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**Gastrointestinal tumors and infectious agents: A wide field to explore**

López-Gómez M *et al*. Overview of pathogen-related malignancies

Miriam López-Gómez, Belén García de Santiago, Pedro-David Delgado-López, Eduardo Malmierca, Jesús González-Olmedo, César Gómez-Raposo, Carmen Sandoval, Pilar Ruiz-Seco, Nora Escribano, Jorge Francisco Gómez-Cerezo, Enrique Casado

**Miriam López-Gómez,** Medical Oncology Department. Precision Oncology Laboratory, Infanta Sofía University Hospital, San Sebastián de los Reyes 28231, Madrid, Spain

**Belén García de Santiago,** Pharmacy Department, Infanta Sofia University Hospital, San Sebastián de los Reyes 28703, Madrid, Spain

**Pedro-David Delgado-López,** Neurosurgery Department, Burgos University Hospital, Burgos 09006, Spain

**Eduardo Malmierca, Pilar Ruiz-Seco, Jorge Francisco Gómez-Cerezo,** Internal Medicine Department, Infanta Sofía University Hospital, San Sebastián de los Reyes 28703, Madrid, Spain

**Jesús González-Olmedo, César Gómez-Raposo, Carmen Sandoval, Enrique Casado,** Medical Oncology Department, Infanta Sofia University Hospital, San Sebastián de los Reyes 28703, Madrid, Spain

**Nora Escribano,** Intensive Care Unit, Jiménez Díaz Foundation, Madrid 28040, Madrid, Spain

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**Corresponding author: Miriam López-Gómez, PhD, Doctor,** Medical Oncology Department. Precision Oncology Laboratory, Infanta Sofía University Hospital, C/Paseo Europa 34, San Sebastián de los Reyes 28231, Madrid, Spain. miriam.lopez@telefonica.net

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**Abstract**

Infection is currently one of the main contributors to carcinogenesis. In fact, the International Agency for Research on Cancer has categorized eleven biological agents as group I carcinogens. It is estimated that around 16% of the 12.7 million new cancers diagnosed in 2008 were attributable to infectious agents. Although underdeveloped regions carry the highest incidence rates, about 7.4% of infection-related cancer cases occur in developed areas. Physicians are increasingly aware of the potential carcinogenic role of common virus like the Human Papilloma virus in cervical cancer, or the hepatitis B and C viruses in hepatocarcinoma. However, the carcinogenic role of several other infectious agents is less recognized. Given that gastrointestinal malignancies carry an overall poor prognosis, a better understanding of the carcinogenic mechanisms triggered by infectious agents is key to decrease the rate of cancer related deaths. Preventive measures directed to such infections would ideally impact survival. In this paper we review the main pathogenic mechanisms related to the development of gastrointestinal malignancies induced by infectious microorganisms and other pathogens which are currently under investigation.

**Key Words:** Gastrointestinal tumors; Infectious agents; Bacteria; Virus; Prevention

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**Core Tip:** Except for pathogens with well-known carcinogenic potential, such as Human Papilloma virus or Hepatitis C virus, physicians are usually unaware of the relationship among other infectious agents and tumors. The identification and subsequent eradication of these pathogens might help to prevent the development of a large number of tumors. Gastrointestinal malignancies are usually related to a very poor outcome. Therefore, detection of carcinogenic pathogens in this population might help to increase overall survival. Screening strategies and further research is required to face with these preventable diseases.

**INTRODUCTION**

During the last decades the causal relation between several pathogens and the onset of cancer has been firmly established[1]. However, the relationship between pathogens and cancer has been subject of research since the end of the XIX century. Rous[2,3] (1879-1970) discovered that sarcomas affecting domestic fowls could be transferred to other fowls through a viral vector, later known as Rous sarcoma virus (RSV). This finding was awarded with the Nobel Prize in 1966 and demonstrated for the first time in history that a malignant tumor could be induced by an infectious agent. In fact, the RSV was considered the first oncogenic retrovirus. Subsequently, other tumor-inducing viruses affecting animals were identified[4-6]. In 1964, the first oncogenic virus affecting humans, the Epstein Barr virus, was identified[7].

At present, a great effort is being done in order to elucidate the underlying connection between infectious agents and cancer. In 2018, an estimated 2.2 million infection-attributable cancer cases were diagnosed worldwide, corresponding to an age-standardized incidence rate (ASIR) of 25.0 per 100.000 person-years[8]. Currently, 11 infectious agents have been classified as Group 1 Carcinogens by the International Agency for Research on Cancer (IARC)[1]. *Helicobacter pylori* (*H. pylori*) (810.000 cases, ASIR 8.7), Human Papilloma virus (690.000, 8.0), Hepatitis B virus (360.000, 4.1) and hepatitis C virus (HCV) (160.000, 1.7) comprise the primary causes of infectious-related tumors, accounting for more than 90% of infection-related cancers worldwide[9].

**VIRAL INFECTIONS**

Viral chronic infection can promote cancer *via* three different pathogenic mechanisms:

(1) Induction of chronic inflammation provoked by the immune response to a persistent infection; HCV-related liver cancer is a paradigmatic example, in which persistence of viral replication within the liver parenchyma maintains a state of local chronic inflammation involved in cancer development[10]; (2) Virus-induced genome transformation secondary to viral persistence in infected cells; This mechanism is typically found in Epstein-Barr virus (EBV) associated Burkitt’s lymphoma. EBV replicating in the oral epithelium can transform resting B lymphocytes into proliferating lymphoblastoid cell lines involved in oncogenesis[11]; and (3) Promotion of chronic suppression of host immune response. Patients infected with the human immunodeficiency virus can be deeply immune-suppressed. These individuals exhibit an increased predisposition to develop infection-driven tumors as the mechanisms of immunosurveillance are disrupted by the viral replication[12].

Although these mechanisms may occur simultaneously[13], some other yet unknown need also be involved, since many other pathogens inducing similar immune alterations do not seem to induce cancer. It is widely recognized that viruses can cause cellular malignant transformation by inducing genetic instability. In fact, viruses are able to fuse their genome with that of the host resulting in activation of multiple oncogenes and intracellular signaling pathways leading to cellular proliferation, inflammation and immune dysregulation[14,15].

**BACTERIAL INFECTIONS**

Recent studies have shown that certain infectious agents like molds, helminths and bacteria, capable of interacting with mammalian host cells, can induce cancer, even in the absence of genomic alteration[16]. Unlike the well-established relation between viruses and carcinogenesis, the oncogenic role of bacterial infection remains controversial[17]. The molecular mechanisms by which bacteria might promote carcinogenesis are currently under research[10], and both bacterial and host factors seem to be involved. Bacterial cell-surface components, toxins and effector proteins can interact with host cells by activating essential signaling pathways involved in cancer formation[16].

***Role of bacterial surface antigens in carcinogenesis***

The bacterial surface exhibits several antigens that interact with the host and activate both innate and adaptative immune responses, allowing them to escape the host immune system. For example, gram-negative bacteria can coat their outer surface with a polysaccharide capsule, thus preventing the activation of the Complement cascade and the phagocytic process[18]. Other bacteria are able to modify some surface molecules, like lypo-polysaccharides, flagella and peptidoglycans, to avoid immune recognition[19]. Additionally, some other bacteria can express a variety of surface proteins that facilitate attachment to host cells and subsequent internalization[20]. These strategies aim to improve bacterial survival by eluding the immune response. However, definitive cellular malignant transformation needs to be induced by specific intracellular signaling cascade activation driven by certain bacterial molecules. For example, *H. pylori* can directly activate the RAS/mitogen activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway resulting in malignant transformation *via* the CagL protein (an adhesin molecule) that binds to the beta5-integrin expressed by host cells[21]; *H. pylori* also expresses the OipA protein that binds to the EGFR host receptor resulting in AKT and beta-catenin signaling activation, which also promotes carcinogenesis[22].

***Immune cell elimination***

To ensure survival among host cells, pathogenic bacteria have developed several strategies to attack the immune system. For example, they can secrete cytolytic toxins through their outer membranes that can affect the endosomal system. Bacterial toxins may induce carcinogenesis altering the host cell environment by inducing genome instability, promoting resistance to cell death signaling, and enhancing proliferative signaling[23].

**Induction of genome instability:** Bacterial toxins are capable of inducing host cell damage in the DNA double helix. Cytolethal Distending Toxin, Collibactin, Shiga toxin and endonucleases are some examples[24]. DNA damage causes immune host cells to arrest the cell cycle at the G1-S or G1-M stages.

**Resistance to cell death signaling and induction of proliferative signaling:**Toxins produced by some pathogens, like *Bacteroides fragilis*, can bind to intestinal epithelial cell receptors and induce cellular proliferation and differentiation. *Bacteroides fragilis* can silence the tumor suppressor protein E-Cadherin, resulting in the activation of beta-catenin/Wnt and nuclear factor kbeta (NF-kB) signaling pathway[25].

***Host cells transformation secondary to bacterial proteins***

To induce malignant transformation, bacteria must ensure a persistent infection within the cells of the new organism. They need to be internalized, must control their own growth and facilitate their release. Usual non-pathogenic bacteria are typically phagocyted in the phagosome, and then merged with the lysosome and turned into a phagolysosome, where they are finally destroyed. However, some bacteria have developed a number of mechanisms that avoid the formation of the phagolysosome, allowing them to freely enter the cytosol[26]; some bacteria, for example, secrete proteins that induce pore formation in the organelle[27]; while others have developed different mechanisms to avoid destruction inside the phagolysosome[28].

The ultimate explanation by which bacteria promote cancer and whether they obtain any survival advantage remains unknown. This is an interesting and fast-growing research field, in which prevention measures directed to infection may impact overall cancer development. The oncogenic role of various infectious agents regarding gastrointestinal tract malignancies are now described. Since these tumors carry relevant mortality rates, screening programs directed to identify such pathogens may be beneficial.

**ESOPHAGEAL CANCER**

The incidence of esophageal tumors differs substantially across countries. The highest rates are found in Southern and Eastern Africa and Eastern Asia. Although the histopathological squamous variant has been associated to several viral subtypes, the pathogenic role of viruses in the development of adenocarcinoma is yet unclear.

