explore the clinical importance of *Mycoplasma* infection in individuals who experienced kidney cancer[97]. Similarly, the occurrence of bladder cancer was formerly related with *Mycoplasma* infection whereby *M. penetrans* was mainly included in the progression of bladder cancer[98].

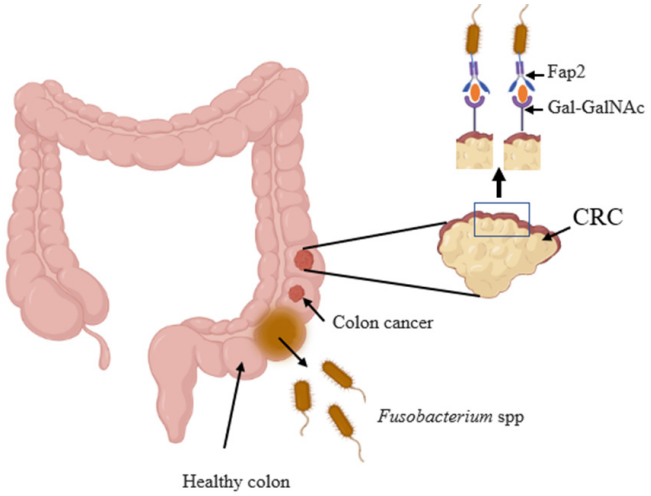


**Fig. 4: Schematic description of the mechanism of *F. nucleatum* mediated colorectal adenocarcinoma**

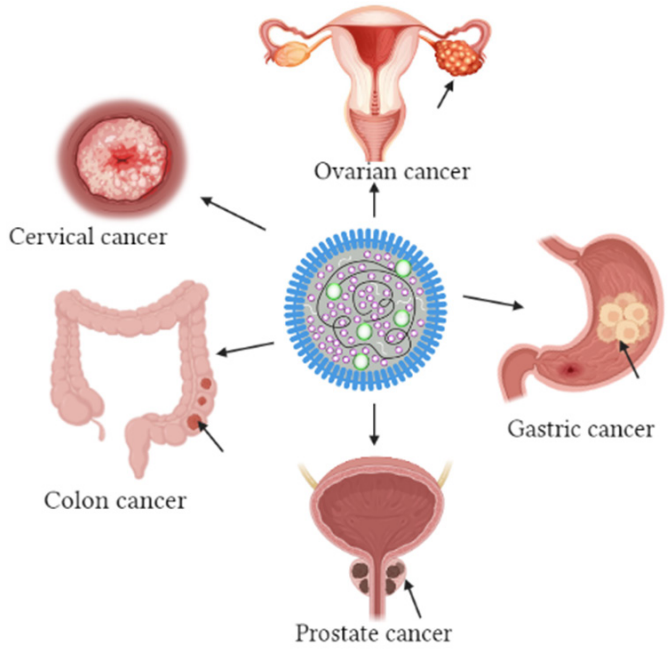


**Fig. 5: Diagram illustrating the major type of cancers associated with *Mycoplasma* infection**

Several species of *Mycoplasma* have been shown to interfere with the coordination of cell cycle checkpoints *in vivo* and *in vitro*. Different cases of chromosomal anomalies, karyotypic and morphological alterations have been linked with *Mycoplasma* infections[99]. *Mycoplasma* is the best example to prove that infection-mediated inflammation helps in the progression of cancer *via* suppression of natural killer cell mediated macrophages[100]. Recent studies indicated that *Mycoplasma hyorhinis* (*M. hyorhinis*) infection enhances the accumulation of β-catenin in nuclear region, thereby facilitating gastric cancer cell motility *via* β-catenin signalling. In a study, *Mycoplasma* DnaK expression enhances the propagation of cancer *via* DNA damage in mouse model. Studies also indicated that *M. hyorhinis* infection directly influences the level of Cluster of Differentiation (CD) $133^{+}$ cells in human CRC cell lines.

