Review Article

Chronic bacterial and parasitic infections and cancer: a review

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Abstract

Background: A relatively underestimated facet of infectious diseases is the association of chronic bacterial and parasitic infections with cancer development. Therefore, we sought to evaluate the evidence regarding the association of such infections with the development of malignancy, excluding the overwhelming evidence of the association of *Helicobacter pylori* and cancer.
Methodology: We searched Pubmed, Cochrane, and Scopus without time limits for relevant articles.
Results: There is evidence that some bacterial and parasitic infections are associated with cancer development. The level of evidence of this association varies from high to low; in any case, a long time interval is mandatory for the development of cancer. A high level of evidence exists for the association of *Salmonella* Typhi with gallbladder and hepatobiliary carcinoma; *Opisthorchis viverrini* and *Clonorchis sinensis* with cholangiocarcinoma; *Schistosoma hematobium* with bladder cancer; chronic osteomyelitis with squamous cell carcinoma of the skin; and hidradenitis suppurativa with squamous cell carcinoma of the skin. In contrast, the level of evidence regarding the association of *Chlamydia* spp. with cancer is low. *Mycobacterium tuberculosis* is associated with lung cancer, albeit probably not etiopathogenetically.
Conclusions: A considerable number of bacterial infections and parasitic infections are associated with the development of cancer. Further research into recognizing additional associations of bacterial and parasitic infections with cancer is mandatory.

Key words: *Salmonella* Typhi, *Chlamydia, Mycobacterium tuberculosis, Schistosoma, Tropheryma whippelii*, chronic osteomyelitis, hidradenitis suppurativa

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Introduction

It is estimated that over 20% of malignancies worldwide can be attributed to infectious agents [1,2]. Indeed, there is a large body of evidence regarding the role of viruses such as hepatitis B virus (HBV), Epstein-Barr virus (EBV) and human papilloma virus (HPV) in the complex processes of carcinogenesis.

Other microorganisms have been implicated in carcinogenesis as well. Early in the nineteenth century the all theory of the possible association between bacterial infection and cancer was proposed [3]. However, the issue of whether specific bacterial species or parasites exhibit tumorigenic properties remains yet rather controversial. Additionally, the specific molecular mechanisms of the neoplastic action of these pathogens have not been elucidated so far.

Literature search

In the present article, we sought to review the evidence regarding associations of human bacterial pathogens and parasites with cancer. Our main purpose was to investigate the relationship between pathogens related to chronic disease and cancer development without referring to and analyzing any association of other inflammatory disorders with oncogenesis (*e.g.*, autoimmune diseases).

We searched Pubmed, Cochrane, and Scopus without time limits. The following search terms were employed in various combinations: "bacterium", "parasite", "cancer", and "infection". As there are many previous studies concerning the relationship between cancer and *Helicobacter pylori* we will not present further evidence on this subject. Bacteria that cause tumors (such as Bartonella species) but not cancer were not included in the analysis; neither were bacteria that are associated with (but not causative of) cancer. In addition, the association of viruses (such as

Hepatitis B virus, Hepatitis C virus and Epstein Barr Virus) with cancer was excluded from the analysis. The reference lists of relevant articles retrieved by the searches were also reviewed. We finally selected 183 articles (published in the English language literature between 1949 and 2007) for further analysis.

The following bacterial and parasitic pathogens were retrieved in association with cancer: *Salmonella* Typhi (*S.* Typhi), Chlamydia species, *Mycobacterium tuberculosis*, Schistosoma species, *Tropheryma whippelii*, liver flukes (*Opisthorchis viverrini* and *Clonorchis sinensis*), as well as various bacterial causative agents of chronic osteomyelitis and hidradenitis suppurativa.

However, it should be noted that, according to the IARC special report on the Meeting on Human Carcinogens held in Lyon, the possible oncogenic role of *S.* Typhi is not considered relevant to cancer development [1]. Moreover, the IARC working group does not refer to agents associated with chronic osteomyelitis or with hidradenitis suppurativa.

Along these lines, our aim was to review the potential association based on the available published evidence plus well-documented reports such as the IARC special report. Furthermore, we discussed the likely oncogenetic mechanisms of the aforementioned pathogens.

Salmonella Typhi and cancer development

Among the several risk factors for gallbladder cancer (cholelithiasis, obesity, exposure to certain chemicals), chronic infection with *S.* Typhi is of great importance [4-7]. Chronic carriers of this pathogen have an approximately eightfold excess risk of developing gallbladder carcinoma than non-carriers and an approximately 200-fold excess risk of developing hepatobiliary carcinoma, compared with people who have had acute typhoid and have cleared the infection [8,9]. Robbins *et al*. described the first documented case of a chronic carrier of *S.* Typhi who subsequently developed cholangiocarcinoma [10].