***Human papilloma virus***

HPV family viruses are non-enveloped DNA tumor viruses transmitted by sexual contact. More than 100 subtypes of HPV have been described, of which at least 14 carry a significantly increased risk of tumor development [29]. HPV infects epithelial cells and is able to integrate itself inside the host genome. Some oncoproteins produced by the virus (mainly E6 and E7) alter tumor suppressor pathways and promote malignant proliferation[30]. In 1982, Syrjänen *et al*[31] observed the typical morphological lesions present in HPV related-condylomas in both benign and cancerous esophageal tissues. These findings supported the hypothesis that HPV was involved in the pathogenesis of esophageal malignancies. Subsequent immunohistochemical studies demonstrated that HPV structural proteins were present in malignant lesions of patients from different continents[32]. In fact, the oncogenic potential role of HPV in the development of squamous esophageal carcinoma has been the subject of several metanalysis[33-35]. The first metanalysis of case-control studies investigating the role of HPV in esophageal tumors was conducted in 2013 by Liyanage *et al*[36]. They gathered 21 studies, including 1223 patients and 1415 controls. The authors calculated a pooled OR for HPV and squamous esophageal tumors of 3.04 [95% confidence interval (CI): 2.20 to 4.20]. Noticeably, countries with a low to medium esophageal cancer incidence showed a stronger relationship (OR 4.65, 95%CI: 2.47 to 8.76) than regions with higher incidence (OR 2.65, 95%CI: 1.80 to 3.91). The authors concluded that HPV infection was associated with a 3-fold risk of squamous esophageal cancer and made an urgent call to the IARC to promote the use of vaccines against HPV in high-risk populations.

In 2016, Wang *et al*[37] published a systematic review and meta-analysis on the association between HPV 16 and 18 subtypes and esophageal cancer worldwide. They included 32 studies and showed that HPV infection rate in the tumoral cohort was 46.5% *vs* 26.2% in controls (OR = 1.62; 95%CI: 1.33–1.98), providing strong epidemiologic evidence supporting the association between HPV infection and esophageal tumors[37].

***EBV***

EBV is an oncogenic virus that belongs to the gamma-herpes virus family. It is a widespread pathogen carried by 95% of the population worldwide. Fortunately, the majority of EBV infections are subclinical[38]. Although, the EBV typically infects B lymphocytes, recent research has shown that it can also infect epithelial cells, and suggests a potential association with esophageal carcinoma, yet to be confirmed. Jenkins *et al*[39] detected for the first time EBV in esophageal tumors, however, only in 5 out of 60 tumors. Awerkiew *et at*[40] demonstrated the presence of EBV-DNA in 35% of squamous cell carcinomas and 36% of adenocarcinomas, using nested polymerase chain reaction (PCR) diagnostic techniques.

In areas with higher incidence of esophageal carcinoma, the association between EBV and esophageal cancer has been investigated. Wu *et al*[41] studied the coinfection of EBV and Herpes Simplex virus (HSV) and detected, by in situ hybridization and immunohistochemistry, the EBER and LMP-1 proteins in 6.1% of carcinoma specimens, preferentially among poorly differentiated squamous cell carcinomas and undifferentiated carcinomas with intense lymphoid infiltration. Other authors have contributed to elucidate the role of EBV in the carcinogenesis of esophageal carcinoma[42,43]. In summary, EBV infection has been related to the etiology of some variants of esophageal carcinoma, at least in countries with increased prevalence. However, more studies are needed to establish the exact pathogenic role of EBV in esophageal carcinogenesis.

***Herpes simplex and Citomegalovirus***

HSV-1 infection occurs mainly in the mouth and has been related to oral cancer[44]. Citomegalovirus (CMV), a common human pathogen has been associated with cervical and non-melanoma skin cancer[45,46]. Zhang *et al*[42] reported an increased predisposition of esophageal carcinoma in patients infected with HSV-1 (OR 10.3 with 95%CI: 3.3‑31.6). HSV infection is primarily related to esophagitis, which usually precedes esophageal carcinoma. However, no CMV was detected in any of the samples[42]. Wu *et at*[41] found HSV DNA and HSVI, II protein expression in 52 (31.7%) of the 164 tumors analyzed supporting the relationship between HSV and esophageal carcinoma cell differentiation with lymphocyte infiltration in the tumoral stroma. However, other authors have failed to demonstrate the relation between HSV/CMV and esophageal carcinoma, therefore leaving the question open[47].

**GASTRIC CANCER**

***H. pylori***

Gastric cancer can be generally classified in cardia (upper stomach) and non-cardia (lower stomach) subtypes. These entities differ in terms of risk factors, carcinogenesis and epidemiologic patterns. Chronic *H. pylori* infection is considered the principal cause of non-cardia gastric cancer, being nearly all cases attributed to this bacterium[48,49]. The worldwide prevalence of *H. pylori* infection is extraordinarily high, affecting around 50% of population[50], and its geographic variability correlates with the incidence of gastric cancer. Yet, less than 5% of infected persons will develop cancer, likely because of differences in bacterial and host genetics, age of infection and environmental factors[51]. In 1994, the World Health Organization categorized *H. pylori* as a Carcinogen type I for gastric cancer on the basis of observational studies reported from the International Agency for Research in Cancer[52].

*H. pylori* infection has been associated with an increased risk of all variants of adenocarcinoma, whether diffuse or intestinal, and whether located in the body of the stomach or in the antrum; actually, it is related to tumors distal to the cardia. Conversely, tumors growing in the esophagogastric junction, usually arising from the altered mucosa in Barrett’s esophagus, have not been linked to *H. pylori* infection[53].

*H. pylori* survives in the gastric acid microenvironment, being able to damage the mucosa. It induces a chronic inflammatory response that results in chronic gastritis and peptic ulceration. Development of gastric cancer is one of the long-term consequences of *H. pylori* infection[54]. Chronic *H. pylori* infection has been also related to gastric MALT (Mucosa associated Lymphoma), which is an extra-node lymphoma variant consisting of a morphologically heterogenous small B cells neoplasm[55].

*H. pylori* is able to dysregulate host signaling pathways and to promote oncogenesis by two main mechanisms: Citotoxin-associated gene A (CagA) and its pathogenic island (Cag PAI); and vacuolating cytotoxin A (VacA). CagA *H. pylori*-protein is encoded by one of the genes located in the CagPAI island. CagA binds to the ectodomain of alfa5beta1 integrin allowing its internalization. Once it has been translocated, CagA binds to the inner surface of the cell membrane and undergoes tyrosine phosphorylation. Both the phosphorylated CagA and the unphosphorylated CagA can interact with a number of host proteins to activate downstream signaling pathways such as the RAS/MEK/ERK pathway, the NF-kB pathway, and the beta-catenin pathway. Such pathways activation enhances the proliferation of gastric epithelial cells[56,57].

The VacA is secreted by *H. pylori* and has a variety of biological functions. It binds to host cells and is internalized creating vacuoles (large vesicles) inside the host cells. This *vacuolization* process leads to the activation of endosomes and early lysosomes. Additionally, VacA can also be transferred to the mitochondria where it alters the membrane barrier that releases cytochrome c which finally activates the pro-apoptotic factor Bcl-2 associated X protein (Bax) leading to apoptosis. Therefore, the alteration of the membrane impermeabilization ends up in preventing apoptosis of gastric cells[58]. Inside the mitochondria, VacA can also activate the dynamic related protein 1 which inhibits the activation of Bax mitochondria outer membrane impermeabilization that prevents death by apoptosis[59]. Further, it can also disrupt the gastric epithelial cell-to-cell unions, which prevents T lymphocyte activation and proliferation in the lamina propria, and ultimately induces inflammation and carcinogenesis by disrupting autophagy in gastric cells[60].

In addition, *H. pylori* induces a chronic inflammatory state by upregulating many pro-inflammatory cytokines, like IL-1, IL-6, IL-8, TNF-alfa, and NF-kB[61]. Among them, activation of NF-kB and upregulation of IL-8 are crucial[62]. Suppressor gene P53 also plays an important role in gastric inflammation and carcinogenesis. Mutations of p53 have been related to the development of gastric cancer. In fact, inactivation of p53 gene is present in 40% of gastric tumors and has been specifically found in patients infected with the CagA positive strain of *H. pylori*[63]. *H. pylori* infection has also been related to epigenetic modification during gastric carcinogenesis by promoting hypermethylation of O6-mehylguanine DNA methyltransferase (MGMT). MGMT protein is essential for the repair of O6-methylguanine, which prevents mutations during DNA replication. Therefore, reduced levels of MGMT can increase mutagenesis in the gastric epithelium[64]. Finally, *H. pylori* has been linked to the oxidative stress that promotes DNA damage in gastric tissue by stimulating the production of intracellular reactive oxygen and nitrogen species in gastric tissues, which can damage DNA tumor suppressor genes like p53 and contribute to gastric carcinogenesis[65].

In summary, the *H. pylori* infection is one of the leading factors in the development of gastric carcinoma. Chronic inflammation induced by *H. pylori* is related to cell proliferation, apoptosis, epigenetic changes of tumor suppressor genes, and alterations of the oxidative stress mechanisms. Eradication of *H. pylori*, especially in endemic areas, should be a healthcare priority in order to decrease gastric cancer-related casualties.

**GALLBLADER CANCER**

Gallbladder cancer (GC) is a common hepatobiliary malignancy that carries very poor prognosis. It is the fifth commonest gastrointestinal tract cancer and is endemic is several countries, with the highest incidence rate reported in Delhi (India), Pakistan and Quito (Ecuador). It shows female preponderance[66], and genetic, infectious, and lifestyle factors have been associated with GC[67]. Infection leads to chronic gallbladder inflammation that seems to contribute to carcinogenesis. Two species- Salmonella Typhi and Helicobacter Pylori- and a liver parasite -Clonorchis sinensis-, among others, have been specifically linked to GC.

***Salmonella Typhi***

The association between chronic typhoid infection and GC was first reported in 1971[68] and confirmed by ulterior studies. For example, in 1964, during the typhoid outbreak in Aberdeen (Scotland), Caygill *et al* studied the mortality rate of infected population and reported a 6% of risk of death attributable to GC among chronic carriers[69].