In an investigation, *M. hominis*, *Mycoplasma arginini*, *M. fermentans* and *Mycoplasma arthritidis* on the NF-κB pathways and tumor protein (p53) suppressor both engaged in the maintenance and stability of the cell cycle[101]. *In vitro* studies conducted on a panel of mice and human cell lines indicated that *Mycoplasma* infection suppressed the activity of p53 and induced NF-κB, which are the main traits of cancer cells in humans[102]. Bacteria encoded proteins such as *M. hyorhinis*-p37, facilitates the colonization of the agent into the human cells. This signifies its involvement in the carcinogenesis process[102]. Significant interaction between *M. hyorhinis* and carcinogenesis has been reported through *in vitro* and *in vivo* studies[103]. Role of *M. hyorhinis* in gastric cancer attained either by inducing the β-catenin signalling route which is vital for tissue homeostasis or the induction of the NLR family Pyrin domain containing 3 (NLRP3) inflammasome, which facilitates the process of pro-inflammatory cytokines maturation[104,105]. *Mycoplasma* species could disturb the anticancer activity of antibiotics either *via* the process of antibiotic resistance or by suppression of natural killer cells activity. Study conducted by Benedetti *et al*.[105], in the USA (Maryland University), chaperone and DnaK showed oncogenetic activities that intercalate with some of the proteins that regulate the critical cellular routes, resulting in reduction of effectiveness of anticancer drugs. Similarly, a group of German and Russian researchers have displayed that the cancer cells sensitivity to anticancer drugs decreases *M. hyorhinis* infection (fig. 6)[99].

### *Bartonella* species:

*Bartonella* species are gram-negative facultative intracellular bacteria. Animals such as cats, rabbits, guinea pigs and dogs are the reservoirs of *Bartonella henselae* (*B. henselae*). Cat flea (*Ctenocephalides felis*) is the principal vector of *B. henselae* and infected flea faeces are the major source of transmission between cats and humans. Ticks (*Ixodes ricinus*) have been identified as potential vectors for transmitting *Bartonellosis* in humans. *Ixodes ricinus* is the most prevalent species in Western Europe, which commonly transmits the disease by biting[106].

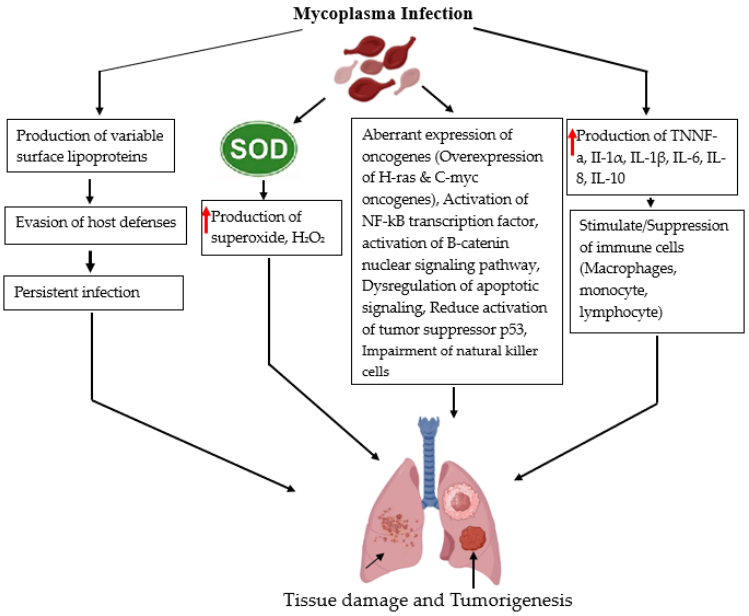


**Fig. 6: Schematic diagram illustrating host-*Mycoplasma* interaction, its mechanism of tissue damage and tumorigenesis**

Diseases caused by *Bartonella* species include asymptomatic skin lesions, unknown fever, local lymphadenopathy, encephalopathy, osteomyelitis, hepatomegaly and endocarditis. In immunosuppressed individuals, *Bartonella* species can cause opportunistic complications like peliosis hepatitis and bacillary angiomatosis[107].