Dutta *et al*. also suggested that gallstones and the chronic typhoid carrier state might co-operate in the pathogenesis of gallbladder carcinoma, though it is difficult to ascertain a cause-and-effect relationship [11]. Moreover, among patients with gallstones, the chronic typhoid carrier state was shown to be the only independent risk factor for the development of gallbladder carcinoma [5]. Finally, studies demonstrated that typhoid carriage was not only associated with an increased risk of gallbladder cancer but also with malignancy in the pancreas, lung and colorectum [8,12].

Consequently, based on the available bibliographical data, we can conclude that *S.* Typhi infection is characterized by a relatively strong association with gallbladder and hepatobiliary carcinoma and by a weak correlation with carcinomas in the pancreas, lung and colorectum [table 1].

Mechanism of tumorigenic action

It is believed that chronic infection of the gallbladder can cause gallbladder carcinoma through different processes. Bacteria are able to produce b-glucuronidase, which subsequently results in deconjugation of conjugated toxins and bile acids. As a consequence, these products may acquire a potentially carcinogenic action [13-15]. According to Kinoshita *et al*., glucuronidase action is responsible for the production of a very active intermediate substance with the ability to bind to DNA and a mutagenic potential [16]. In this framework, the increased production of free radicals in the gallbladder of patients suffering from chronic typhoid infection plays an essential role [11,17]. The exact pathogenetic process by which chronic *S.* Typhi carriage leads to tumor development has yet to be determined; however, there is increasing evidence that the products of the degradation of bile salts by intestinal bacteria may contribute to tumorigenesis [18,19].

Chlamydia species and cancer development

Chlamydia pneumoniae (*C. pneumoniae*) is a Gram-negative bacillus and a compulsory intracellular parasite [20,21]. It causes respiratory infection in more than 50% of adults leading to a higher incidence of pneumonia [22,23].

It has been suggested that persistent *C. pneumoniae* inflammation correlates with increased risk of lung cancer [7,23-26]. According to some data, elevated *C. pneumoniae* antibody titers have been observed in lung cancer [27]. It has been reported that individuals with elevated IgA antibody titers to this organism have up to a twofold increased lung cancer risk [25]. Specifically, elevated IgA

Table 1.

Pathogens	Main associated cancer	Level of evidence High vs Low*
***Salmonella*Typhi**	Gallbladder carcinoma	High [4-10]§
	Hepatobiliary carcinoma	High [8-9]
	Carcinomas in pancreas, lung and colorectum	Low [8,12]
Chlamydia species		
1.*Chlamydia pneumoniae*	Lung carcinoma	High [7,23-29]
2. *Chlamydia trachomatis*	Ovarian carcinoma	Low [30]
3. *Chlamydia psittaci*	Ocular lymphoma	Low [33]
Mycobacterium tuberculosis	Lung carcinoma	Low [38-40,41-43]
	Kaposi's sarcoma	Low [44,45]
Schistosoma species		
1.*Schistosoma haematobium*	Bladder carcinoma	High [54-55,59-67,73]
	Cervical carcinoma	Low [56,74-78]
2. *Schistosoma mansoni*	Colorectal carcinoma	Low [70]
3. *Schistosoma japonicum*	Liver carcinoma	Low [80]
	Colorectal carcinoma	Low [81-82]
Tropheryma whippelii	Lymphoma	Low [108]
	Gastric adenocarcinoma	Low [110]
Liver flukes		
1.*Opisthorchis viverrini*	Cholangiocarcinoma	High [113.120-126]
2. *Clonorchis sinensis*	Cholangiocarcinoma	Low [113,120-126]
Various causative agents of Chronic Osteomyelitis	Squamous cell carcinoma of the skin	High [14 141-152]
	Basal cell carcinoma of the skin	Low [153]
	Fibrosarcoma	Low [154,156,158,160-161]
	Myeloma	Low [155]
	Angiosarcoma	Low [157]
	Rhabdomyosarcoma	Low [157]
Various causative agents of Hidradenitis Suppurativa	Lymphoma	Low [165]
	Squamous cell carcinoma of the skin	High [172,174-177,180]
	Liver carcinoma	Low [179]

*Based on the available published data; § corresponding reference numbers

against *C. pneumoniae* were reported to be correlated with squamous cell carcinomas and to a lesser extent with small cell carcinomas and adenocarcinomas of the lung [7,25].