Further studies from Northern India reported a 7.9-fold increased risk of GC among infected persons. Species of Salmonella typhi and paratyphi-A could be isolated from bile, gallbladder tissue and stones in patients with GC. Bacterial serologic detection was related to a 9.2-fold increased risk of developing GC.

Another study from India, using nested PCR technique in hepatobiliary specimens, detected a 67.3% of typhoid carriers among GC patients compared to 8.3% of controls. The authors concluded that the liver served as a preferential survival niche for *Salmonella* Typhi (*S*. Typhi)[70]. As *Salmonella* spp. are excreted in the gallbladder, the multiplying bacteria secrete toxins and metabolites that favor mutational changes. Several carcinogens have been proposed: bacterial glucuronidase, bacterial enzymes and the production of nitrous compounds from nitrates[71,72].

Additionally, *S*. Typhi produces a genotoxin, the cytolethal distending toxin (CDT) that allows bacteria to internalize inside the host cells. Then, they are able to avoid the usual endocytic pathway that leads to the formation of destructive lysosomes and finally reaches a specific intracellular compartment where it can survive and replicate[73]. Once in the cytosol, the CDT facilitates the persistence of infection thanks to its immunomodulatory activity. Later on, it can reach the nucleus causing irreversible DNA damage[74].

***Helicobacter spp.***

*H. bilis*, *H. pullorum*, *H. hepaticus,* and *H. pylori* have been suspected to cause biliary tract diseases. *Helicobacter* spp. cause persistent infection in the biliary tract inducing chronic inflammation and gallstone formation, mainly *via* urease production[75,76]. *Helicobacter* spp. can produce several carcinogenic toxins and metabolites that initiate malignant cell transformation within the gallbladder[77]. Helicobacter bilis specific DNA sequences have been amplified in 27.2% of gallbladder and in 33.3% of biliary duct cancers[77].

***Escherichia coli***

*Escherichia coli* (*E. coli*) is part of the regular human intestinal microbiota but may become highly pathogenic following the acquisition of virulence factors, like the cytotoxic necrotizing factor I -CDT I-. The presence of genotoxin colibactin, related to *E. coli* infection, is known to be capable of inducing double stranded DNA breaks[10].

***Opisthorchis viverrini* and *Clonorchis sinensis***

Liver fluke *Clonorchis sinensis* (*C. sinensis*) is a high-risk pathogenic parasitic helminth endemic in some Asian countries. This parasite is classified among the Group I of human carcinogens by the IARCC[1]. Fresh water snails and several species of fish serve as secondary intermediate hosts. Humans and other fish-eating animals are infected through the ingestion of raw or undercooked freshwater fish that contains meta-cercariae. After ingestion, the meta-cercaria excysts in the duodenum and ascends the biliary tract through the ampulla of Vater[78].

Infection with *Opisthorchis viverrini* has been related to cholangiocarcinoma upon the results of several cross-sectional and case-control studies[79]. The association between *C. sinensis* infection and cholangiocarcinoma is even better substantiated and the IARCC has already classified it as a probable carcinogenic for humans (Group 2A)[80,81].

Liver fluke pathogens cause mechanical injury and inflammation in the biliary tree, leading to metaplasia of mucin-producing cells, periductal fibrosis and hyperplasia of epithelial cells[82]. The severity of these changes correlates with the duration of the infection, the parasite load and the susceptibility of the host. The molecular mechanisms involved in the development of cholangiocarcinoma are poorly known, and a multistep process has been proposed: chronic inflammation damages cholangiocytes which in turn promotes cell proliferation and genetic and epigenetic mutations, finally transforming cholangiocytes into malignant cells[83]. Other carcinogenetic mechanisms include genomic instability, transcriptomic, proteomic and microRNA profile alterations and dysregulation of immune response.

**LIVER CANCER**

Worldwide, liver cancer is the sixth most common cancer, yet the second leading cause of cancer-related death in men, with 745000 deaths per year[84]. Hepatocellular carcinoma (HCC) represents approximately 90% of all primary liver cancers. It preferentially affects males and presents a wide geographical variation. However, chronic Hepatitis B virus and HCV infections are the leading cause of HCC, being responsible for 60%-80% of all these tumors worldwide, especially in developing countries.

Hepatitis B virus (HBV) is a partially double-stranded DNA virus that replicates *via* reverse transcription. It is highly contagious and is transmitted by percutaneous and permucosal exposure to infected blood and other body fluids. HBV particles package the incomplete double-stranded DNA into the nucleus of the host, where the virus is recognized as damaged and induces a DNA repair response, resulting in virus replication[85]. Chronic HBV infection is one of the leading causes of HCC worldwide. HBV typically replicates inside the hepatocytes. Virions bind to the surface of the hepatocytes and the nucleocapsid is released into the cytoplasm and translocated by microtubules to the microtubule-organizing center near the nucleus. Once inside the nucleus, HBV can lead to histone degradation, which enhances chromatin dynamics and may promote genetic instability, chromosomal alterations, and can also initiate oncogene mutation[86]. However, HBV integration into the hepatocytes occurs randomly -at one or multiple sites- and occasionally may promote direct oncogene activation or inactivate tumor suppressor genes[87]. While viral integration is an early event, selective clonal amplification of hepatocytes occurs throughout progression of the disease[88]. It is known that both the HBV-encoded envelope and the regulatory HBx protein directly contribute to hepatocyte transformation: HBx regulates expression of many genes involved in signal transduction pathways, cell cycle control, metastases, and avoidance of immune response. Several cohorts and case-control studies have assessed the risk of HCC among individuals infected with HBV[89,90]. The ability of antivirals to inhibit HCC progression is limited, likely because hepatocarcinogenesis seems to occur prior to the onset of liver fibrosis/cirrhosis. Therefore, once the disease is established, there is no turning back.

HCV is a single-stranded, positive sense RNA virus that encodes a single polyprotein that can form structural -which constitute the viral particle, such as the core protein- and non-structural proteins which support viral genomic replication. Seven genotypes have been described. Epidemiological studies show than infection with genotypes 1b and 3 is associated with an increased risk of developing HCC[91]. HCV replicates in the cytoplasm of hepatocytes and is unique among cancer-causing viruses by not encoding oncoproteins or integrating its genome into the host chromosomal DNA. In fact, HCV core genes variants have been associated with HCC even in patients in which the infection had already disappeared[92]. This suggests that viral factors influence progressive liver disease. HCV associated carcinogenesis includes increased hepatocyte proliferation and steatosis; virus-induced inflammation and oxidative stress which induces genomic mutations and genome instability; mitochondrial damage and induction of reactive oxygen species; and inhibition of host immune responses[93]. HCC is associated with the development of multifocal, genetically distinct tumors throughout the liver, suggesting that the entire organ is altered.

**COLON CANCER**

Colorectal cancer is the leading cause of mortality regarding gastrointestinal neoplasms worldwide[94]. Pathogenic microorganisms able to induce intestinal dysbiosis have become the spotlight of current research in this area, as they carry the potential for colorectal tumorigenesis. Fusobacterium nucleatum, *E. coli*, *Bacterioides fragilis* (*B. fragilis*) and *Salmonella enterica* (*S. enterica*) have been reported as high-risk oncogenic pathogens.

***Fusobacterium nucleatum***

*Fusobacterium nucleatum* (*F. nucleatum*) is an adherent and invasive Gram-negative anaerobic bacterium frequently found in the oral cavity. Current research relates *F. nucleatum* to the development and progression of colon cancer, and has been found in primary lesions and stools of patients with colon cancer[95], especially those located in the cecum and rectum[96]. Tumoral cells over-express Gal-GalNAc molecules, which promote bacterial adhesion through the Fap2 protein[97].

Additionally, *F. nucleatum* infection has been related to a decreased survival rate among colon cancer patients and an increased resistance to chemotherapy agents[98,99]. The presence of *F. nucleatum* in colon cancer patients varies worldwide, ranging from 15% in North American to 60% in Chinese patients[100]. Interestingly, tumors infected with *F. nucleatum* show three similarities: they are microsatellite unstable, show a methylation phenotype of CpG island, and exhibit mutations in the BRAF/KRAS genes[101]. Microsatellite instability is responsible for the ability of infected cells to elude the immune response[102] and has also been related to the activation of beta-catenin signaling pathway, commonly unregulated in colon cancer[103]. *F. nucleatum* also promotes inflammation, by increasing TNF-alfa and IL-10 Levels in adenomas and Il-6 and IL-8 in carcinomas, both regulated by the NF-kB transcription factor[104].

***E. coli***

*E. coli* is a widely distributed Gram-negative bacterium that can alter the intestinal microbiome. The B2 *E. coli* strains have been related to colon cancer[105]. *E. coli* promotes colon pathologic inflammation -as in Chron’s disease- which seems to be a relevant factor in colon cancer formation[106]. However, the exact role of *E. coli* in the pathogenesis of colon cancer is not completely known. Recent studies have identified two potentially pathogenic *E. coli* strains: Adherent-invasive *E. coli* (AIEC) and enteropathogenic *E. coli* (EPEC). During infection, AIEC binds to CEACAM6 (a cellular adhesion receptor associated to carcinoembryonic antigen- CEA- which is overexpressed in colon cancer cells[107]. Infection stimulates IL6 production, which together with the increased expression of CEACAM6 can promote carcinogenesis. AIEC also secretes colibactin, a secondary metabolite associated to DNA damage acting as an alkylating agent and promoting tumor development[108]. EPEC is thought to stimulate macrophage-inhibitory cytokine-1 production - a cytokine related to metastasis- and inducing autophosphorylation of EGFR receptor[109,110]

***B. fragilis***

The *Bacteroides* spp. are regularly found in the human intestine and comprises 30% of the microbiota[111]. *B. fragilis* is an anaerobic Gram-negative bacterium colonizing about 0.5%-2% of the entire human intestine. A toxigenic *B. fragilis* strain -also known as ETBF- has a pathogenicity island encoding a metalloproteinase, the *B. fragilis* toxin (BFT) which is associated to increased inflammatory bowel disease and colitis, both considered high risk factors to develop colon cancer[112]. *B. fragilis* has also been detected in stool from cancer patients. Although the exact role of enterotoxigenic *B. fragilis* has not been completely described, it is believed that carcinogenesis is either induced by BFT toxin secretion or through host immune system dysregulation[113]. It can also trigger carcinogenesis through the beta catenin pathway activation by disrupting the adherent e-cadherin gap unions[114]

***S. enterica***

*S. enterica* includes serotypes of Salmonella typhi, Salmonella paratyphi, Salmonella enteritidis and Salmonella typhimurium. In recent years, it has been found that bacteria may modulate host immune response in two different ways: First, it can promote carcinogenesis inducing both DNA damage and increasing cell abnormal proliferation; and second, it can induce cell migration as a result of chronic inflammation[17].