*Bartonella* species are neglected and emergent bacteria that cause disease worldwide[108]. In humans, *Bartonella* species cause neurological symptoms, endocarditis, trench fever, bacillary peliosis, bacillary angiomatosis and cat-scratch disease[109,110]. *Bartonellosis* is potentially fatal, particularly in immunodeficient people[111]. Uniquely many *Bartonella* species including *B. henselae*, stimulate Vascular Endothelial Growth Factor (VEGF) production causing the proliferation of blood vessels[112], which is also hallmark of malignant melanoma. It has been recognized that infection of melanoma cell cultures with *B. henselae in vitro* resulted in alteration of the cell morphology[113]. According to the study conducted by investigators, the infection cause by *Bartonella* species is linked with increased pro-angiogenic cytokine expression and inhibition of apoptosis in endothelial cells[108]. Published studies indicated that the expression of VEGF-C in melanoma cells co-cultured with *B. henselae* is upregulated like the case of formerly reported investigations of *B. henselae* co-cultures with Henrietta Lacks (HeLa) or endothelial cells[114], whereby the organism upregulates the expression of IL-8 in endothelial cell lines[115]. Practically, *Bartonella* species rise VEGF-C expression in connection with cutaneous vasoproliferative metastasis growth, which is also crucial for the melanoma growth factor (fig. 7)[116].

*B. fragilis* is gram-negative, obligatory anaerobic bacterium that colonizes the colon of humans and is considered as one of the normal commensals of human colon. *B. fragilis* is categorized into two classes based on the toxin production, as Non-Toxigenic *B. fragilis* (NTBF) and ETBF; latter produced *B. fragilis* Toxin (BFT) is encoded by a chromosomal gene[117].

*B. fragilis* fragilysin, commonly called BFT, is a 20 kDa zinc dependent metalloproteinase toxin which participated in colon carcinogensis *via* formation of biofilm and enteritis that adversely affects the intestinal epithelium tight junction, resulting in increased permeability of the intestine. It has been recognized that tissue injury mediated by chronic inflammation accelerates the carcinogenesis process in *B. fragilis* infected individuals[117].

Several different mechanisms (fig. 8) have been involved in colon carcinogenesis mediated by the induction of the cleavage of E-cadherin, T Cell Factor (TCF)-dependent β-catenin pathway, stimulation of IL-8 production leading to persistent proliferation of GIT epithelial cells (fig. 8). Further, BFT results in DNA damage, provokes the production of Reactive Oxygen Species (ROS) and proliferation of GIT epithelial cell *via* involvement of Spermine Oxidase (SMO) and cellular-Inhibitor of Apoptosis Protein 2 (c-IAP2)[119].