In addition, other seroepidemiological studies have indicated a possible relation between *C. pneumoniae* infection and lung carcinoma [23,27-28]. Interestingly, investigators observed that the high *C. pneumoniae* antibody titers detected in lung carcinomas were found in smokers [23,27-29]. Laurila *et al*. reported that *C. pneumoniae* infection was present principally in patients with small-cell and squamous cell carcinomas, among 230 smokers with lung carcinoma [29]. Koyi *et al*., after studying 117 smokers with lung carcinoma, observed that seropositivity ratios were different from the control group [28]. Moreover, Kocazeybek examined 123 smokers diagnosed with lung carcinoma; in this study, chronic *C. pneumoniae* infection seropositivity was found in 50% of the patient group, and small-cell and squamous cell carcinomas of the lung were detected especially in the cases with chronic *C. pneumoniae* infection seropositivity [23]. It is worth mentioning that chronic *C. pneumoniae* infections were seen statistically more often in male patients with carcinoma who were 55 years old or younger. This study further supported the idea that chronic *C. pneumoniae* infection increases the risk of lung carcinoma.

On the other hand, *Chlamydia trachomatis* species are often involved in chronic persistent infections of the upper genital tract, which are clinically ''silent'' [30]. It has been reported that these microorganisms may be responsible for

significant damage to the reproductive organs, resulting in epithelial ovarian cancer [30].

Finally, Chlamydia have been associated with lymphoproliferative disorders in adults [31,32]; in particular, ocular lymphomas have been linked to *Chlamydia psittaci* [33]. On the contrary, it is believed that there is no convincing proof for association between Chlamydia and leukaemia [34].

Therefore, concerning the specific level of evidence, *Chlamydia trachomatis* and *Chlamydiae psittaci* infections are weakly linked to ovarian carcinoma and ocular lymphoma, respectively [table 1]. On the contrary, *Chlamydia pneumoniae* infection seems to be strongly associated with lung carcinoma [table 1].

Mechanism of tumorigenic action

According to some studies, smoking assists *C. pneumoniae* to invade the lung. In this complex framework of interactions, superoxide oxygen radicals, TNF-a, IL1β and IL8 play an essential role, contributing to lung tissue and DNA damage that eventually results in carcinogenesis [35,36]. Another suggestion is that, by unknown mechanisms, *C. pneumoniae* infection causes irregular apoptosis in tissues [37]. Concerning the pathogenesis of ovarian cancer, Chlamydia infections are thought to induce a state of persistent inflammation that subsequently increases the risk for tumor development in the ovarian surface epithelium [30].

Mycobacterium tuberculosis and cancer development

Several findings led to the suggestion that *Mycobacterium tuberculosis* can cause the development of malignant diseases [38]. Steinitz reported that individuals with clinical history of tuberculosis had a five-fold (ten-fold for female patients) higher risk of lung carcinoma than control subjects [39]. Further studies also showed that there was a tendency of the developed bronchogenic carcinomas to be localized in the lobe of the lung, which was involved in the tuberculous infection [40]. Other studies have also reported a higher lung cancer risk in association with tuberculosis [41-43].

Moreover, tuberculosis has been suggested to be a determinant of Kaposi's sarcoma growth [44,45]. In two kidney allograft recipients with extensive cutaneous Kaposi's sarcoma, disappearance of the sarcoma was reported, once pulmonary tuberculosis had been treated, without any reduction in immunosuppressive therapy [44].

Therefore, we suggest that *Mycobacterium tuberculosis* infection is characterized by a low level of evidence regarding its association with lung carcinoma and Kaposi's sarcoma [table 1].

Mechanism of tumorigenic action

According to researchers, any connection between active tuberculosis and malignancy is attributed to reactivation of infection in immunocompromised patients suffered from cancer rather than to a cause-and-effect relationship between infection and neoplasm [46-48]. Regarding Kaposi's sarcoma association with tuberculosis, it has been hypothesized that constantly increased levels of circulating VEGF related to this pathogen might result in the carcinogenesis [45].