Two proteins of *S. enterica* have been associated with an increased risk of developing colon cancer: typhoid toxin and AvrA effector protein. Typhoid toxin is a cyclomodulin that, similar to *E. coli* CDT, increases cell survival and promotes intestinal dysbiosis, resulting in the development of inflammatory bowel disease and colon cancer[115,116]. AvrA is secreted by bacteria and has been found in stool samples from colon cancer[117]. AvrA may promote inflammatory and immune dysregulation through several mechanisms: the inhibition of NF kappa-beta signaling pathway, the inhibition of IL-12, INF-c and TNF-α secretion, the inhibition of IL-6 transcription, and the increase of IL-10 transcription[118,119]. On the other hand, AvrA might also activate the Wnt/β catenin pathway inducing cellular proliferation, by both β catenin phosphorylation and deubiquitination[120].

**ANAL CANAL**

Anal cancer refers to the malignancy of the intestinal mucosa arising in the anatomic anal canal, defined as beginning at the dentate line and ending at the anal verge. Eighty-five percent of anal tumors are of squamous cell origin, approximately 10% are adenocarcinomas, and the remaining 5% are other neoplasms (melanoma, small cell carcinoma…)[121]. Although it comprises 2.7% of all gastrointestinal malignancies, anal cancer incidence has been increasing over the last few decades[122].

As previously highlighted in the paper, HPV are small DNA viruses that infect various epithelial tissues. They also include the anogenital tract, and HPV is recognized as the causative agent of more than 80% of cases of anal cancer[123]. The difference in their ability to promote malignant transformation is the basis for the classification of HPV into low and high-risk variants. Mainly two HPV oncogenic subtypes, 16 and 18, are related to the development of squamous anal cancer[124]. HPV can integrate into the host DNA. Epithelial cells that harbor integrated HPV 16 DNA have a selective growth advantage over cells that carry normal extrachromosomal viral genomes; this growth advantage correlates with the increased expression of two viral genes in particular, E6 and E7[125]. The early proteins, E6 and E7, bind and inactivate the tumor-suppressor gene p53, and the retinoblastoma tumor-suppressor protein (pRb), respectively[126-128].

**GUT MICROBIOTA**

Most of the literature summarized in the present paper has been published previous to 2016 as research over the last years is focused in the role of gut microbiota in human carcinogenesis. Although it is not the scope of our review, we cannot conclude our review without summarizing intestinal microbiota key points. Gut microbiota consists of viruses, fungi and more than 1000 bacteria which are crucial for maintaining the gut barrier, metabolism and immunity. Disruption of the host relationship with the microbiota might result in oxidative stress, chronic inflammation and dysbiosis which can finally promote carcinogenesis[129]. The influence of gut microbiota relies mainly on cancers in the gastrointestinal tract, and the regulation of microbiota by diet, prebiotics, probiotics, symbiotics and antibiotics are proposed as new strategies to be explored in the future[130]. Gut microbiota is thought to play an important role in colon -stool samples of patients with CRC have higher proportions of Escherichia and Fusobacterium and lower concentrations of Firmicutes and Actinobacteria[131], HCC[132] and GC[133], Interactions between gut microbiota and GI cancers are likely to yield new opportunities to reduce cancer morbidity and mortality (Table 1).

**CONCLUSION**

Cancers arise from the transformation of a single cell so that its behavior is no longer under the control of normal regulatory pathways. The relationship between some pathogens and gastrointestinal tumor carcinogenesis has been well stablished. However, this relation is difficult to determine with many other agents as cancer is a multistep process. Besides, the presence of bacteria at the site of a tumor does not itself implies causation. There is a long time period between the onset of carcinogenesis and the development of overt disease, and randomized studies are expensive and extremely difficult to make (one cannot, for example, infect a person with an agent and then wait to see if cancer develops). However, the occurrence of cancer attributable to infections is a global concern especially in underdeveloped regions. Chronic infections can mimic precancerous lesions that could be treated with antibiotics or antiviral treatment and therefore prevent the onset of carcinogenesis. Greater understanding of the consequences of long-term infections will help to elucidate the exact pathogenic processes involved in the development of some pathogen-related neoplasms. Preventive measures (like vaccines and antimicrobial agents) aimed to eradicate these oncogenic microorganisms should ideally interrupt the carcinogenetic pathways and avoid the formation of a relevant proportion of gastrointestinal cancers. Only global effort and an international strategy might help to decrease gastrointestinal cancer related deaths secondary to infectious pathogens. New molecular techniques are needed to identify new infectious agents in tissues. However, caution is requested not to overemphasize the association between pathogens and gastrointestinal malignancies without a proper causation proof.

**REFERENCES**

1 **IARC Working Group on the Evaluation of Carcinogenic Risks to Humans.** Biological agents. Volume 100 B. A review of human carcinogens. *IARC Monogr Eval Carcinog Risks Hum* 2012; **100**: 1-441 [PMID: 23189750 DOI: 10.1016/0753-3322(90)90146-z]

2 **Rous P**. A Transmissible avian neoplasm. (sarcoma of the common fowl). *J Exp Med* 1910; **12**: 696-705 [PMID: 19867354 DOI: 10.1084/jem.12.5.696]

3 **Rous P**. A sarcoma of the fowl transmissible by an agent separable from the tumor cells. *J Exp Med* 1911; **13**: 397-411 [PMID: 19867421 DOI: 10.1084/jem.13.4.397]

4 **Shope RE**, Hurst EW. Infectious papillomatosis of rabbits: With a note on the histopathology. *J Exp Med* 1933; **58**: 607-624 [PMID: 19870219 DOI: 10.1084/jem.58.5.607]

5 **Bittner JJ**. The milk-influence of breast tumors in mice. *Science* 1942; **95**: 462-463 [PMID: 17736889 DOI: 10.1126/science.95.2470.462]

6 **Sweet BH**, Hilleman MR. The vacuolating virus, S.V. 40. *Proc Soc Exp Biol Med* 1960; **105**: 420-427 [PMID: 13774265 DOI: 10.3181/00379727-105-26128]

7 **Epstein MA**, Achong BG, Barr YM. virus particles in cultured lymphoblasts from burkitt's lymphoma. *Lancet* 1964; **1**: 702-703 [PMID: 14107961 DOI: 10.1016/s0140-6736(64)91524-7]

8 **de Martel C**, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. *Lancet Glob Health* 2020; **8**: e180-e190 [PMID: 31862245 DOI: 10.1016/S2214-109X(19)30488-7]

9 **Plummer M**, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. *Lancet Glob Health* 2016; **4**: e609-e616 [PMID: 27470177 DOI: 10.1016/S2214-109X(16)30143-7]

10 **Lax AJ**, Thomas W. How bacteria could cause cancer: one step at a time. *Trends Microbiol* 2002; **10**: 293-299 [PMID: 12088666 DOI: 10.1016/s0966-842x(02)02360-0]

11 **Shaklawoon K**, Altagazi N, Altorjman F, Alturki A, Eltaweel M, Alqawi O. Molecular detection of Epstein-Barr virus in different types of lymphoma. *Mol Biol Rep* 2020; **47**: 1803-1807 [PMID: 31993862 DOI: 10.1007/s11033-020-05274-0]

12 **Nasti G**, Vaccher E, Errante D, Tirelli U. Malignant tumors and AIDS. *Biomed Pharmacother* 1997; **51**: 243-251 [PMID: 9309244 DOI: 10.1016/S0753-3322(97)83539-1]

13 **Dalton-Griffin L**, Kellam P. Infectious causes of cancer and their detection. *J Biol* 2009; **8**: 67 [PMID: 19678917 DOI: 10.1186/jbiol168]

14 **Neuveut C**, Wei Y, Buendia MA. Mechanisms of HBV-related hepatocarcinogenesis. *J Hepatol* 2010; **52**: 594-604 [PMID: 20185200 DOI: 10.1016/j.jhep.2009.10.033]

15 **Münger K**, Baldwin A, Edwards KM, Hayakawa H, Nguyen CL, Owens M, Grace M, Huh K. Mechanisms of human papillomavirus-induced oncogenesis. *J Virol* 2004; **78**: 11451-11460 [PMID: 15479788 DOI: 10.1128/jvi.78.21.11451-11460.2004]

16 **van Elsland D**, Neefjes J. Bacterial infections and cancer. *EMBO Rep* 2018; **19** [PMID: 30348892 DOI: 10.15252/embr.201846632]

17 **Kuper H**, Adami HO, Trichopoulos D. Infections as a major preventable cause of human cancer. *J Intern Med* 2000; **248**: 171-183 [PMID: 10971784 DOI: 10.1046/j.1365-2796.2000.00742.x]

18 **Pluschke G**, Mayden J, Achtman M, Levine RP. Role of the capsule and the O antigen in resistance of O18:K1 Escherichia coli to complement-mediated killing. *Infect Immun* 1983; **42**: 907-913 [PMID: 6196296 DOI: 10.1128/iai.42.3.907-913.1983]

19 **Mattsby-Baltzer I**, Mielniczuk Z, Larsson L, Lindgren K, Goodwin S. Lipid A in Helicobacter pylori. *Infect Immun* 1992; **60**: 4383-4387 [PMID: 1398948 DOI: 10.1128/iai.60.10.4383-4387.1992]

20 **Popp A**, Billker O, Rudel T. Signal transduction pathways induced by virulence factors of Neisseria gonorrhoeae. *Int J Med Microbiol* 2001; **291**: 307-314 [PMID: 11680791 DOI: 10.1078/1438-4221-00134]

