# **Review Article**

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# Effects of infections on the pathogenesis of cancer

Rocco Luca Emanuele Liardo<sup>1</sup>, Antonio Maria Borzì<sup>2</sup>, Corrado Spatola<sup>1</sup>, Barbara Martino<sup>2</sup>, Giuseppe Privitera<sup>1</sup>, Francesco Basile<sup>2</sup>, Antonio Biondi<sup>2</sup> & Marco Vacante<sup>2</sup>

<sup>1</sup>Radiodiagnostic & Oncological Radiotherapy Unit & <sup>2</sup>Department of General Surgery & Medical-Surgical Specialties, University of Catania, 'Policlinico G. Rodolico – San Marco' Catania, Italy

Several studies have shown an inverse relationship between acute infections and cancer development. On the other hand, there is a growing evidence that chronic infections may contribute significantly to the carcinogenesis. Factors responsible for increased susceptibility to infections may include modifications of normal defence mechanisms or impairment of host immunity due to altered immune function, genetic polymorphisms, ageing and malnourishment. Studies have demonstrated that children exposed to febrile infectious diseases show a subsequent reduced risk for ovarian cancer, melanoma and many other cancers, while common acute infections in adults are associated with reduced risks for melanoma, glioma, meningioma and multiple cancers. Chronic inflammation associated with certain infectious diseases has been suggested as a cause for the development of tumours. Mechanisms of carcinogenesis due to infections include cell proliferation and DNA replication by mitogen-activated protein kinase pathway, production of toxins that affect the cell cycle and lead to abnormal cell growth and inhibition of apoptosis. This review was aimed to summarize the available evidence on acute infections as a means of cancer prevention and on the role of chronic infections in the development and progression of cancer.

Key words Bacterial - cancer - carcinogenesis - immune system - infections - MAPK pathway - pathogenesis - virus

The complex association between infectious diseases and cancer has been widely discussed since the beginning of the twentieth century. Around 2.2 million new cases of cancer diagnosed in 2012, were attributable to carcinogenic infections. Among the most important infectious agents involved in cancer development and progression, *Helicobacter pylori* (HP) (770,000 cases), human papillomavirus (HPV) (640,000), hepatitis B virus (HBV) (420,000), hepatitis C virus (HCV) (170,000) and Epstein–Barr virus (EBV) (120,000) have been indicated to play a prominent role<sup>1</sup>. Infectious agents and related biochemical species are able to modulate a broad range of host immune responses and in turn may

affect tumour development and progression. However, the factors related to infection-mediated immunity that influences carcinogenesis has not been completely understood. Acute and chronic infections may play different roles in carcinogenesis; epidemiological studies have shown that acute infections antagonize the onset of cancer while chronic infections are able to favour carcinogenesis<sup>2</sup>. Acute infections are characterized by rapid onset and short duration and are usually associated with fever, synthesis of hepatic acute-phase proteins and production of cytokines and other inflammatory mediators. In some cases, chronic infections could be a consequence of failed or deficient immune response<sup>3</sup>. Factors responsible for increased susceptibility to infections include alterations of normal defence mechanisms or impairment of host immunity, abnormal immune function, genetic polymorphisms, ageing and malnourishment. Other factors that may determine whether infections occur are the biological characteristics of viruses, bacteria and parasites such as pathogenicity, virulence, invasiveness infective load, toxinogenesis, contagiousness, tenacity and vitality<sup>4</sup>. In industrialized countries, some tumours such as melanoma, colorectal, breast, kidney, testicular and prostate cancers are more common among people of higher socio-economic status (SES), while the prevalence of lung, liver, cervical and stomach cancers is higher in people of low SES<sup>5</sup>. In low SES groups, there is a higher concurrent use of tobacco and alcohol, responsible for lung and liver cancers, and a higher prevalence of chronic infections such as HPV, HP, HBV and HCV, which have been associated with uterine cervix, stomach and liver cancers<sup>6,7</sup>. There could be a possible inverse relationship between the decrease of incidence and mortality from infectious diseases and the increase in death rates due to cancer<sup>2,8</sup>. Mastrangelo *et al*<sup>8</sup> observed the simultaneous reduction of infections and growth of tumours in Italy. This trend could be explained through a decrease in the activation of immunological mechanisms against transformed cells in early phases of carcinogenesis<sup>8</sup>. There is evidence that West Nile virus, mumps virus, reovirus, Newcastle disease virus and other viruses may act as oncolytic viruses, causing lysis of infected cells and activation of antitumoural immunity, thus leading to possible spontaneous cancer remission<sup>9</sup>. Epidemiological studies reported a protective role of childhood mumps against ovarian cancer; the protective mechanism could involve the expression of mucin 1 (MUC1), a cell surface glycoprotein and tumour-associated antigen, which is able to generate immune surveillance of ovarian cancer cells<sup>10</sup>. Mink et al11 showed an increased incidence of ovarian cancer mediated by anti-MUC1 antibodies among White females. These data supported the hypothesis of an association between the increased incidence of ovarian cancer and the decrease of mumps parotitis infections through vaccination<sup>12</sup>. Lehrer and Rheinstein<sup>13</sup> pointed out that polio virus infection in colon epithelial cells might provide protection against the development of colon cancer. The reduction of death rate from colon cancer due to polio virus infection seems to be mediated by CD155 and polio virus cellular receptor<sup>13</sup>. Here we summarize the available knowledge on acute infections as a means of cancer prevention and on