Schistosoma species and cancer development

Schistosomes are dioecious parasitic blood flukes, which have a mammalian host and an intermediate invertebrate host: fresh water snails [49]. In particular, *Schistosoma haematobium* (*S. haematobium*), is a digenetic trematode or blood fluke, which resides in the systemic venules and capillaries of the human bladder and other pelvic organs [50]. Approximately 200 million people are infected with schistosomes [51], most commonly with *S. haematobium* and *Schistosoma mansoni* (*S. mansoni*). The peak of the schistosoma infection occurs in the second decade of life [49]. Schistosomiasis has been associated with various types of malignancy such as carcinoma of the intestine, liver, uterus, and bladder [52-59].

Schistosoma infections of the urinary tract are endemic in countries such as Egypt, Iraq, and Sudan, in which increased rates of bladder cancer are also observed [55,59,60]. There is a large body of knowledge regarding the association between inflammation from schistosomal infections and squamous cell carcinoma of the bladder, especially in countries in Africa and the Middle East [54,55,61-65]. In some countries with a high rate of schistosomal infections (such as Iraq, Malawi, Zambia, and Kuwait), bladder cancer was reported to be the leading malignant disease [59,66,67]. Based on all these findings, the International Agency for Research on Cancer has classified *S. haematobium* infection as carcinogenic [57].

S. haematobium-associated bladder cancer is histopathologically distinct from non-*S. haematobium*

associated bladder cancer that occurs in North America and Europe. The former cancer is usually a high-grade squamous cell carcinoma that mainly affects individuals of middle age, sparing the bladder's trigone [14,49,58,69,71-74]. There is a noteworthy relationship between the long duration of the inflammatory process due to *S. haematobium* and the increased possibility for development of malignant disease [68].

Although the majority of bladder tumors formed due to schistosoma infection are squamous cell carcinomas, adenocarcinomas and transitional cell carcinomas or undifferentiated carcinomas can develop [73]. Furthermore, it appears that there is a proportional increase of transitional cell carcinomas due to schistosomal infections over time [58,69]. Some researchers believe that transitional cell carcinomas need more time to progress than squamous cell carcinomas and are closely related with a less devastating inflammatory infiltrate [69].

Interestingly, *S. mansoni* infection has also been associated with colorectal carcinoma. Madbouly *et al*. compared histopathologic and genetic changes in schistosomal colitis-associated colorectal cancer with colorectal cancer in a group of patients from the same population not affected by the disease [70]. Their data suggested that schistosomal colitis was commonly associated with earlier onset of multicentric colorectal cancer, higher percentage of mucinous adenocarcinoma, and presentation of the carcinoma at an advanced stage [70].

Furthermore, involvement of the female genital tract by Schistosomas (and particularly *S. haematobium*) is well recognized. Charlewood *et al*. reported that cervical schistosomiasis may progress to squamous cell carcinoma of the cervix [74]. Indeed, the uterine cervix is the most frequent site of involvement and it has been suggested that schistosomiasis of the cervix may lead to the development of cervical carcinoma [58]. Squamous cell carcinoma occurring in association with cervical schistosomiasis has also been described by Badawy; the suggestion was made that schistosomiasis induces premalignant cervical lesions and, finally, carcinoma *in situ* [75]. In addition, Berry reported two cases of cervical carcinoma *in situ* associated with schistosomiasis [76]. Youssef *et al*., in a series of cervical schistosomiasis cases from Egypt, demonstrated 15 cases of invasive squamous cell carcinomas and one case of carcinoma *in situ* in which *S. haematobium* ova were identified within the tumor [77]. Finally, Al-Adnani and Saleh have also reported the association of *S. haematobium* with cervical cancer in one out of seven cases of cervical schistosomiasis [78]. Additionally, Coelho *et al*. described 16 cases of invasive and microinvasive squamous cell carcinoma and 51 cases of severe dysplasia and carcinoma *in situ* associated with *S. mansoni* infection [79].

On the other hand, *Schistosoma japonicum* (*S. japonicum*) has been linked, as an etiological factor, to liver carcinoma in Japan and colorectal carcinoma in China and the Philippines [49,56,57,59,68,80-82]. Thus this parasite has been characterized as potentially carcinogenic to humans, though its role needs further investigation. Finally, studies have suggested a connection between lymphomas and leukemias and schistosomiasis [54], whereas increased frequency of giant follicular lymphoma of the spleen has been reported in correlation to hepatosplenic disease caused by *S. mansoni* [83].

Thus *S. haematobium* infection seems to be strongly correlated with bladder carcinoma [table 1]. On the other hand, the aforementioned infection as well as *S. mansoni* and *S. japonicum* infections are weakly linked to cervical, colorectal, liver and colorectal carcinomas [table 1].