21 **Wiedemann T**, Hofbaur S, Tegtmeyer N, Huber S, Sewald N, Wessler S, Backert S, Rieder G. Helicobacter pylori CagL dependent induction of gastrin expression via a novel αvβ5-integrin-integrin linked kinase signalling complex. *Gut* 2012; **61**: 986-996 [PMID: 22287591 DOI: 10.1136/gutjnl-2011-300525]

22 **Tabassam FH**, Graham DY, Yamaoka Y. Helicobacter pylori activate epidermal growth factor receptor- and phosphatidylinositol 3-OH kinase-dependent Akt and glycogen synthase kinase 3beta phosphorylation. *Cell Microbiol* 2009; **11**: 70-82 [PMID: 18782353 DOI: 10.1111/j.1462-5822.2008.01237.x]

23 **Rosadi F**, Fiorentini C, Fabbri A. Bacterial protein toxins in human cancers. *Pathog Dis* 2016; **74**: ftv105 [PMID: 26534910 DOI: 10.1093/femspd/ftv105]

24 **Guerra L**, Carr HS, Richter-Dahlfors A, Masucci MG, Thelestam M, Frost JA, Frisan T. A bacterial cytotoxin identifies the RhoA exchange factor Net1 as a key effector in the response to DNA damage. *PLoS One* 2008; **3**: e2254 [PMID: 18509476 DOI: 10.1371/journal.pone.0002254]

25 **Wu S**, Powell J, Mathioudakis N, Kane S, Fernandez E, Sears CL. *Bacteroides fragilis* enterotoxin induces intestinal epithelial cell secretion of interleukin-8 through mitogen-activated protein kinases and a tyrosine kinase-regulated nuclear factor-kappaB pathway. *Infect Immun* 2004; **72**: 5832-5839 [PMID: 15385484 DOI: 10.1128/IAI.72.10.5832-5839.2004]

26 **Fredlund J**, Enninga J. Cytoplasmic access by intracellular bacterial pathogens. *Trends Microbiol* 2014; **22**: 128-137 [PMID: 24530174 DOI: 10.1016/j.tim.2014.01.003]

27 **Senerovic L**, Tsunoda SP, Goosmann C, Brinkmann V, Zychlinsky A, Meissner F, Kolbe M. Spontaneous formation of IpaB ion channels in host cell membranes reveals how Shigella induces pyroptosis in macrophages. *Cell Death Dis* 2012; **3**: e384 [PMID: 22951981 DOI: 10.1038/cddis.2012.124]

28 **Nagai H**, Kagan JC, Zhu X, Kahn RA, Roy CR. A bacterial guanine nucleotide exchange factor activates ARF on Legionella phagosomes. *Science* 2002; **295**: 679-682 [PMID: 11809974 DOI: 10.1126/science.1067025]

29 **World Health Organization.** Human papillomavirus (HPV) and cervical cancer. [cited 15 March 2021]. Available from: https://www.who.int/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer2020

30 **von Knebel Doeberitz M**, Oltersdorf T, Schwarz E, Gissmann L. Correlation of modified human papilloma virus early gene expression with altered growth properties in C4-1 cervical carcinoma cells. *Cancer Res* 1988; **48**: 3780-3786 [PMID: 2837324]

31 **Syrjänen K**, Pyrhönen S, Aukee S, Koskela E. Squamous cell papilloma of the esophagus: a tumour probably caused by human papilloma virus (HPV). *Diagn Histopathol* 1982; **5**: 291-296 [PMID: 6188592]

32 **Hille JJ**, Margolius KA, Markowitz S, Isaacson C. Human papillomavirus infection related to oesophageal carcinoma in black South Africans. A preliminary study. *S Afr Med J* 1986; **69**: 417-420 [PMID: 3008356]

33 **Hardefeldt HA**, Cox MR, Eslick GD. Association between human papillomavirus (HPV) and oesophageal squamous cell carcinoma: a meta-analysis. *Epidemiol Infect* 2014; **142**: 1119-1137 [PMID: 24721187 DOI: 10.1017/S0950268814000016]

34 **Petrick JL**, Wyss AB, Butler AM, Cummings C, Sun X, Poole C, Smith JS, Olshan AF. Prevalence of human papillomavirus among oesophageal squamous cell carcinoma cases: systematic review and meta-analysis. *Br J Cancer* 2014; **110**: 2369-2377 [PMID: 24619077 DOI: 10.1038/bjc.2014.96]

35 **Zhu C**, Ling Y, Dong C, Zhou X, Wang F. The relationship between oral squamous cell carcinoma and human papillomavirus: a meta-analysis of a Chinese population (1994-2011). *PLoS One* 2012; **7**: e36294 [PMID: 22570701 DOI: 10.1371/journal.pone.0036294]

36 **Liyanage SS**, Rahman B, Ridda I, Newall AT, Tabrizi SN, Garland SM, Segelov E, Seale H, Crowe PJ, Moa A, Macintyre CR. The aetiological role of human papillomavirus in oesophageal squamous cell carcinoma: a meta-analysis. *PLoS One* 2013; **8**: e69238 [PMID: 23894436 DOI: 10.1371/journal.pone.0069238]

37 **Wang J**, Zhao L, Yan H, Che J, Huihui L, Jun W, Liu B, Cao B. A Meta-Analysis and Systematic Review on the Association between Human Papillomavirus (Types 16 and 18) Infection and Esophageal Cancer Worldwide. *PLoS One* 2016; **11**: e0159140 [PMID: 27409078 DOI: 10.1371/journal.pone.0159140]

38 **Young LS**, Rickinson AB. Epstein-Barr virus: 40 years on. *Nat Rev Cancer* 2004; **4**: 757-768 [PMID: 15510157 DOI: 10.1038/nrc1452]

39 **Jenkins TD**, Nakagawa H, Rustgi AK. The association of Epstein-Barr virus DNA with esophageal squamous cell carcinoma. *Oncogene* 1996; **13**: 1809-1813 [PMID: 8895528]

40 **Awerkiew S**, Bollschweiler E, Metzger R, Schneider PM, Hölscher AH, Pfister H. Esophageal cancer in Germany is associated with Epstein-Barr-virus but not with papillomaviruses. *Med Microbiol Immunol* 2003; **192**: 137-140 [PMID: 12920588 DOI: 10.1007/s00430-002-0128-z]

41 **Wu MY**, Wu XY, Zhuang CX. Detection of HSV and EBV in esophageal carcinomas from a high-incidence area in Shantou China. *Dis Esophagus* 2005; **18**: 46-50 [PMID: 15773842 DOI: 10.1111/j.1442-2050.2005.00423.x]

42 **Zhang DH**, Zhang QY, Hong CQ, Chen JY, Shen ZY, Zhu Y. Prevalence and association of human papillomavirus 16, Epstein-Barr virus, herpes simplex virus-1 and cytomegalovirus infection with human esophageal carcinoma: a case-control study. *Oncol Rep* 2011; **25**: 1731-1738 [PMID: 21455581 DOI: 10.3892/or.2011.1234]

43 **Wang LS**, Chow KC, Wu YC, Li WY, Huang MH. Detection of Epstein-Barr virus in esophageal squamous cell carcinoma in Taiwan. *Am J Gastroenterol* 1999; **94**: 2834-2839 [PMID: 10520830 DOI: 10.1111/j.1572-0241.1999.01425.x]

44 **Yang YY**, Koh LW, Tsai JH, Tsai CH, Wong EF, Lin SJ, Yang CC. Involvement of viral and chemical factors with oral cancer in Taiwan. *Jpn J Clin Oncol* 2004; **34**: 176-183 [PMID: 15121752 DOI: 10.1093/jjco/hyh037]

45 **Tan HH**, Goh CL. Viral infections affecting the skin in organ transplant recipients: epidemiology and current management strategies. *Am J Clin Dermatol* 2006; **7**: 13-29 [PMID: 16489840 DOI: 10.2165/00128071-200607010-00003]

46 **Han XY**. Epidemiologic analysis of reactivated cytomegalovirus antigenemia in patients with cancer. *J Clin Microbiol* 2007; **45**: 1126-1132 [PMID: 17287334 DOI: 10.1128/jcm.01670-06]

47 **Chang F**, Syrjänen S, Shen Q, Cintorino M, Santopietro R, Tosi P, Syrjänen K. Evaluation of HPV, CMV, HSV and EBV in esophageal squamous cell carcinomas from a high-incidence area of China. *Anticancer Res* 2000; **20**: 3935-3940 [PMID: 11268480]

48 Infection with Helicobacter pylori. *IARC Monogr Eval Carcinog Risks Hum* 1994; **61**: 177-240 [PMID: 7715070]

49 **Plummer M**, Franceschi S, Vignat J, Forman D, de Martel C. Global burden of gastric cancer attributable to Helicobacter pylori. *Int J Cancer* 2015; **136**: 487-490 [PMID: 24889903 DOI: 10.1002/ijc.28999]

50 **Hooi JKY**, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, Malfertheiner P, Graham DY, Wong VWS, Wu JCY, Chan FKL, Sung JJY, Kaplan GG, Ng SC. Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis. *Gastroenterology* 2017; **153**: 420-429 [PMID: 28456631 DOI: 10.1053/j.gastro.2017.04.022]

51 **Kidd M**, Lastovica AJ, Atherton JC, Louw JA. Heterogeneity in the Helicobacter pylori vacA and cagA genes: association with gastroduodenal disease in South Africa? *Gut* 1999; **45**: 499-502 [PMID: 10486355 DOI: 10.1136/gut.45.4.499]

52 **The American Cancer Society medical and editorial content team.** Known and Probable Human Carcinogens. [cited 15 March 2021]. Available from: https://www.cancer.org/cancer/cancer-causes/general-info/known-and-probable-human-carcinogens.html

53 **Parsonnet J**, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, Sibley RK. Helicobacter pylori infection and the risk of gastric carcinoma. *N Engl J Med* 1991; **325**: 1127-1131 [PMID: 1891020 DOI: 10.1056/NEJM199110173251603]

54 **Wang F**, Meng W, Wang B, Qiao L. Helicobacter pylori-induced gastric inflammation and gastric cancer. *Cancer Lett* 2014; **345**: 196-202 [PMID: 23981572 DOI: 10.1016/j.canlet.2013.08.016]