the role of chronic infections in the development and progression of cancer.

# Acute infections

There is evidence that certain acute infections may inhibit neoplastic growth<sup>14</sup>. Infectious agents and cell damage are able to trigger inflammatory signalling pathways, such as nuclear factor-kB (NF-kB), mitogen-activated protein kinase (MAPK) and Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathways<sup>15</sup>. Inflammatory cells can produce pro-angiogenic factors, such as vascular endothelial growth factor (VEGF) and prostaglandin E2. The creation of new blood vessels during acute inflammation may have detrimental effects such as the increase of oedema and tissue damage mediated by neutrophils. Some infection-induced factors (TNF- $\alpha$ , IFN- $\alpha/\beta/\gamma$ , IL-12, TGF- $\beta$  and acute-phase proteins) are critical regulators of acute inflammation and prevent neo-angiogenesis<sup>16</sup>. Pathogen-associated molecular patterns (PAMPs), which include lipopolysaccarides (LPS), a constituent of bacterial cell walls, play a key role in anti-tumour response through the binding with Toll-like receptors (TLRs) on different immune cells, such as neutrophils, T lymphocytes and dendritic cells. During a bacterial infection, PAMPs stimulate the production of pro-inflammatory cytokines (such as IL-1 $\beta$ , TNF- $\alpha$  and IL-12), thus leading to maturation of dendritic cells and initiation of a cytotoxic T-cell-mediated anticancer response<sup>17</sup> (Table 1A and B). Hoption Cann et al<sup>20</sup> observed that acute infectious diseases of childhood were associated with a reduced risk of future development of melanoma, ovarian cancer and multiple tumours. Acute infections seem to provide protection against cancer also after neonatal and infant life, but this effect decreases with age, consistently with the decline of the immune response<sup>2</sup>. In adult individuals, there is a reduced risk of developing gliomas, meningiomas, melanomas and multiple tumours after acute infections<sup>20,21</sup>. Spontaneous regression in cancer associated with bacterial, fungal, viral or protozoan infections has been observed in the majority of cancers and most frequently in embryonal and breast cancer, melanoma, neuroblastoma, renal adenocarcinoma, lymhomas/leukaemias and sarcoma or carcinoma of the urinary bladder<sup>22</sup>. However, spontaneous regression is a rare event; for example, the rate of spontaneous regression for melanoma has been estimated around 1/400 patients, and spontaneous regression of other tumours such as haematologic cancers, is even rarer<sup>23</sup>. Many microorganisms, such