Mechanism of tumorigenic action

Schistosomas may cause bladder cancer through bladder irritation, inflammation [84,85] and concurrent chronic bacterial infections [59]. More analytically, Schistosomiasis mainly causes tumors due to the deposition of worms and eggs in the tissue, resulting in a chronic inflammatory reaction [49]. This inflammatory infiltrate predominantly consists of macrophages and neutrophils, which are significant sources of endogenous oxygen radicals. These radicals are associated with the formation of carcinogenic N-nitrosamines [86]. Furthermore, inflammatory cells, through the formation and release of hydroxyl radicals, are responsible for various mutations [87], sister chromatid exchanges [88], and breaks of the DNA strand [89]. What is more, inflammatory cells contribute to the activation of aromatic amines and polycyclic hydrocarbons. The final result is the production of specific metabolites with carcinogenic action [90].

It should be noted that nitrate-reducing bacteria and increased levels of urinary and saliva N-nitrosamines levels were observed to be highest in patients with schistosomal infections compared to those in healthy controls [59,65,91,92]. This observation lends credence to the notion that

nitrosamines play an essential role in schistosomiasis-associated bladder cancer [69,73,93]. Therefore, it is believed that inflammatory cells in the urinary bladder of patients suffering by schistosomal infections may enhance the potential of aromatic amines to lead to cancer formation [59].

Furthermore, studies on molecular events associated with specific genes that trigger neoplastic progression during the course of schistosomal infections of the bladder were conducted [94-96]. These events include the activation of H-ras [96], the inactivation of p53 [95], and the inactivation of the retinoblastoma gene [94]. Emphasis has also been given to products of specific oncogenes, which regulate cell cycle procedures, leading ultimately to uncontrolled cell growth and tumor formation [59].

Finally, regarding colorectal carcinomas, the identification of a higher incidence of altered p53 expression in the schistosomal colitis-associated colorectal cancer group makes possible an association between schistosomiasis and alterations in p53 activation as an initial event for the development of these neoplasms [70]. Nonetheless, these findings need further verification to clarify the exact role of p53 gene inactivation.

Tropheryma whippelii and cancer development

Whipple's disease is a rare inflammatory disorder caused by the Gram-positive bacterium *Tropheryma whippelii (T. Whippelii)* [99,100]. These bacteria are mainly found in the soil and in sewage but not in animal hosts. It is believed that white males are most commonly affected by this pathogen, especially farmers and outdoor workers [100]. Although this recently described pathogen initially infects the gastrointestinal tract, it can trigger a chronic generalized infection involving nearly every organ [101]. Patients usually present with gastrointestinal symptoms (mainly diarrhoea) or migratory arthralgias, weight loss, fever and night sweats [100,104].

There is a great deal of debate regarding the possible oncogenic action of this bacterium, largely because many local manifestations of Whipple's disease may mimick malignant neoplasm, specially a lymphoma [103]. Along these lines many cases of Whipple's disease clinically present with lymphadenopathy, mainly affecting the mesenteric, retroperitoneal and paraaortic lymph nodes [103,104]. For that reason, the differential diagnosis becomes quite difficult, demanding the exclusion of a possible primary lymphoma [104].

On the other hand, the association of Whipple's disease with well-documented malignant neoplasms has been reported. Gillen *et al*. reported the first case of extraintestinal lymphoma in association with Whipple's disease. They presented a case of a 45-year-old man with Whipple's disease who subsequently developed fever and a mass in the neck and died despite therapeutical interventions. Necropsy documented extraintestinal lymphoma [108]. According to the authors' opinion, the neoplasm had been triggered by the initial inflammatory process due to the infectious agent. Gruner *et al*. described a 60-year-old man with multifocal lymphadenopathy who had been suffering six years from Whipple's disease. A diagnosis of a malignant non-Hodgkin-Lymphoma was made. Interestingly, the authors highlighted the fact that this malignant lymphoma could be a direct consequence of Whipple's disease or a second neoplastic disease [109]. Moreover, Whipple's disease has been associated with the development of other neoplasms. Cadenas *et al*. described the case of a 57-year-old male with Whipple's disease who eight years after the initial manifestations of the infection developed an intramucosal gastric adenocarcinoma [110]. Nevertheless, a clear causal relationship between the aforementioned infection and the malignant tumor is difficult to establish.

Thus, according to the published data, there is a relatively weak liaison between *Tropheryma whippelii* infection and cancer development [table 1].