55 **Asenjo LM**, Gisbert JP. [Prevalence of Helicobacter pylori infection in gastric MALT lymphoma: a systematic review]. *Rev Esp Enferm Dig* 2007; **99**: 398-404 [PMID: 17973584 DOI: 10.4321/s1130-01082007000700006]

56 **Xu X**, Liu Z, Fang M, Yu H, Liang X, Li X, Liu X, Chen C, Jia J. Helicobacter pylori CagA induces ornithine decarboxylase upregulation via Src/MEK/ERK/c-Myc pathway: implication for progression of gastric diseases. *Exp Biol Med (Maywood)* 2012; **237**: 435-441 [PMID: 22442341 DOI: 10.1258/ebm.2011.011199]

57 **Mueller D**, Tegtmeyer N, Brandt S, Yamaoka Y, De Poire E, Sgouras D, Wessler S, Torres J, Smolka A, Backert S. c-Src and c-Abl kinases control hierarchic phosphorylation and function of the CagA effector protein in Western and East Asian Helicobacter pylori strains. *J Clin Invest* 2012; **122**: 1553-1566 [PMID: 22378042 DOI: 10.1172/JCI61143]

58 **Rassow J**, Meinecke M. Helicobacter pylori VacA: a new perspective on an invasive chloride channel. *Microbes Infect* 2012; **14**: 1026-1033 [PMID: 22796385 DOI: 10.1016/j.micinf.2012.07.002]

59 **Jain P**, Luo ZQ, Blanke SR. Helicobacter pylori vacuolating cytotoxin A (VacA) engages the mitochondrial fission machinery to induce host cell death. *Proc Natl Acad Sci U S A* 2011; **108**: 16032-16037 [PMID: 21903925 DOI: 10.1073/pnas.1105175108]

60 **Raju D**, Hussey S, Ang M, Terebiznik MR, Sibony M, Galindo-Mata E, Gupta V, Blanke SR, Delgado A, Romero-Gallo J, Ramjeet MS, Mascarenhas H, Peek RM, Correa P, Streutker C, Hold G, Kunstmann E, Yoshimori T, Silverberg MS, Girardin SE, Philpott DJ, El Omar E, Jones NL. Vacuolating cytotoxin and variants in Atg16L1 that disrupt autophagy promote Helicobacter pylori infection in humans. *Gastroenterology* 2012; **142**: 1160-1171 [PMID: 22333951 DOI: 10.1053/j.gastro.2012.01.043]

61 **Lamb A**, Chen LF. Role of the Helicobacter pylori-induced inflammatory response in the development of gastric cancer. *J Cell Biochem* 2013; **114**: 491-497 [PMID: 22961880 DOI: 10.1002/jcb.24389]

62 **Brandt S**, Kwok T, Hartig R, König W, Backert S. NF-kappaB activation and potentiation of proinflammatory responses by the Helicobacter pylori CagA protein. *Proc Natl Acad Sci U S A* 2005; **102**: 9300-9305 [PMID: 15972330 DOI: 10.1073/pnas.0409873102]

63 **Wei J**, Nagy TA, Vilgelm A, Zaika E, Ogden SR, Romero-Gallo J, Piazuelo MB, Correa P, Washington MK, El-Rifai W, Peek RM, Zaika A. Regulation of p53 tumor suppressor by Helicobacter pylori in gastric epithelial cells. *Gastroenterology* 2010; **139**: 1333-1343 [PMID: 20547161 DOI: 10.1053/j.gastro.2010.06.018]

64 **Sepulveda AR**, Yao Y, Yan W, Park DI, Kim JJ, Gooding W, Abudayyeh S, Graham DY. CpG methylation and reduced expression of O6-methylguanine DNA methyltransferase is associated with Helicobacter pylori infection. *Gastroenterology* 2010; **138**: 1836-1844 [PMID: 20044995 DOI: 10.1053/j.gastro.2009.12.042]

65 **Handa O**, Naito Y, Yoshikawa T. Redox biology and gastric carcinogenesis: the role of Helicobacter pylori. *Redox Rep* 2011; **16**: 1-7 [PMID: 21605492 DOI: 10.1179/174329211X12968219310756]

66 **Lazcano-Ponce EC**, Miquel JF, Muñoz N, Herrero R, Ferrecio C, Wistuba II, Alonso de Ruiz P, Aristi Urista G, Nervi F. Epidemiology and molecular pathology of gallbladder cancer. *CA Cancer J Clin* 2001; **51**: 349-364 [PMID: 11760569 DOI: 10.3322/canjclin.51.6.349]

67 **Randi G**, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. *Int J Cancer* 2006; **118**: 1591-1602 [PMID: 16397865 DOI: 10.1002/ijc.21683]

68 **Axelrod L**, Munster AM, O'Brien TF. Typhoid cholecystitis and gallbladder carcinoma after interval of 67 years. *JAMA* 1971; **217**: 83 [PMID: 5108716]

69 **Caygill CP**, Hill MJ, Braddick M, Sharp JC. Cancer mortality in chronic typhoid and paratyphoid carriers. *Lancet* 1994; **343**: 83-84 [PMID: 7903779 DOI: 10.1016/s0140-6736(94)90816-8]

70 **Nath G**, Singh YK, Maurya P, Gulati AK, Srivastava RC, Tripathi SK. Does Salmonella Typhi primarily reside in the liver of chronic typhoid carriers? *J Infect Dev Ctries* 2010; **4**: 259-261 [PMID: 20440067 DOI: 10.3855/jidc.820]

71 **Shukla VK**, Tiwari SC, Roy SK. Biliary bile acids in cholelithiasis and carcinoma of the gall bladder. *Eur J Cancer Prev* 1993; **2**: 155-160 [PMID: 8461866 DOI: 10.1097/00008469-199303000-00008]

72 **Viani F**, Siegrist HH, Pignatelli B, Cederberg C, Idström JP, Verdu EF, Fried M, Blum AL, Armstrong D. The effect of intra-gastric acidity and flora on the concentration of N-nitroso compounds in the stomach. *Eur J Gastroenterol Hepatol* 2000; **12**: 165-173 [PMID: 10741930 DOI: 10.1097/00042737-200012020-00006]

73 **Haghjoo E**, Galán JE. Salmonella typhi encodes a functional cytolethal distending toxin that is delivered into host cells by a bacterial-internalization pathway. *Proc Natl Acad Sci U S A* 2004; **101**: 4614-4619 [PMID: 15070766 DOI: 10.1073/pnas.0400932101]

74 **Shenker BJ**, McKay T, Datar S, Miller M, Chowhan R, Demuth D. Actinobacillus actinomycetemcomitans immunosuppressive protein is a member of the family of cytolethal distending toxins capable of causing a G2 arrest in human T cells. *J Immunol* 1999; **162**: 4773-4780 [PMID: 10202019]

75 **Belzer C**, Kusters JG, Kuipers EJ, van Vliet AH. Urease induced calcium precipitation by Helicobacter species may initiate gallstone formation. *Gut* 2006; **55**: 1678-1679 [PMID: 17047128 DOI: 10.1136/gut.2006.098319]

76 **Maurer KJ**, Rao VP, Ge Z, Rogers AB, Oura TJ, Carey MC, Fox JG. T-cell function is critical for murine cholesterol gallstone formation. *Gastroenterology* 2007; **133**: 1304-1315 [PMID: 17919501 DOI: 10.1053/j.gastro.2007.07.005]

77 **Jergens AE**, Wilson-Welder JH, Dorn A, Henderson A, Liu Z, Evans RB, Hostetter J, Wannemuehler MJ. Helicobacter bilis triggers persistent immune reactivity to antigens derived from the commensal bacteria in gnotobiotic C3H/HeN mice. *Gut* 2007; **56**: 934-940 [PMID: 17145736 DOI: 10.1136/gut.2006.099242]

78 **Sripa B**, Pairojkul C. Cholangiocarcinoma: lessons from Thailand. *Curr Opin Gastroenterol* 2008; **24**: 349-356 [PMID: 18408464 DOI: 10.1097/mog.0b013e3282fbf9b3]

79 **Kurathong S**, Lerdverasirikul P, Wongpaitoon V, Pramoolsinsap C, Kanjanapitak A, Varavithya W, Phuapradit P, Bunyaratvej S, Upatham ES, Brockelman WY. Opisthorchis viverrini infection and cholangiocarcinoma. A prospective, case-controlled study. *Gastroenterology* 1985; **89**: 151-156 [PMID: 2989071 DOI: 10.1016/0016-5085(85)90755-3]

80 **Qeios**. Peripheral Intrahepatic Cholangiocarcinoma. [cited 15 March 2021]. Available from: https://www.qeios.com/read/5Z3JBD

81 **Coulier B**, Mailleux P. Fatty filum terminale: A prospective CT study. *Clinical Imaging* 1995; **19**: 221 [DOI: 10.1016/0899-7071(95)98191-2]

82 **Lim MK**, Ju YH, Franceschi S, Oh JK, Kong HJ, Hwang SS, Park SK, Cho SI, Sohn WM, Kim DI, Yoo KY, Hong ST, Shin HR. Clonorchis sinensis infection and increasing risk of cholangiocarcinoma in the Republic of Korea. *Am J Trop Med Hyg* 2006; **75**: 93-96 [PMID: 16837714]

83 **Hong S,** Huh S, Kho W. Changes in histopathological and serological findings of the liver after treatment in rabbit clonorchiasis. *Seoul J Med* 1990; **31**: 117-127 [DOI: 10.3347/kjp.2009.47.1.19]

84 **Fava G**, Lorenzini I. Molecular pathogenesis of cholangiocarcinoma. *Int J Hepatol* 2012; **2012**: 630543 [PMID: 21994887 DOI: 10.1155/2012/630543]

85 **Ferlay J**, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-E386 [PMID: 25220842 DOI: 10.1002/ijc.29210]

86 **Nassal M**. HBV cccDNA: viral persistence reservoir and key obstacle for a cure of chronic hepatitis B. *Gut* 2015; **64**: 1972-1984 [PMID: 26048673 DOI: 10.1136/gutjnl-2015-309809]

87 **Buendia MA**, Neuveut C. Hepatocellular carcinoma. *Cold Spring Harb Perspect Med* 2015; **5**: a021444 [PMID: 25646384 DOI: 10.1101/cshperspect.a021444]