| Table 1. (A) Differences between acute and chronic infections and biological implications  |  |  |
|--|--|--|
| Acute infections   | Chronic infections   |  |
| Inhibition of neoplastic growth  | Risk factor for cancer development and progression   |  |
| Prevention of neo-angiogenesis through<br>infection-induced factors (TNF- $\alpha$ , IFN- $\alpha$ /<br>$\beta/\gamma$ , IL-12, TGF- $\beta$ and acute-phase proteins) | Promotion of tumour angiogenesis, survival, proliferation and dissemination                      |  |
| Anti-tumour response of LPS through the<br>binding with TLRs on different immune<br>cells (T-cells, neutrophils and dendritic cells)                                   | Inhibition of T-cell activity<br>Expression of immune checkpoint<br>regulators (CTLA-4 and PD-1) |  |

LPS, lipopolysaccarides; TLRs, Toll-like receptors; TNF- $\alpha$ , tumour necrosis factor alpha; IFN, interferon; IL, interleukin; TGF- $\beta$ , transforming growth factor  $\beta$ ; CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed cell death protein-1. *Source*: Refs 16-19

| Table 1. (B) Differences between acute and chronic infections and biological implications  |  |  |
|--|--|--|
| Acute infections   | Chronic infections   |  |
| Production of pro-inflammatory cytokines (IL-1 $\beta$ , TNF- $\alpha$ and IL-12) in response to receptor stimulation by PAMPs                           | Production of anti-inflammatory cytokines  |  |
| Maturation of dendritic cells  | Activation of NF-κB and induction of different genes responsible for cell proliferation, survival and invasion |  |
| Initiation of cytotoxic T-cell-mediated anticancer response  | Inhibition of growth regulators ( <i>e.g.</i> tumour suppressor p53)   |  |
| PAMPs, pathogen-associated molecular patterns; IL, interleukin; TNF-α, tumour necrosis factor alpha; NFκB, Nuclear factor-κB. <i>Source</i> : Refs 16-19 |  |  |

as Vibrio cholerae, Salmonella spp., Escherichia coli, Clostridium spp., Bifidobacterium spp. and Listeria spp., have been evaluated as potential anticancer agents or for the production of vaccines<sup>24</sup>. Other bacterial infections associated with spontaneous cancer regression include syphilis, tuberculosis, gonorrhoea and diphtheria, whereas viral infections include influenza, rubella, smallpox and hepatitis virus. Protozoa such as Toxoplasma gondii and Besnoitia jellisoni may also cause tumour regression<sup>25</sup>. In some cases of superficial bladder cancer, live bacillus Calmette-Guèrin (BCG) was administered into the bladder after surgical resection, as it led to a local immune response with production of cytokines such as IL-2, TNF- $\alpha$  and IFN- $\gamma$  that may destroy residual cancer cells and thereby prevent recurrence<sup>24</sup>.

### **Chronic infections**

Some microorganisms are able to cause chronic infections and to induce DNA mutations; this in turn, can be correlated with tumour development. Chronic infections and cancer development can be associated with immunological mechanisms, such as induction of regulatory T-cells, production of anti-inflammatory cytokines and expression of immune checkpoint regulators [cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein-1 (PD-1)]. CTLA-4, expressed on T-cells, can interact with CD80 and CD86 to inhibit T-cell activation, thus leading to anergy<sup>18</sup>. PD-1, mostly expressed on T-cells, can interact with programmed death-ligand 1 and ligand 2, expressed on antigen-presenting cells (APCs) and tumour cells, inhibiting T-cell activity<sup>19</sup>. Inflammation may act as a promoter on the 'initiated cells' accumulated during life driving the progression of cancer. Biosynthesis of biochemical and metabolic intermediates during tumour growth and inflammatory process may damage DNA and other biomolecules leading to the development of malignant lesions<sup>26</sup>. Macrophages are a major component of the tumour microenvironment, where these generally play a pro-tumour role by promoting tumour survival, angiogenesis, proliferation and dissemination<sup>27</sup>. In patients with chronic infections, NF-KB may lead to the initiation and progression of cancer by the induction of different specific genes responsible for cell proliferation, survival and invasion while antagonizing growth regulators such as tumour suppressor p53<sup>28</sup>. There is evidence of regression of low-grade mucosaassociated lymphoid tissue (MALT) lymphomas as well as lymphoma of the stomach, bowel, bladder, larynx, lung, salivary glands, spleen and thyroid after antibiotic therapy<sup>29</sup>. Some types of lymphoma may be associated with HP, Campylobacter jejuni, HCV or

