

# An Update on Infection and Cancer

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## ABSTRACT

Association of microbes in different cancers' initiation and progression is very old and is still considered as an emerging field in cancer biology. Knowledge about the functional link between different microbes and cancer has enabled us in taking preventive measures against different cancers like gastric and cervical cancer. In the recent past, various clinical and experimental studies have shown presence of certain specific microorganisms in different cancer tissues that were not addressed before. Importantly, availability of certain animal models have helped in establishing the functional association between microbes and cancers. In this particular review, we have briefly summarized the role of commonly known microbes in various cancers and importantly discussed about the recent contribution of metagenomics analysis in this particular field.

**Key words:** Infection, Cancer, Mouse model, Cancer associated microbiota, Metagenomics.

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## INTRODUCTION

Cancer is a multifactorial disease resulting from the clonal expansion of cells from normal tissues. Starting from the cancer initiation, promotion and progression, cells undergo many irreversible genomic changes. Out of those factors that predispose the normal cells to undergo various genomic changes and initiate and/or promote cancer, infection with certain organisms has been suggested to be an important risk factor. It has been shown that in the year 2008 around 2 million cancer cases were caused by infectious agents globally, which was around 16.1% of the total estimated cancer incidence of that year.<sup>[1]</sup> Furthermore, the proportion of infection-related cancer is around three times higher in developing worlds, like Asia, than developed countries like UK. The link between infection and cancer is a very old concept. In the year 1911 for the first time Dr. Rous showed that cancer can originate from an infectious agent. This was shown by injecting cell-free filtrate obtained from chicken sarcoma and producing a fresh tumor after injecting the same in a second fowl.<sup>[2]</sup> The infectious agent was later on identified as a RNA virus and eventually called as Rous sarcoma virus. This finding was later on followed by many novel discoveries that showed association of infectious agents with various malignancies.

Despite long-lasting belief that infectious agents could have functional role in different cancer progression, for a long time the scientific community was unable to identify new cancer-associated infectious agents. Absence of suitable culture conditions to isolate all kinds of microbes and difficulties to identify uncharacterized organisms are two major bottlenecks that have handicapped investigators in

exploring novel association between different microbes and cancer. Fortunately, the recent advancement in the metagenomics analysis or next generation sequencing has substantially helped to identify microorganisms that are differentially enriched in cancer tissues. In this review we have briefly conversed about some of the very commonly known cancer associated microorganisms and their functional role in different cancers. Importantly, we have discussed about the contribution of metagenomics analysis of microbial population to this field.

## Cancer associated infectious agents

Certain viral, bacterial and parasitic infections have been considered as potential risk factors for definite cancers.<sup>[3]</sup> The major infectious agents that have contributed significantly to the global cancer burden are: *Helicobacter pylori* (*H. pylori*), human papilloma viruses (HPV) and hepatitis B and C viruses. *H. pylori* a gram negative bacteria, is a well-established carcinogen for the development of gastric cancer.<sup>[4]</sup> This association has been established through various epidemiological, clinical and experimental evidences. Likewise, chronic infections due to *Salmonella typhi*, another Gram-negative bacillus have been shown to be associated with gall bladder and hepatobiliary carcinomas.<sup>[5]</sup> *Fusobacterium nucleatum* is an oral commensalism, causally associated with periodontal disease.<sup>[6]</sup> In the recent past, by adopting metagenomic analyses it has been found that *Fusobacterium* species particularly *Fusobacterium nucleatum* is enriched in colorectal cancer as compared to normal adjacent tissues.<sup>[7,8]</sup> Among the viral infectious agents, Hepatitis B virus (HBV), a circular DNA