88 **Lau CC**, Sun T, Ching AK, He M, Li JW, Wong AM, Co NN, Chan AW, Li PS, Lung RW, Tong JH, Lai PB, Chan HL, To KF, Chan TF, Wong N. Viral-human chimeric transcript predisposes risk to liver cancer development and progression. *Cancer Cell* 2014; **25**: 335-349 [PMID: 24582836 DOI: 10.1016/j.ccr.2014.01.030]

89 **Minami M**, Daimon Y, Mori K, Takashima H, Nakajima T, Itoh Y, Okanoue T. Hepatitis B virus-related insertional mutagenesis in chronic hepatitis B patients as an early drastic genetic change leading to hepatocarcinogenesis. *Oncogene* 2005; **24**: 4340-4348 [PMID: 15806150 DOI: 10.1038/sj.onc.1208628]

90 **Lu P**, Kuang S, Wang J. [Hepatitis B virus infection and aflatoxin exposure in the development of primary liver cancer]. *Zhonghua Yixue Zazhi* 1998; **78**: 340-342 [PMID: 10923435]

91 **Evans AA**, O'Connell AP, Pugh JC, Mason WS, Shen FM, Chen GC, Lin WY, Dia A, M'Boup S, Dramé B, London WT. Geographic variation in viral load among hepatitis B carriers with differing risks of hepatocellular carcinoma. *Cancer Epidemiol Biomarkers Prev* 1998; **7**: 559-565 [PMID: 9681522]

92 **Raimondi S**, Bruno S, Mondelli MU, Maisonneuve P. Hepatitis C virus genotype 1b as a risk factor for hepatocellular carcinoma development: a meta-analysis. *J Hepatol* 2009; **50**: 1142-1154 [PMID: 19395111 DOI: 10.1016/j.jhep.2009.01.019]

93 **Akuta N**, Suzuki F, Kobayashi M, Sezaki H, Kawamura Y, Hosaka T, Kobayashi M, Saitoh S, Suzuki Y, Arase Y, Ikeda K, Kumada H. Impact of Mutations at Amino Acid 70 in Hepatitis C Virus (HCV) Genotype 1b Core Region on Hepatocarcinogenesis following Eradication of HCV RNA. *J Clin Microbiol* 2015; **53**: 3039-3041 [PMID: 26135874 DOI: 10.1128/JCM.01457-15]

94 **Thorgeirsson SS**, Grisham JW. Molecular pathogenesis of human hepatocellular carcinoma. *Nat Genet* 2002; **31**: 339-346 [PMID: 12149612 DOI: 10.1038/ng0802-339]

95 **IARC W**. Global cancer observatory. [cited 15 March 2021]. Available from: https://gco.iarc.fr/: IARC. International Agency for Research on Cancer

96 **Kostic AD**, Gevers D, Pedamallu CS, Michaud M, Duke F, Earl AM, Ojesina AI, Jung J, Bass AJ, Tabernero J, Baselga J, Liu C, Shivdasani RA, Ogino S, Birren BW, Huttenhower C, Garrett WS, Meyerson M. Genomic analysis identifies association of Fusobacterium with colorectal carcinoma. *Genome Res* 2012; **22**: 292-298 [PMID: 22009990 DOI: 10.1101/gr.126573.111]

97 **Tahara T**, Yamamoto E, Suzuki H, Maruyama R, Chung W, Garriga J, Jelinek J, Yamano HO, Sugai T, An B, Shureiqi I, Toyota M, Kondo Y, Estécio MR, Issa JP. Fusobacterium in colonic flora and molecular features of colorectal carcinoma. *Cancer Res* 2014; **74**: 1311-1318 [PMID: 24385213 DOI: 10.1158/0008-5472.CAN-13-1865]

98 **Abed J**, Emgård JE, Zamir G, Faroja M, Almogy G, Grenov A, Sol A, Naor R, Pikarsky E, Atlan KA, Mellul A, Chaushu S, Manson AL, Earl AM, Ou N, Brennan CA, Garrett WS, Bachrach G. Fap2 Mediates Fusobacterium nucleatum Colorectal Adenocarcinoma Enrichment by Binding to Tumor-Expressed Gal-GalNAc. *Cell Host Microbe* 2016; **20**: 215-225 [PMID: 27512904 DOI: 10.1016/j.chom.2016.07.006]

99 **Mima K**, Nishihara R, Qian ZR, Cao Y, Sukawa Y, Nowak JA, Yang J, Dou R, Masugi Y, Song M, Kostic AD, Giannakis M, Bullman S, Milner DA, Baba H, Giovannucci EL, Garraway LA, Freeman GJ, Dranoff G, Garrett WS, Huttenhower C, Meyerson M, Meyerhardt JA, Chan AT, Fuchs CS, Ogino S. Fusobacterium nucleatum in colorectal carcinoma tissue and patient prognosis. *Gut* 2016; **65**: 1973-1980 [PMID: 26311717 DOI: 10.1136/gutjnl-2015-310101]

100 **Yu T**, Guo F, Yu Y, Sun T, Ma D, Han J, Qian Y, Kryczek I, Sun D, Nagarsheth N, Chen Y, Chen H, Hong J, Zou W, Fang JY. Fusobacterium nucleatum Promotes Chemoresistance to Colorectal Cancer by Modulating Autophagy. *Cell* 2017; **170**: 548-563.e16 [PMID: 28753429 DOI: 10.1016/j.cell.2017.07.008]

101 **Li YY**, Ge QX, Cao J, Zhou YJ, Du YL, Shen B, Wan YJ, Nie YQ. Association of Fusobacterium nucleatum infection with colorectal cancer in Chinese patients. *World J Gastroenterol* 2016; **22**: 3227-3233 [PMID: 27004000 DOI: 10.3748/wjg.v22.i11.3227]

102 **Oh HJ**, Kim JH, Bae JM, Kim HJ, Cho NY, Kang GH. Prognostic Impact of Fusobacterium nucleatum Depends on Combined Tumor Location and Microsatellite Instability Status in Stage II/III Colorectal Cancers Treated with Adjuvant Chemotherapy. *J Pathol Transl Med* 2019; **53**: 40-49 [PMID: 30586952 DOI: 10.4132/jptm.2018.11.29]

103 **Hamada T**, Zhang X, Mima K, Bullman S, Sukawa Y, Nowak JA, Kosumi K, Masugi Y, Twombly TS, Cao Y, Song M, Liu L, da Silva A, Shi Y, Gu M, Li W, Koh H, Nosho K, Inamura K, Keum N, Wu K, Meyerhardt JA, Kostic AD, Huttenhower C, Garrett WS, Meyerson M, Giovannucci EL, Chan AT, Fuchs CS, Nishihara R, Giannakis M, Ogino S. *Fusobacterium nucleatum* in Colorectal Cancer Relates to Immune Response Differentially by Tumor Microsatellite Instability Status. *Cancer Immunol Res* 2018; **6**: 1327-1336 [PMID: 30228205 DOI: 10.1158/2326-6066.CIR-18-0174]

104 **Bahrami A**, Amerizadeh F, ShahidSales S, Khazaei M, Ghayour-Mobarhan M, Sadeghnia HR, Maftouh M, Hassanian SM, Avan A. Therapeutic Potential of Targeting Wnt/β-Catenin Pathway in Treatment of Colorectal Cancer: Rational and Progress. *J Cell Biochem* 2017; **118**: 1979-1983 [PMID: 28109136 DOI: 10.1002/jcb.25903]

105 **Castellarin M**, Warren RL, Freeman JD, Dreolini L, Krzywinski M, Strauss J, Barnes R, Watson P, Allen-Vercoe E, Moore RA, Holt RA. Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma. *Genome Res* 2012; **22**: 299-306 [PMID: 22009989 DOI: 10.1101/gr.126516.111]

106 **Swidsinski A**, Khilkin M, Kerjaschki D, Schreiber S, Ortner M, Weber J, Lochs H. Association between intraepithelial Escherichia coli and colorectal cancer. *Gastroenterology* 1998; **115**: 281-286 [PMID: 9679033 DOI: 10.1016/s0016-5085(98)70194-5]

107 **Darfeuille-Michaud A**, Boudeau J, Bulois P, Neut C, Glasser AL, Barnich N, Bringer MA, Swidsinski A, Beaugerie L, Colombel JF. High prevalence of adherent-invasive Escherichia coli associated with ileal mucosa in Crohn's disease. *Gastroenterology* 2004; **127**: 412-421 [PMID: 15300573 DOI: 10.1053/j.gastro.2004.04.061]

108 **Kim KS**, Kim JT, Lee SJ, Kang MA, Choe IS, Kang YH, Kim SY, Yeom YI, Lee YH, Kim JH, Kim KH, Kim CN, Kim JW, Nam MS, Lee HG. Overexpression and clinical significance of carcinoembryonic antigen-related cell adhesion molecule 6 in colorectal cancer. *Clin Chim Acta* 2013; **415**: 12-19 [PMID: 22975528 DOI: 10.1016/j.cca.2012.09.003]

109 **Balskus EP**. Colibactin: understanding an elusive gut bacterial genotoxin. *Nat Prod Rep* 2015; **32**: 1534-1540 [PMID: 26390983 DOI: 10.1039/c5np00091b]

110 **Choi HJ**, Kim J, Do KH, Park SH, Moon Y. Enteropathogenic Escherichia coli-induced macrophage inhibitory cytokine 1 mediates cancer cell survival: an in vitro implication of infection-linked tumor dissemination. *Oncogene* 2013; **32**: 4960-4969 [PMID: 23503457 DOI: 10.1038/onc.2012.508]

111 **Roxas JL**, Koutsouris A, Viswanathan VK. Enteropathogenic Escherichia coli-induced epidermal growth factor receptor activation contributes to physiological alterations in intestinal epithelial cells. *Infect Immun* 2007; **75**: 2316-2324 [PMID: 17339360 DOI: 10.1128/iai.01690-06]