other microorganisms, and, HP eradication therapy is considered as the first therapeutic approach for low-grade gastric MALT lymphoma<sup>30</sup>. The regression of benign and malignant lesions caused by HPV has been reported after treatment with antiviral drugs<sup>31,32</sup>. Topical treatment with imiquimod, an immune response modifier, or cidofovir, an inhibitor of viral replication, has been shown to be effective (~50-60%) for both anogenital warts and high-grade vulvar intraepithelial neoplasia<sup>32</sup>. In a phase II randomized controlled trial, topical treatment with the antiviral drug AV2<sup>®</sup> showed promising results in reducing the size of cervical lesions associated with HPV<sup>31</sup>. However, these findings need to be confirmed in further well-designed trials.

# Viral infections

Viruses have the capability to reverse physiological functions of host cell and pathways regulating growth arrest and apoptosis. Transforming viruses carry oncogenes derived from cellular genes that are involved in mitogenic signalling, cell proliferation and regulation of programmed cell death<sup>33</sup>. The process of carcinogenesis consists of multiple steps, and viruses associated with cancer such as HBV, HPV and EBV may share common pathways including the functional inactivation of p53 by virally encoded oncoproteins<sup>34</sup>. Host immunity may influence tumour progression, as many years may pass between the onset of infection and the development of cancer, and carcinogenesis process can be affected by direct and indirect mechanisms such as possible synergy between viruses and environmental cofactors<sup>35</sup>. So far, seven viruses [EBV, Kaposi's sarcoma-associated human herpes virus (KSHV), HPV, MCPV, HBV, HCV and human T-cell leukaemia virus type 1 (HTLV1)] have been shown to be associated with various types of human cancer<sup>36</sup>. Tables II and III show the DNA and RNA viruses associated with cancer.

#### Epstein–Barr virus (EBV)

EBV was discovered in the cultured cancer cells obtained from a Burkitt lymphoma (BL) biopsy<sup>56</sup>. EBV is considered, along with other factors, a causal agent for the development of BL, undifferentiated nasopharyngeal carcinoma, immunoblastic lymphomas lymphoproliferative disorders and in immunocompromised patients<sup>57</sup>. Furthermore, EBV infection represents a risk factor for Hodgkin's non-Hodgkin's disease, lymphoma, thymic lymphoepithelioma, salivary gland and urogenital



**Fig. 1.** Pathogenetic mechanisms of Epstein–Barr virus on carcinogenesis. EBV is associated with different human tumours. EBV may infect B lymphocytes, leading to a malignant transformation into a lymphoma. Also, EBV may transform epithelial cells into epithelial tumours, LMP: EBV latent membrane protein; EBV, Epstein–Barr virus. *Source*: Ref 56.

carcinoma in immunocompetent hosts<sup>58</sup> (Fig.1). In patients with autoimmune diseases, with HIV infection or treated with immunosuppressive therapy after an organ transplant, EBV is strongly associated with leiomyomas, leiomyosarcomas and other smooth muscle neoplasms<sup>59</sup>. A high worldwide prevalence of EBV (around 8.29%) has been reported in patients with gastric adenocarcinoma<sup>60</sup>. However, it is unclear whether EBV infection is involved in gastric cancer development or is a consequence of gastric inflammation due to immunosuppressive therapies<sup>60</sup>.