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virus, is a definite cause for hepatocellular carcinoma.<sup>[9]</sup> HBV has ability to initiate and promote cancer; therefore, like *H. pylori*, it has properties of a complete carcinogen. Hepatitis C virus (HCV), an RNA virus, is also believed to be a risk factor for hepatocellular carcinoma.<sup>[10]</sup> Cancer causing strains of Human papilloma virus (HPV) are very well-known contributing factors for cervical cancer.<sup>[11]</sup> It causes approximately 80-90% of the cervical cancer worldwide. Additionally, it has also been associated with vulval, penis, anus and head and neck cancer.<sup>[12]</sup> In addition to these major cancer-associated microbes, Epstein-Barr virus (EBV) and Human herpes virus 8 (HHV8) are linked to non-Hodgkin's lymphoma and Kaposi's sarcoma, respectively.<sup>[13]</sup> Though human immunodeficiency virus (HIV) has not been shown to have a direct role in any cancer, but due to its immunosuppressive role, it is considered to be a potential risk factor for many cancers and these cancers (particularly Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer) are known as AIDS-defining cancers.<sup>[14]</sup>

Other than the aforementioned bacterial and viral infectious agents, some parasites with possible roles in the development and progression of various types of cancers have also been reported in literature. Among this category of cancer causing infectious agents are few members of class trematode such as *Opisthorchis viverrini* and *Clonorchis sinensis*, which, in their adult form, are found to reside in the intra-hepatic bile ducts of humans. These two liver fluke species for which humans act as a definite host have been found to be positively associated with the cholangiocarcinoma and liver cancer.<sup>[15]</sup> Similarly infection caused by another member of this class, *Schistosomiasis haematobium*, a blood dwelling fluke worm, has been linked to the occurrence of the urinary bladder cancer.<sup>[16]</sup>

### Role of infectious agents in cancer initiation and/or progression

Irrespective of the etiological factors, normal cells have to undergo some permanent genetic alterations that drive cancer initiation. Always infection-induced cancer initiation is a long term process, which indicates that multiple molecular changes are required for infection-induced carcinogenesis. The mechanisms behind many infection-induced cancers are not yet fully understood. In general, infections can cause cancer in four different mechanisms: (i) by creating chronic inflammation,<sup>[17]</sup> (ii) by direct insertion into the genome,<sup>[18]</sup> (iii) by host immunosuppression<sup>[19]</sup> and (iv) by producing genotoxins.<sup>[20]</sup>

The *H. pylori* infection is believed to produce chronic inflammation, which can lead to atrophic gastritis followed by metaplasia, dysplasia and finally gastric cancer.<sup>[21]</sup> The role of chronic inflammation in cancer is discussed in the succeeding section. In this process different other co-factors like dietary carcinogens might have a role in promoting *H. pylori*-induced gastric cancer. Similarly, experimentally it has been shown that *Fusobacterium nucleatum* directly promotes colorectal cancer growth through inducing E-Cadherin/ $\beta$ -Catenin signaling via binding of its FadA Adhesin protein to E-cadherin of cancer cells.<sup>[22]</sup> Analyzing CRC tissues for FadA gene and its expression level suggests immense difference of FadA gene copies between noncancerous controls and CRC tissues. Expression of Fad mRNA also correlates with the *fadA* gene copy numbers and grade of CRC.<sup>[22]</sup> Moreover oral feeding of *F.nucleatum* to C57BL/6 ApcMin/+ mice aggravates the incidence of intestinal tumor in these mice. Immune profiling of these tumors reveal that *F.nucleatum* feeding selectively enhance infiltration of CD11b<sup>+</sup> myeloid cells specifically Myeloid-derived suppressor cells (MDSCs) including monocytes (M-MDSCs) and granulocytic (G-MDSCs), dendritic cells, M2 type tumor associated macrophages (TAMs). This modulation of tumor immune microenvironment by *F.nucleatum* creates an advantageous condition for intestinal neoplasia progression.<sup>[23]</sup> Tumor residing *F.nucleatum* also inhibits NK cell-mediated killing of cancer cells thor-

ough binding of its Fap2 protein to immune cells inhibitory receptor TIGIT of tumor-infiltrating lymphocytes.<sup>[24]</sup> In Nitroquinoline 1-oxide (*4NQO*) carcinogen induced oral tumor model, *F. nucleatum* and *P. gingivalis* enhance the severity of tumor development, along with activation of STAT3 and expression of IL-6 in tongue epithelium.<sup>[25]</sup>