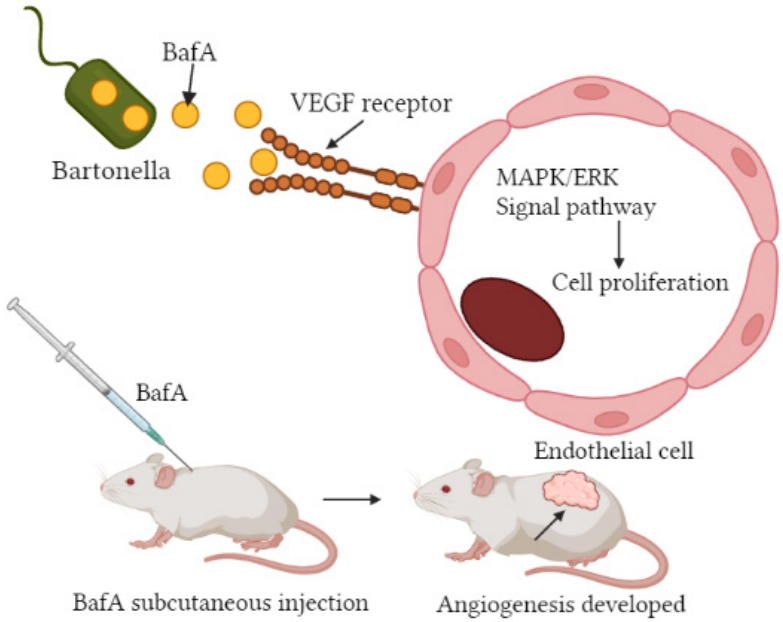


**Fig. 7: Mechanism of tumorigenesis linked with *Bartonella* infection**

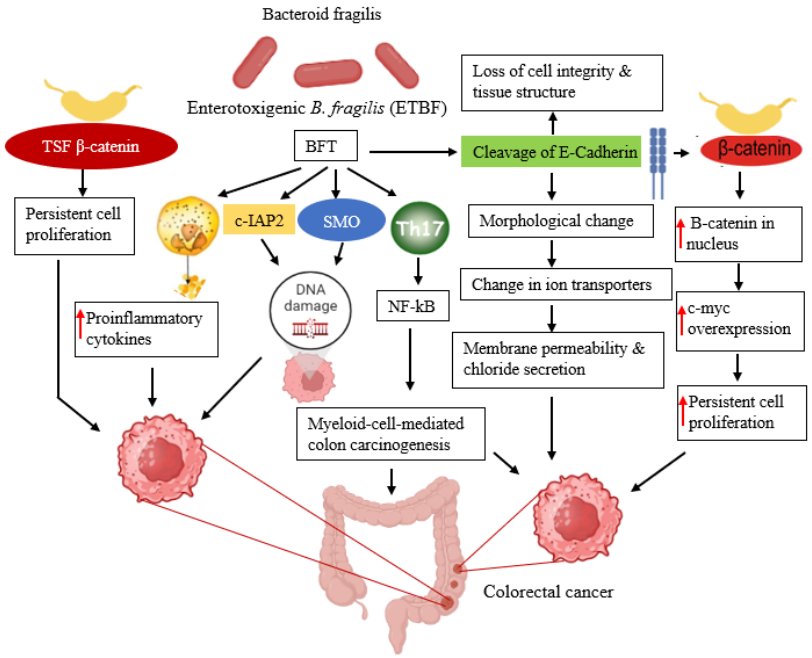


**Fig. 8: Mechanisms involved in BFT mediated colon carcinogenesis**

## CONCLUSION

The interaction between infectious agents and development of cancer has been investigated previously. However, there are inadequate research findings on the causal relationship between mutagenic bacteria and proposed tumorigenesis pathways. Except for some findings, the mechanism of action of how bacterial infections predispose individuals for different types of cancer is not clearly elucidated. This review discussed the interaction between bacterial infection and development of different types of cancer in humans. As we discussed, several clues were presented by different researchers supporting the etiological role bacterial infection for the progression of cancer in humans. Therefore, it is impossible to neglect the contribution of bacterial infection in cancer development. This study also provides an idea that the limitations of the diagnostic assays are key factors which hindered such interactions. Hence, more detailed investigations are needed to explore the underlying mechanisms of action of tumor formation in humans. Advanced research is needed to identify the bacterial metabolites and/or

bacterial specific proteins which facilite tumorigenesis process, for which highly sensitive as well as specific diagnostic assays would be needed.

To understand the actual interaction between different types of cancer and bacterial infections and/or their by-products, it would be crucial to follow-up patients with or without antibiotic interventions for a protracted period. Furthermore, *in vivo* and *in vitro* studies should be conducted to determine the mutagenic potential of bacterial pathogens and their associated precursors.

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**Conflict of interest:**

The authors declared no conflict of interests.

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