#### Hepatitis B virus (HBV)

Chronic infections caused by HBV and HCV represent the main risk factor for the development of hepatocellular carcinoma (HCC). HBV is a non-cytopathic, partially double-stranded hepatotropic DNA virus which belongs to Hepadnaviridae family. There are eight HBV genotypes (designated A-H) and four serotypes (adv, ayw, adr and ayr) characterized by different geographic distribution and clinical differences. Studies on HBV infection showed that genetic characteristics, including viral genotypes and specific mutations, may contribute to the development of HCC through direct and indirect pathways<sup>61</sup>. HBV can integrate its genome into the human genome, leading to alterations of transcription and cell growth. Integrated HBV sequences have been observed in established hepatoma cell lines and in about 80 per cent of human HBV-related HCCs<sup>62</sup>. The integration of HBV DNA does not play an essential role in viral

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| Table II. DNA viruses known to be associated with cancer   |  |  |  |
|--|--|--|--|
| Virus  | Tumour   | Odds Ratio (OR)  |  |
| EBV  | NPC, BL, HD  | NPC: Polymorphism at EBV-encoded gene, RPMS1 OR=5.27 <sup>37</sup><br>BL: In association with malaria OR=13.2 <sup>38</sup> ; EBV-alone OR=4.50 <sup>39</sup><br>HD: Prior history of infective mononucleosis OR=2.43; EBV-positive OR=9.16 <sup>40</sup>  |  |
| HBV  | HCC, NHL   | HCC: OR=5.389 <sup>41</sup><br>NHL: OR=2.50 <sup>42</sup>  |  |
| HPV  | Cervical cancer,<br>squamous carcinoma<br>of the vulva, penis and<br>anus, head and neck<br>cancer, oesophageal<br>cancer, breast cancer | Cervical cancer: HPV 16 OR=2770;<br>HPV 18 OR=950 <sup>43</sup><br>Oropharyngeal cancer: HPV-16 OR=14.6 <sup>44</sup><br>Carcinoma of the head and neck: HPV-16 OR=2.2 <sup>45</sup><br>Anal and perianal skin cancer: HPV 16 OR=3.0; and HPV 18 OR=4.4 <sup>46</sup><br>Oesophageal squamous cell carcinoma: HPV 16 OR=1.0; and HPV 18 OR=0.5 <sup>47</sup><br>Adenocarcinoma of the oesophagus: HPV 16 OR=1.2; and HPV 18 OR=0.2 <sup>47</sup><br>Breast cancer: Mixed genotypes, HPV 18, 16, 33, 6 and 11 OR=4.92 <sup>48</sup> |  |
| HHV8 or KSHV   | KS, BCBL, CL   | KS: OR 8.6 <sup>49</sup>   |  |
| MCV  | MCC  | MCC: OR 4.4 <sup>50</sup>  |  |
| EBV, Epstein-Barr virus; NPC, nasopharyngeal carcinoma; BL, Burkitt lymphoma; HD, Hodgkin's disease; HBV, hepatitis B virus; |  |  |  |

HPV, human papillomavirus; HCC, hepatocellular carcinoma; HL, Hodgkin's lymphoma; NHL, non-HL; HHV8, Human herpesvirus 8; KS, Kaposi's sarcoma; KSHV, KS associated human virus; BCBL, body cavity-based lymphoma; CL, Castleman lymphadenopathy; MCC, Merkel cell carcinoma; MCV, Merkel cell polyomavirus