Mechanism of tumorigenic action

It has been suggested that the delayed diagnosis of Whipple's disease and the subsequent non-effective antibiotic treatment might result in abnormalities in both the humoral response and T-cell function [108]. In this context, Wang *et al*. pointed out that a possible underlying mechanism of lymphoma development could be an established immunodeficiency status in patients suffering from this infectious process [100]. Taken together, these abnormalities may contribute to the progression of an associated extraintestinal lymphoma [100,108].

Other researchers have underlined the occurrence of t(14;18) translocation in lymphocytes in some cases of Whipple's disease. As this translocation can be detected in most cases of centroblastic/centrocytic follicular lymphomas, it has also been suggested that this acts as a causative factor for the development of

a malignant lymphoma in patients infected with *T. whippelii* [111].

Liver flukes (*Opisthorchis viverrini* and *Clonorchis sinensis*) and cancer development

Liver flukes constitute a polyphyletic group of trematodes (phylum Platyelminthes). Adults of liver flukes are characteristically localized in the liver, bile ducts, and gallbladder of various mammals, including humans. They encompass various species but of particular interest are two parasites: *Opisthorchis viverrini* (*O. viverrini*) and *Clonorchis sinensis* (*C. sinensis*) [112].

More specifically, *Opisthorchis* and *Clonorchis* infect the bile ducts of millions of persons in the Far East [113]. Indeed, according to calculations, more than 600 million people are at risk of infection with these pathogens [114]. *O. viverrini* is endemic in Southeast Asia, while *C. sinensis* mainly infects rural provinces of China [115]. In Thailand, particularly, the traditional habit of eating ground, raw freshwater and salt-fermented fish on a daily basis is believed to have as a consequence a continuous exposure to liver flukes [116]. In this country, current data demonstrate that about 6 million people are infected with *O. viverrini* [117].

The great majority of people with opisthorchiasis or clonorchiasis is asymptomatic or has non-specific symptoms such as right upper quadrant abdominal pain and fatigue [118]. However, chronic infection with these parasites is thought to be related to various diseases of the hepatobiliary tract, such as cholangitis, jaundice, periportal fibrosis, cholelithiasis and cholecystitis [119].

Furthermore, the most interesting issue regarding infections with the aforementioned flukes is that they can potentially trigger the development of cholangiocarcinomas [113,120]. Sonakul *et al*., studying 87 cases of primary hepatic carcinomas associated with opisthorchiasis, concluded that the great majority of these tumors were cholangiocarcinomas (77%), whereas hepatocellular carcinomas, mixed hepato-cholangiocarcinomas, squamous-cell carcinomas and undifferentiated carcinomas followed in frequency [121]. Along these lines, Schwartz reported a clinically silent *C. sinensis* infection linked to cholangiocarcinoma in a Chinese patient, whereas Sher *et al*. described the development of cholangiocarcinoma in a Laotian immigrant to the United States of America who suffered from clonorchiasis, emphasizing to the necessity of early diagnosis of this infectious process [120,122]. Other investigators, additionally, reported two cases of clonorchis-associated cholangiocarcinoma highlighting their cholangiographic features and the various local complications [123]. Finally, various other epidemiological studies as well as histopathological characteristics lend credence to the notion that *C. sinensis* and *O. viverrini* are predisposing factors for the pathogenesis of cholangiocarcinoma in endemic countries [124,125].

Investigators attempted also to shed light on the possible association between liver cancer and *O. viverrini* infection in five different areas of Thailand. They compared the incidence of hepatocellular carcinoma and cholangiocarcinoma with the prevalence of exposure to the main risk factors in samples of the population of these areas. They deduced that cholangiocarcinoma showed remarkable variations in incidence, which were intimately associated with exposure to *O. viverrini*. The same was not true concerning the incidence of hepatocellular carcinoma [126].

Thus it is currently believed that *O. viverrini* constitutes a definite cause of human cholangiocarcinoma while *C. sinensis* is a probable cause [68, table 1].

Mechanism of tumorigenic action

Regarding the pathogenesis of the abovementioned tumorigenic process, it should be pointed out that it remains yet unclear. However, given that *C. sinensis* and *O. viverrini* infections lead to quite similar tissue reactions in bile ducts [125], it has been suggested that chronic severe infection, immunologic disturbances, and various carcinogenic products, could ultimately lead to tumor development [113].

Indeed, the initial pathologic alteration, which is an epithelial desquamation probably due to chronic irritation triggered by the liver flukes or their metabolic products, could subsequently contribute to regenerative changes, epithelial hyperplasia, goblet cell metaplasia and adenomatous hyperplasia [119,125]. Accordingly, this hyperplastic epithelium might be vulnerable to various exogenous and endogenous carcinogens [127,128]. Moreover, activation of drug metabolizing enzymes (such as p-450) as well as increased nitric oxide production can result in DNA damage [129,130] and cytotoxicity [112,128,131], respectively.