112 **Arumugam M**, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, Fernandes GR, Tap J, Bruls T, Batto JM, Bertalan M, Borruel N, Casellas F, Fernandez L, Gautier L, Hansen T, Hattori M, Hayashi T, Kleerebezem M, Kurokawa K, Leclerc M, Levenez F, Manichanh C, Nielsen HB, Nielsen T, Pons N, Poulain J, Qin J, Sicheritz-Ponten T, Tims S, Torrents D, Ugarte E, Zoetendal EG, Wang J, Guarner F, Pedersen O, de Vos WM, Brunak S, Doré J; MetaHIT Consortium, Antolín M, Artiguenave F, Blottiere HM, Almeida M, Brechot C, Cara C, Chervaux C, Cultrone A, Delorme C, Denariaz G, Dervyn R, Foerstner KU, Friss C, van de Guchte M, Guedon E, Haimet F, Huber W, van Hylckama-Vlieg J, Jamet A, Juste C, Kaci G, Knol J, Lakhdari O, Layec S, Le Roux K, Maguin E, Mérieux A, Melo Minardi R, M'rini C, Muller J, Oozeer R, Parkhill J, Renault P, Rescigno M, Sanchez N, Sunagawa S, Torrejon A, Turner K, Vandemeulebrouck G, Varela E, Winogradsky Y, Zeller G, Weissenbach J, Ehrlich SD, Bork P. Enterotypes of the human gut microbiome. *Nature* 2011; **473**: 174-180 [PMID: 21508958 DOI: 10.1038/nature09944]

113 **Sears CL**, Geis AL, Housseau F. *Bacteroides fragilis* subverts mucosal biology: from symbiont to colon carcinogenesis. *J Clin Invest* 2014; **124**: 4166-4172 [PMID: 25105360 DOI: 10.1172/JCI72334]

114 **Snezhkina AV**, Krasnov GS, Lipatova AV, Sadritdinova AF, Kardymon OL, Fedorova MS, Melnikova NV, Stepanov OA, Zaretsky AR, Kaprin AD, Alekseev BY, Dmitriev AA, Kudryavtseva AV. The Dysregulation of Polyamine Metabolism in Colorectal Cancer Is Associated with Overexpression of c-Myc and C/EBPβ rather than Enterotoxigenic *Bacteroides fragilis* Infection. *Oxid Med Cell Longev* 2016; **2016**: 2353560 [PMID: 27433286 DOI: 10.1155/2016/2353560]

115 **Remacle AG**, Shiryaev SA, Strongin AY. Distinct interactions with cellular E-cadherin of the two virulent metalloproteinases encoded by a *Bacteroides fragilis* pathogenicity island. *PLoS One* 2014; **9**: e113896 [PMID: 25411788 DOI: 10.1371/journal.pone.0113896]

116 **Del Bel Belluz L**, Guidi R, Pateras IS, Levi L, Mihaljevic B, Rouf SF, Wrande M, Candela M, Turroni S, Nastasi C, Consolandi C, Peano C, Tebaldi T, Viero G, Gorgoulis VG, Krejsgaard T, Rhen M, Frisan T. The Typhoid Toxin Promotes Host Survival and the Establishment of a Persistent Asymptomatic Infection. *PLoS Pathog* 2016; **12**: e1005528 [PMID: 27055274 DOI: 10.1371/journal.ppat.1005528]

117 **Kang M**, Martin A. Microbiome and colorectal cancer: Unraveling host-microbiota interactions in colitis-associated colorectal cancer development. *Semin Immunol* 2017; **32**: 3-13 [PMID: 28465070 DOI: 10.1016/j.smim.2017.04.003]

118 **Lu R**, Bosland M, Xia Y, Zhang YG, Kato I, Sun J. Presence of *Salmonella* AvrA in colorectal tumor and its precursor lesions in mouse intestine and human specimens. *Oncotarget* 2017; **8**: 55104-55115 [PMID: 28903406 DOI: 10.18632/oncotarget.19052]

119 **Lu R**, Wu S, Liu X, Xia Y, Zhang YG, Sun J. Chronic effects of a Salmonella type III secretion effector protein AvrA in vivo. *PLoS One* 2010; **5**: e10505 [PMID: 20463922 DOI: 10.1371/journal.pone.0010505]

120 **Lu R**, Liu X, Wu S, Xia Y, Zhang YG, Petrof EO, Claud EC, Sun J. Consistent activation of the β-catenin pathway by Salmonella type-three secretion effector protein AvrA in chronically infected intestine. *Am J Physiol Gastrointest Liver Physiol* 2012; **303**: G1113-G1125 [PMID: 22982337 DOI: 10.1152/ajpgi.00453.2011]

121 **Liu X**, Lu R, Wu S, Sun J. Salmonella regulation of intestinal stem cells through the Wnt/beta-catenin pathway. *FEBS Lett* 2010; **584**: 911-916 [PMID: 20083111 DOI: 10.1016/j.febslet.2010.01.024]

122 **Longacre TA**, Kong CS, Welton ML. Diagnostic problems in anal pathology. *Adv Anat Pathol* 2008; **15**: 263-278 [PMID: 18724100 DOI: 10.1097/pap.0b013e318183234b]

123 **Johnson LG**, Madeleine MM, Newcomer LM, Schwartz SM, Daling JR. Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973-2000. *Cancer* 2004; **101**: 281-288 [PMID: 15241824 DOI: 10.1002/cncr.20364]

124 **De Vuyst H**, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. *Int J Cancer* 2009; **124**: 1626-1636 [PMID: 19115209 DOI: 10.1002/ijc.24116]

125 **Palefsky J**. Human papillomavirus and anal neoplasia. *Curr HIV/AIDS Rep* 2008; **5**: 78-85 [PMID: 18510893 DOI: 10.1007/s11904-008-0013-5]

126 **Jeon S**, Lambert PF. Integration of human papillomavirus type 16 DNA into the human genome leads to increased stability of E6 and E7 mRNAs: implications for cervical carcinogenesis. *Proc Natl Acad Sci U S A* 1995; **92**: 1654-1658 [PMID: 7878034 DOI: 10.1073/pnas.92.5.1654]

127 **Dyson N**, Howley PM, Münger K, Harlow E. The human papilloma virus-16 E7 oncoprotein is able to bind to the retinoblastoma gene product. *Science* 1989; **243**: 934-937 [PMID: 2537532 DOI: 10.1126/science.2537532]

128 **Münger K**, Werness BA, Dyson N, Phelps WC, Harlow E, Howley PM. Complex formation of human papillomavirus E7 proteins with the retinoblastoma tumor suppressor gene product. *EMBO J* 1989; **8**: 4099-4105 [PMID: 2556261]

129 **Werness BA**, Levine AJ, Howley PM. Association of human papillomavirus types 16 and 18 E6 proteins with p53. *Science* 1990; **248**: 76-79 [PMID: 2157286 DOI: 10.1126/science.2157286]

130 **Weng MT**, Chiu YT, Wei PY, Chiang CW, Fang HL, Wei SC. Microbiota and gastrointestinal cancer. *J Formos Med Assoc* 2019; **118** Suppl 1: S32-S41 [PMID: 30655033 DOI: 10.1016/j.jfma.2019.01.002.]

131 **Meng C**, Bai C, Brown TD, Hood LE, Tian Q. Human Gut Microbiota and Gastrointestinal Cancer. *Genomics Proteomics Bioinformatics* 2018; **16**: 33-49 [PMID: 29474889 DOI: 10.1016/j.gpb.2017.06.002.]

132 **Flemer B**, Lynch DB, Brown JM, Jeffery IB, Ryan FJ, Claesson MJ, O'Riordain M, Shanahan F, O'Toole PW. Tumour-associated and non-tumour-associated microbiota in colorectal cancer. *Gut* 2017; **66**: 633-643 [PMID: 26992426 DOI: 10.1136/gutjnl-2015-309595]

133 **Yu LX**, Schwabe RF. The gut microbiome and liver cancer: mechanisms and clinical translation. *Nat Rev Gastroenterol Hepatol* 2017; **14**: 527-539 [PMID: 28676707 DOI: 10.1038/nrgastro.2017.72]

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**Table 1 Pathogens related to gastrointestinal malignancies**

|  |  |  |  |
| --- | --- | --- | --- |
| **Ref.** | **Primary tumor** | **Pathogen** | **Molecular mechanisms** |
| von Knebel Doeberitz *et al*[30], Syrjänen *et al*[31], Liyanage *et al*[36] | Esophageal | HPV | Oncoproteins E6 and E7 |
| Wu *et al*[41], Zhang *et al*[42], Wang *et al*[43] | EBV | Oncoproteins EBER and LMP-1 |
| Yang *et al*[44], Tan *et al*[45], Han *et al*[46] | Herpes Simplex and CMV | Unknown |
| Xu *et al*[56], Mueller *et al*[57] | Gastric | Helicobacter pylori | Cag A *H. pylori* protein |
| Rassow *et al*[58], Jain *et al*[59] | VacA |
| Lamb and Chen[61], Brandt *et al*[62] | Interleukins, NFbeta, p53 |
| Haghjoo and Galán[73] | Gallblader | Salmonella typhi | Cytolethal Distending Toxin |
| Belzer *et al*[75], Maurer *et al*[76] | *Helicobacter* spp. | Urease production |
| Lax and Thomas[10] | Escherichia coli | Cytotoxic necrotizing factor I |
| Sripa and Pairojkul[78], Kurathong *et al*[79] | Opisthorchis vierrini and Clonorchis sinensis | Poorly known |
| Lau *et al*[88], Minami *et al*[89] | Liver | Hepatitis B virus | HBx protein |
| Raimondi *et al*[92], Akuta *et al*[93] | Hepatitis C virus | HCV core protein |
| Tahara *et al*[97], Abed *et al*[98] | Colon | Fusobacterium nucleatum | Fap2 protein |
| Choi *et al*[110], Roxas *et al*[111] | Escherichia coli | CEACAM6, MIC-1 |
| Arumugam *et al*[112], Sears *et al*[113] | *Bacteroides fragilis* | BFT |
| Del Bel Belluz *et al*[116], Kang *et al*[117] | Salmonella enterica | Typhoid toxin, AvrA effector protein |
| Palefsky[125], Dyson *et al*[127] | Anal cancer | HPV | E6, E7, p53 |

HPV: Human Papilloma virus; EBV: Epstein Barr virus; CMV: Citomegalovirus; VacA: Vacuolating cytotoxin; BFT: *Bacteroides Fragilis* toxin.



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