| Table III. RNA viruses known to be associated with cancer  |   |  |
|--|---|--|
| Virus  | Tumour  | Odds ratio (OR)  |
| HTLV-1   | ATL   | ATL: Rate ratio=2.50, Cumulative risk: 6.6% for men and 2.1% for women <sup>51</sup> Positive anti-HTLV-I OR=1.6 per two-fold dilution <sup>52</sup>   |
| HIV-1  | NHL, KS, head and neck cancer, testicular cancer, melanoma, anal cancer, HD | NHL: OR=4.4 <sup>53</sup><br>KS: OR=93.5 <sup>53</sup><br>SIRs: anal (SIR=28), liver (SIR=5.6) HL (SIR=11), laryngeal cancer (SIR=1.5) <sup>54</sup>   |
| HCV  | HCC, pancreatic cancer,<br>skin cancer, myelodysplastic<br>syndrome, DLBCL  | HCC: OR=31.5; Intrahepatic bile duct tumour: OR=3.40; extrahepatic bile duct tumour: OR=1.90; pancreatic cancer: OR=1.23; anus: OR=1.97; Non-melanoma non-epithelial skin cancer: OR=1.53; myelodysplastic syndrome: OR=1.56; DLBCL: OR=1.57 <sup>55</sup> |
| HTLV-1, human T leukaemia virus type 1; ATL, adult T-cell leukaemia; HIV-1, human immunodeficiency virus-1; HL, Hodgkin's lymphoma; NHL, non-HL; KS, Kaposi's sarcoma; HD, Hodgkin disease; SIRs, standardized incidence ratios; HCV, hepatitis C virus; |   |  |

HCC, hepatocellular carcinoma; DLBCL, diffuse large B-cell lymphoma

replication but may cause viral genome persistence and poses high risk for hepatic cancer. The risk for HCC is increased in patients with active hepatitis and in cirrhotic patients, although HBV may cause cancer even in the absence of cirrhosis<sup>63</sup>. Continuous injury and regeneration of cirrhotic liver may lead to increased liver cells turnover, favouring genome critical mutations, chromosomal rearrangements, activation of oncogenes and inactivation of tumour suppressor genes. The T-cells immune response, elicited to contrast viral infection, contributes to hepatocytes necrosis, inflammation and regeneration<sup>64</sup>. HBV can replicate within the pancreas, and higher serum and urinary levels of pancreatic enzymes are frequently observed in patients with HBV chronic infection<sup>65</sup>. A meta-analysis of eight studies showed an association between past exposure to HBV and increased risk for pancreatic cancer development [odds ratio (OR)=1.24] mainly among individuals without natural immunity [anti-hepatitis B core (HBc)-positive/anti-hepatitis B surface antibody (anti-HBs) negative], with an OR of 1.67<sup>66</sup>. Chronic hepatitis B- and HBsAg-positive patients had a significantly increased risk for pancreatic cancer (OR=1.20); past exposure to HBV with natural immunity (anti-HBc positive/anti-HBs positive) had no association with pancreatic cancer development with an OR=0.98. Anti-HBs-positive patients showed a lower risk of pancreatic cancer compared to anti-HBs-negative patients (OR=0.54)<sup>67,68</sup>. Further research is needed to explain the pathogenetic mechanisms involved in the progression from active hepatitis virus infection to chronic inflammatory response associated to pancreatic carcinogenesis.

# Human papillomavirus (HPV)

HPV, a virus belonging to the *Papovavirus* group, is responsible for common infections contracted through sexual, oral and skin contact. It is estimated that over 70 per cent of women contract genital HPV infection during their lives, but a large number of infections disappears spontaneously over a few months due to the activity of immune system<sup>69</sup>. There are more than 100 types of HPV, and most of these do not cause serious disease; however, about 15 genotypes are known to be carcinogenic principally in the transformation zone between different types of epithelium<sup>70</sup>. This process has been observed in almost all uterine cervix cancers, in which HPV is able to induce different grades of cervical intraepithelial neoplasia (CIN). HPV-16 and HPV-18, the two most carcinogenic genotypes, are responsible for about 50 per cent of CIN3 and 70 per cent of cervical cancer<sup>71</sup> (Fig. 2). The use of prophylactic vaccination against HPV infection is efficient and represents the most useful way of cervical cancer prevention. Other cancers associated with HPV infection, are breast, anus, prostate, penis, vagina, vulva, oropharynx, conjunctiva and non-melanoma skin cancers<sup>72</sup>. Potential cofactors involved in CIN development may include HIV, Chlamydia trachomatis, herpes simplex virus type 2 and immunosuppression<sup>72</sup>.