Chronic osteomyelitis and cancer development

Among bacterial inflammatory processes, chronic osteomyelitis was the first to be convincingly connected with cancer in humans [42]. The term "Marjolin ulcer" has been proposed for this phenomenon, describing any malignant degeneration of a chronic inflammatory skin lesion, independently from the origin of the lesion and the type of cancer developing in the lesion [132].

By definition, "Marjolin ulcers" include carcinomas that transform from chronic open wounds of pressure sores or burn scars [133]. These carcinomas typically arise in the draining sinus tract of chronic osteomyelitis; they are aggressive and have a tendency for local recurrence and lymph node metastases [133]. However, this malignant degeneration appears to be a local phenomenon, and if diagnosed early, has a rather favorable outcome following complete excision [134].

Chronic osteomyelitis affects predominantly middle-aged and older men, usually involves the lower extremity, and most often occurs in the tibia. The presence of a painful ulcer over the affected bone should raise suspicion regarding its malignant nature [135]. A long-standing infection, clinically identified by a draining sinus tract, is believed to lead to the process of oncogenesis. Nevertheless, investigators point out that carcinomas can also occur in scars overlying quiescent osteomyelitis (*e.g.*, in burn scars) [135]. The aforementioned neoplasms are largely localized in the tibia [135] but also in the foot and ankle [137], in the patella [138] and in a toe [139].

Look *et al*. reviewed 230 patients (mean age ~55 years) with carcinomas arising from chronic osteomyelitis. According to their findings, malignancy resulted in about 1.5% of the cases of chronic osteomyelitis. Interestingly, males were afflicted seven times more frequently than females. There was a long time interval, extending beyond three decades, from the initial diagnosis of the infection up to the diagnosis of the malignancy [140].

The tumors that develop on chronic osteomyelitis are generally squamous cell carcinomas [14, 141-152]. Nonetheless, basal cell carcinoma, fibrosarcoma, myeloma, angiosarcoma, rhabdomyosarcoma, and lymphoma have also been reported [153-161]. Among squamous cell carcinomas the most common histological form is spinocellular squamous cell carcinoma followed by verrucous squamous cell carcinoma [162]. The incidence of the abovementioned malignant transformation is estimated between 0.2% and 1.7% of cases of chronic osteomyelitis [14,132,134,163-164].

In a study conducted by McGrory *et al*., in patients (mean age 59 years) with chronic osteomyelitis that developed malignancy in the sinus tract, the vast majority (50 out of 53 patients) developed squamous cell carcinomas. The other patients had a fibrosarcoma, a myeloma, and a lymphoma respectively [165].

Therefore, it seems that among the various causative agents of chronic osteomyelitis and basal cell carcinoma of the skin, fibrosarcoma, myeloma, angiosarcoma, rhabdomyosarcoma and lymphoma, a low level of bibliographical evidence exists, regarding the possible oncogenic role of the former pathogens. However, squamouscell carcinoma of the skin appears to be strongly associated with the various causative pathogens of chronic osteomyelitis [table 1].

Mechanism of tumorigenic action

As far as the mechanisms of carcinogenesis are concerned, the constant irritation of a draining sinus tract by inflammatory exudates of the underlying bone seems to predispose the host to develop carcinoma of the skin, regardless of the specific bacterial pathogen involved [42,144]. As a matter of fact, there is a broad spectrum of pathogens such as *Staphylococcus aureus*, *Streptococcus pyogenes*, *Haemophilus influenzae* implicated in cases of hematogenous or anaerobic bacteria in non-hematogenous osteomyelitis [166].

Moreover, it is believed that the unstable wounds and scar tissue around the chronic osteomyelitis areas can become complicated by malignant degeneration after a long time interval [132,134,166]. The exact physiopathological mechanisms of this transformation are unknown. The chronic irritation of the skin and the exposure of the soft tissue to different growth factors undoubtedly play a pivotal role [132,167]. It is possible that increased rates of DNA turnover associated with chronic inflammatory processes secondarily predispose cells to malignant transformation by primary carcinogens [14].

Hidradenitis suppurativa (HS) and cancer development

Hidradenitis suppurativa is a recurrent chronic inflammatory disease of the apocrine glands that most commonly involves the axillary, perianal,

perineal, and inframammary regions [168-171] and less commonly the buttocks and upper thighs [168].