Most of the viral infection associated with cancer are known for their role in the process of oncogenesis. Cancer causing strains of HPV induce various molecular changes that promote uncontrolled cell division and accumulation of deleterious mutations that eventually help in cellular transformation. E6 and E7 oncogene of HPV are the major risk factor for cancer.<sup>[26]</sup> The products of these two genes alter host-cell metabolism to favor neoplastic development. The integration of HPV DNA into the host DNA increases cellular proliferation and the chance of malignancy. The E6/E7 proteins also inactivate two tumor suppressor proteins, p53 (inactivated by E6) and pRb (inactivated by E7).<sup>[27,28]</sup> After HBV infection, HBV-DNA might integrate into the human genome and produce insertional mutagenesis.<sup>[29]</sup> Further, the X protein coded by HBV genome may play an important role in the pathogenesis of liver cancer.<sup>[30]</sup> Studies have also suggested that the HBV-induced inflammatory process might have role in generating liver cirrhosis followed by cancer. On the other hand, unlike HBV, HCV doesn't integrate into host genome; therefore, HCV-induced liver cancer might be due to its role in generating liver damage and persuading the immune responses by chronic inflammation process.

### Link between infection, inflammation and cancer

At the moment, it has been realized that inflammatory cells and various inflammation mediators including cytokines, chemokines, and enzymes might carry out cancer driven by inflammation. Chronic infection/inflammation, over time leads to repetitive injury and repair resulting in generation and accumulation of cytokines, growth factors, free radicals, enzymes and prostaglandins. These factors induce several protumorigenic alterations like DNA damage, deregulated expression of proteins, protein modifications, and change in miRNA expression pattern. Further, these changes result in hyperproliferation, an increased mitotic error, and progression to adenocarcinoma. The inflammatory microenvironment not only affect the epithelial cells rather it also attract other cells like bone marrow-derived cells that can specifically home to the site of chronic inflammation and promote cancer initiation and/or progression.<sup>[31]</sup>

### Contribution of Metagenomic analysis to identify cancer associated pathogens

Every organ has its own normal microbiota population, which maintains the normal physiology of particulate organ. The normal microbiota of human and animals mostly depends on their environment and food habits. However, in diseased condition, the normal microbiota gets altered and some specific bacteria or groups of bacteria get enriched in particular tissues. As discussed above and at other places, microbial infection might have a context dependent pro or antitumor effect on cancer initiation and progression.<sup>[32]</sup> While the antitumor effect is believed through activation of host immune cells, the pro-tumorigenic effect of microbes could be through their direct effect on pre-malignant cells or indirect effect through activation of immune cells. Initially, differential culture methods were employed to identify the microbiota of diverse patient sample like tumor tissues and biological fluids. However, these conventional culture methods are associated with multiple drawbacks like inability to culture all the microbes, inefficiency to detect low abundant microbes and incompetence to grow and identify uncharacterized bacteria. Thankfully, the significant advancement in the affordable next generation sequencing methods has made it possible to do profiling of whole microbiota present in different pathological and normal samples. Moreover, high throughput sequencing associated with

robust analytical tools has helped to have a comprehensive idea about the type, abundance and function of different microbes present in these tissues. Currently, microbiota study in cancer research is one of the fastest growing scientific areas. Recognition of the microbial composition and their functions, defines the role of microbial populations in various cancers. Though the human microbiome consists of bacteria, virus and fungi, largest focus has been given on bacterial constituent. The information given in Table 1 shows the recent contribution of metagenomic analysis in identifying different cancer associated bacteria. Microbiota analysis through metagenomic approach has significantly enriched our understanding about the presence of various cancer associated-microbes (particularly bacteria). However, metagenomic analysis carried out with genomic DNA isolated from patient tissue samples doesn't provide information about the viability of detected microbes and functional proteins or metabolites expressed by them. Hence, integration of metaproteomics and/or metabolomics approaches with metagenomic and metatranscriptomics would provide holistic information about the functional association between different microbes with cancer initiation and/or progression.