#### Merkel cell polyomavirus

Merkel cell polyomavirus is found in tumour tissues of Merkel cell carcinoma (MCC). MCC is a rare and aggressive neuroectodermal cancer frequently observed in transplant recipients, immunocompromised those, patients with B-cell lymphoid tumours and patients with acquired immune deficiency syndrome (AIDS)<sup>73</sup>. Clonal integration of viral DNA into tumour cell genome has been observed in patients with MCC. Treatment protocols include the administration of bleomycin, a drug with direct antiviral effects against HCV and HIV<sup>74</sup>.

# Kaposi's sarcoma-associated human herpes virus (KSHV)

KSHV, also known as human herpes virus 8 (HHV8), is considered the cause of various types of Kaposi's sarcoma (KS), such as AIDS-associated, classic, endemic, African and iatrogenic. HHV8 encodes for homologues of several cytokines and their receptors, but the exact role of virus in cancer induction is not



**Fig. 2.** Effects of human papillomavirus (HPV) on the development of cervical cancer. The oncogenic proteins E6 and E7 affect control of the cell cycle by their interaction with p53 and retinoblastoma protein. HPV induces cervical intraepithelial neoplasia (CIN), which may develop into cervical cancer through changes in cytokine levels and reduction of apoptosis. CIN, cervical intraepithelial neoplasia; pRB, retinoblastoma protein; IL-10, interleukin 10; IFN-α, interferon alpha; IFN-β, interferon beta. *Source*: Ref. 71.

yet clear<sup>75</sup>. The viral genome of HHV8 has been found in primary effusion lymphoma, multicentric Castleman disease, angioimmunoblastic lymphadenopathy and in some cases of reactive lymphadenopathies. HHV8 is also considered as a cause of body cavity-based lymphomas<sup>76</sup>.

#### Parvovirus B19

Parvovirus B19 infection may play a role in the pathogenesis of rheumatic diseases and acute lymphoblastic and myeloblastic leukaemia<sup>77</sup>. Parvovirus DNA and viral proteins have been detected in neoplastic epithelium of patients with papillary thyroid carcinoma (PTC)<sup>78</sup>. The possible role of B19 in pathogenesis of thyroid tumours is suggested by the involvement of immune system, NF-κB, IL-6 and viral proteins. The tax- and tat-mediated NF-κB activation plays a crucial role in the HTLV-1-induced acute leukaemia and HIV-induced KS; NF-κB is also significantly increased and co-localized with viral DNA in PTC tissues<sup>79</sup>. One of the non-structural proteins (NS1) encoded by the viral genome is cytotoxic to the host cells and linked to NF- $\kappa$ B and IL-6<sup>80</sup>. This association is probably due to the fact that nonstructural viral proteins resemble tax protein of HTLV-1 and tat protein of type 1-HIV. These all play a part in the viral propagation and activate IL-6 production through the NF- $\kappa$ B-binding site in the IL-6 promoter<sup>81</sup>. These findings suggested a link between parvovirus B19 and thyroid carcinoma.

# Human T-cell leukaemia virus type 1 (HTLV-1)

HTLV-1 is a single-stranded RNA retrovirus predominantly associated to adult T-cell leukaemia (ATL), an aggressive malignancy characterized by uncontrolled growth of CD4+ T-lymphocytes, lymphadenopathy, hypercalcaemia, immunodeficiency and unfavourable prognosis<sup>82</sup>. HTLV-1 may have a long latent period of several decades after the initial infection. Mechanisms leading to ATL are not well understood; a multi-step leukaemogenic process has been hypothesized, in which the main roles are played by viral genes, their products and host immune status<sup>83</sup>. High levels of NF- $\kappa$ B, a regulator of immune response against infections, strongly associated with carcinogenesis, have been observed in ATL cells<sup>75</sup>.