The etiology of this suppurative and cicatricial disorder [168] is poorly understood; however, a genetic component, hormonal influence, and obesity are linked to its expression [172]. Characteristic histopathological findings include dilated keratin-filled pores, abscesses, scarring, sinus tract formation, malodorous discharge and inflammation with secondary infection [170].

Along these lines, a retrospective review of the microbiological and clinical data of 17 specimens obtained from axillary HS over a period of 6 years was performed by Brook *et al*. [173]. According to their results, the predominant aerobic bacteria were *Staphylococcus aureus*, *Streptococcus pyogenes* and *Pseudomonas aeruginosa*. On the other hand, the most commonly isolated anaerobes were *Peptostreptococcus* spp., *Prevotella* spp. and microaerophilic streptococci. Their study highlighted the polymicrobial population and predominance of anaerobic bacteria in axillary HS [173].

However, independently from the bacterial pathogens, which can be involved in cases of HS, the most serious, devastating and simultaneously rare complication of this disease is squamous cell carcinoma [172,174]. Alexander reported a case of squamous cell carcinoma arising in HS of over 20 years duration. Interestingly, this carcinoma exhibited metastases in almost all organs [175]. Zachary *et al*. described a squamous cell carcinoma that developed only three years after the appearance of severe HS of the perineum [176].

Moreover, HS of 35 years' duration, localized in the buttocks of a 57-year-old man, has been reported, which was finally complicated by a large, ulcerated, well-differentiated squamous cell carcinoma [177]. Williams *et al*., additionally, presented two patients with advanced longstanding perineal HS, giving emphasis to the necessity of early diagnosis so that the risk for further complications can be minimized [178].

Furthermore, researchers have found an increased risk among patients with HS not only for the development of non-melanoma skin cancer (such as squamous cell carcinoma) but also for the progression of buccal cancer and primary liver cancer. However, for the latter two malignancies, the observed relationship was somewhat weak due to statistical bias (combination of multiple significance testing and few observed cases) [179].

Crain *et al*., in accordance with the aforementioned data, inferred that an association between chronic HS and squamous cell carcinoma exists. Once again, a long latent period for the development of cancer was noted [180]. It is also noteworthy that squamous cell carcinoma has been associated with paraneoplastic neuropathy, presenting with subacute muscle weakness and sensory symptoms, in a patient with extensive perineal HS [174].

Other investigators have highlighted the fact that this inflammatory lesion can occur in patients with long-standing Crohn's disease, and have reported a case of chronic HS complicated by a vulval squamous cell carcinoma [181]. Finally, Maclean *et al*., referring to advanced cases of squamous cell carcinoma (SCC) arising in chronic HS, have advocated that HS arising in extra-axillary sites is a pre-malignant condition [182]. Taken together, all these data lead to the conclusion that HS can trigger the development of squamous cell carcinomas, depending mostly on the duration of the inflammatory process of hidradenitis.

Consequently, the various pathogens associated with HS are featured by a strong relationship with squamous cell carcinoma of the skin and by a weak correlation with liver carcinoma [table 1].

Mechanism of tumorigenic action

It is believed that the chronic irritation of the skin and secondary bacterial infections may lead to proliferative epidermal changes, including cancer [169,179]. More specifically, it has been proposed that the rupture of the follicular epithelium, during the inflammatory process, followed by the accumulation of corneocytes, bacteria, sebum products, and hair into the dermis, can trigger the formation of foreign body granulomas. Subsequently, sinus tracts, lined by epithelial tissue, are formed. As a next step, secondary bacterial colonization (mainly with coagulase-negative staphylococci) [183] in this long-standing inflammatory environment may contribute to the process of tumorigenesis.

Conclusions

In conclusion, there is no doubt that specific bacteria species and parasites can cause cancer through different and complex mechanisms. It is of note, however, that although the bacterial species associated with cancer are diverse, they share an important common characteristic: the time-interval between bacterial infection and cancer development,

in the majority of cases, is often many years. The paradigms of the tumorigenic action of *S.* Typhi, as well as the cases of chronic osteomyelitis and hidradenits suppurativa, are quite representative. Additionally, the clinical evidence regarding the association of each pathogen with malignant diseases varies significantly. For some bacterial species (*e.g*., *S.* Typhi) this relationship is well established, whereas for other pathogens (*e.g*., *C. psittaci* and ocular lymphomas) it is somewhat weak, making further studies necessary.

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