### CONCLUSION AND PERSPECTIVES

As the functional role of different infectious agents in cancer is becoming clearer, there is a growing interest in the use of different anti-infectious agents as preventive and therapeutic agent for cancer. It has been proposed that, anti-infectious agents target genes or proteins of infectious organisms; therefore, therapeutics against those proteins might have a

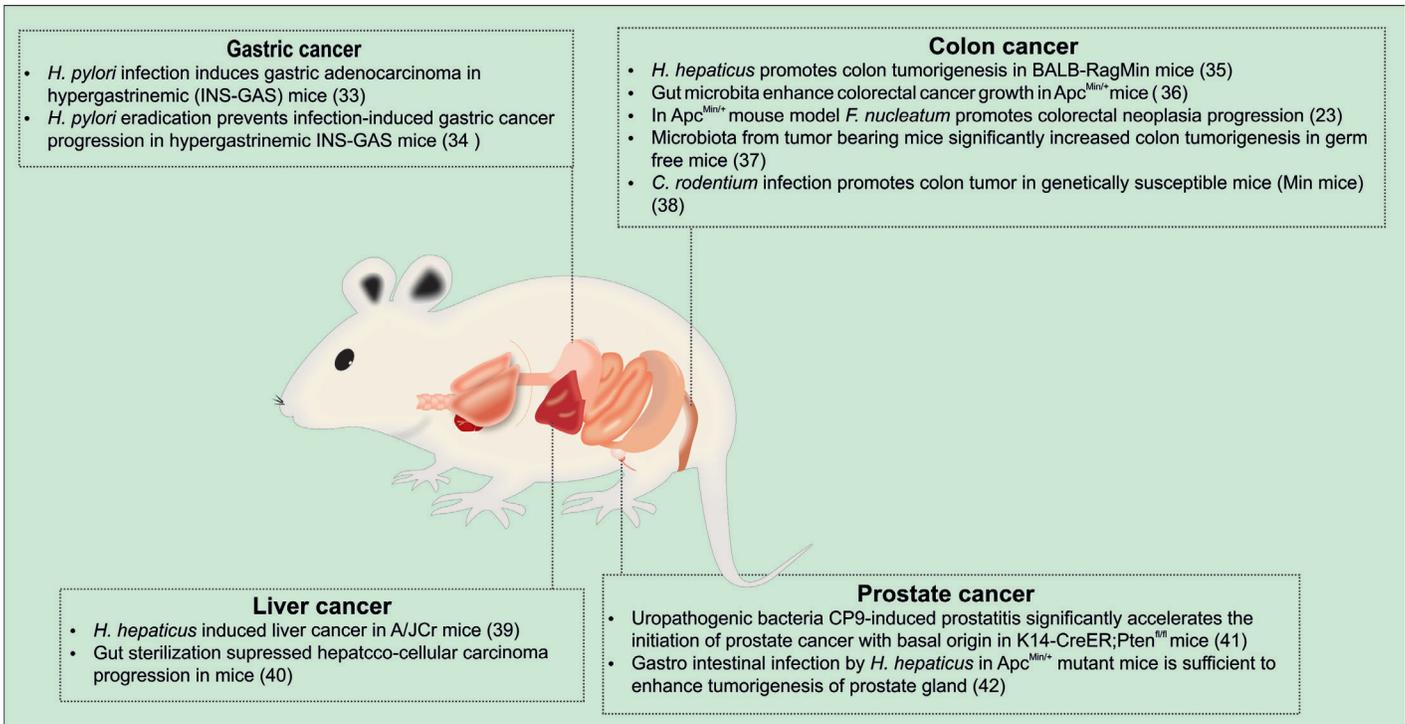
less off-target effect on host. However, use of anti-infectious agents for cancer therapy completely depends on the actual functional involvement of particular bacteria/microbes in a cancer initiation and/or progression events. Different mouse models have been very instrumental to investigate the functional role of bacterial infection in various cancers' initiation and/or progression (Figure 1). Unfortunately, many human-associated pathogens don't grow or manifest similar diseases in animal models. Hence, in this context we need to develop more clinically relevant animal models, which will help in understanding the actual functional role of an infectious agent in cancer development and also to evaluate the efficacy of different therapeutic agents. Furthermore, efforts should be given in developing better screening process to detect transmission of different infectious agents like HBV, HCV and HIV. Identification of cancer specific microbial signature would have paramount implication in cancer prevention and/or therapy. Last but not the least, it is also very important to aware people about the role of different infections in cancer, and they should also be educated about different preventive measures that could help in preventing infection and cancer.

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**Table 1: Contribution of metagenomic analysis in identifying different cancer associated bacteria.**

Cancer Type	Approach	Sample Analyzed	Enriched bacterial phylotypes	Ref.
Head and neck squamous carcinoma	V3-V5 16S rRNA sequencing	Saliva	<i>Streptococcus spp.</i> and <i>Lactobacillus spp.</i>	(43)
	V1-V4 16S rRNA sequencing	Tumor	<i>Parvimonas</i>	(44)
Oral cancer	V4-V5 16S rRNA sequencing	Saliva	<i>Streptococcus</i> , <i>Gemella</i> , <i>Rothia</i> , <i>Peptostreptococcus</i> , <i>Porphyromonas</i> , and <i>Lactobacillus</i>	(45)
Prostate cancer	V3 16S rRNA sequencing	Urine	<i>Bacteroidetes bacteria</i> , <i>Alphaproteobacteria</i> , <i>Firmicutes bacteria</i> , <i>Lachnospiraceae</i> , <i>Propionimonas</i> , and <i>Sphingomonas</i>	(46)
Breast cancer	V6 16S rRNA sequencing	Tumor	<i>Bacillus</i> , <i>Enterobacteriaceae</i> and <i>Staphylococcus</i>	(47)
Lung cancer	V1-V2 16S rRNA sequencing	Sputum	<i>Granulicatella</i> , <i>Abiotrophia</i> , and <i>Streptococcus</i>	(48)
	V3-V4 16S rRNA sequencing	Tumor	<i>Thermus</i> , and <i>Legionella</i>	(49)
colorectal cancer	V3 16S rRNA sequencing	Tumor	<i>Lactococcusand</i> and <i>Fusobacterium</i>	(50)
	V1-V2 16S rRNA sequencing	Tumor	<i>EikenellaFusobacterium</i> , <i>Bulleida</i> , <i>Gemella</i> , <i>Parvimonas</i> , <i>Campylobacter</i> and <i>Streptococcus</i>	(51)
	V3 -V4 16S rRNA sequencing	Fecal	<i>Fusobacteriu</i> , and <i>Porphyromonas</i>	(52)
Colorectal Adenomas	16S rRNA sequencing	Tumor	<i>Bifidobacterium sp.</i> and <i>Eubacteria</i>	(53)
Adenomatous polyps	16S rRNA sequencing	Fecal	<i>Mogibacterium</i> , and <i>Bacteroidetes sp.</i>	(54)
Rectal Carcinoma	V4-V5 16S rRNA sequencing	Tumor	<i>Bacteroides</i> , <i>Phascolarctobacterium</i> , <i>Parabacteroides</i> , <i>Desulfovibrio</i> , and <i>Odoribacter</i>	(55)
Gastric cancer	16S rRNA sequencing	Tumor	<i>Helicobacter pylori</i>	(56)
Gastric cancer	16S rRNA PCR and T-RFLP	Tumor	<i>Streptococcus</i> , <i>Lactobacillus</i> , <i>Veillonella</i> and <i>Prevotella</i>	(57)
Biliary tract cancer	V4 16S rRNA sequencing	Tumor	<i>Methylophilaceae</i> , <i>Fusobacterium</i> , <i>Prevotella</i> , <i>Actinomyces</i> , <i>Novosphingobium</i> and <i>H. pylori</i>	(58)



**Figure 1: Experimental evidences from mouse models that showed functional association between bacterial infections and cancers.** Mouse models have been very instrumental to understand the infection-mediated tumorigenesis of different organs, and bridge the gap between laboratory findings and their clinical use. Mice of dissimilar genetic background are differentially susceptible to infections and might manifest unlike complications after infection with specific microbes. Hence, to understand the mechanistic role of bacterial infections in different cancers, sustained efforts should be made to establish and characterize novel mouse models.

## CONFLICT OF INTEREST

The authors declare no conflict of interests.

## ABBREVIATION USED

HBV: Hepatitis B virus; HPV: human papillomaviruses; HCV: Hepatitis C virus; HIV: human immunodeficiency virus; CRC: colorectal cancer; MDSCs: Myeloid-derived suppressor cells; 4NQO: Nitroquinoline 1-oxide.

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