# Human immunodeficiency virus (HIV)

HIV is a RNA virus of the Lentivirus genus divided into two strains: HIV-1 and HIV-2. The viral infection is responsible for the AIDS, a disease defined as a set of clinical manifestations due to the depletion of T lymphocyte. HIV is also able to infect other cell types such as lymphocytes, macrophages, microglia and dendritic cells. Patients with HIV showed an increased risk to develop cancers such as KS, non-Hodgkin's lymphoma B-cell, primitive brain lymphoma B-cells and invasive carcinoma of the uterine cervix<sup>84</sup>. Other HIV/AIDS-related cancers include Hodgkin's disease and cancers of the lung, mouth and digestive system<sup>85</sup>. Opportunistic infections caused by viruses, bacteria, fungi and parasites are the leading causes of deaths in patients with AIDS (Table IV). The higher risk of developing opportunistic infections, as well as the increased incidence of cancer in HIV-infected patients, is mainly associated with immunosuppression<sup>88</sup>. The use of highly active antiretroviral therapy (HAART) has led to an increase of life expectancy, progressively transforming HIV into a chronically manageable infection. However, patients treated with HAART

showed an increased risk of cancer such as lung, digestive system and liver cancers not necessarily associated with HIV infection<sup>89</sup>.

# Hepatitis C virus (HCV)

HCV is a non-cytopathic RNA virus of the family Flaviviridae, and is an important risk factor for HCC development in Western countries. To date, at least six major genotypes of HCV have been identified<sup>90</sup>. HCV is not able to integrate its genome into host cells because of the absence of reverse transcriptase activity and may cause HCC by indirect pathways such as severe chronic hepatitis, cell death and proliferation which usually progress towards cirrhosis. Furthermore, HCV can evade host immune responses to cause a persistent infection in the liver<sup>91</sup>. Continuous cycles of death and regeneration in hepatocytes may favour the accumulation of mutations. HCV-infected patients have a higher risk of developing HCC compared with HCV-negative individuals, also depending on the degree of fibrosis and duration of viral infection<sup>92</sup>.

#### **Bacterial infections and cancer**

The effects of bacterial infections on carcinogenesis may depend on many factors, such as the host immune response, promotion of cell proliferation, suppression of apoptosis and production of bacterial toxins<sup>93</sup>. Some bacterial infections may cause hyperplasia or promote inflammatory response releasing reactive oxygen and nitrogen intermediates which can directly lead to DNA damage94. Bacterial infections may interfere with the fine regulation of host cells signal pathways, which have a central role in cancer development or inhibition. Bacteria generate several effector molecules that interact with the host cells regulating adhesion, modulating cytoskeletal or junctional function and activating specific eukaryotic signalling pathways. These virulence factors can act on cancer promotion, by their direct action on cellular processes<sup>93</sup>. Suppression of apoptosis is an important step for the development of neoplastic cells, especially during infections caused by intracellular pathogens. This is usually the result of many extracellular stimuli represented by the release of serine protease granzyme B and TNF-a by CD8+ T-cells. High levels of NF-KB can inhibit TNF-α-induced apoptosis<sup>95</sup>. Bacteria, through the blockage of apoptosis, could facilitate the escape of transformed cells from the destruction mechanisms, thus favouring carcinogenesis%. Escherichia coli cytotoxic necrotizing factor is able to activate Rho family proteins, and Pasteurella multocida toxin,

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|   | Table IV. Opportunistic infections in individuals with HIV infection   |
|---|--|
| System/organ  | Opportunistic pathogen   |
| Respiratory<br>system   | Pneumocystis carinii<br>Mycobacterium avium<br>Candida and C. neoformans<br>Cytomegalovirus (S. pneumoniae, H. influenzae, M. pneumoniae, L. pneumophila and respiratory viruses)*   |
| Digestive system  | <i>Candida</i><br>Herpes simplex<br>Cytomegalovirus  |
| Central and<br>peripheral nervous<br>system   | Cytomegalovirus<br>JC polyomavirus<br>Toxoplasma gondii<br>Cryptococcus neoformans   |
| Skin and mucosal surface  | Candida<br>Varicella-zoster virus<br>Herpes simplex<br>Poxvirus<br>HPV   |
| *Patients suffering from A<br>in immunocompetent ind<br>pneumonia; H. influenza,<br>HPV, human papillomay | AIDS are also subject to infections by micro-organisms that may cause pneumonia and bronchopneumonia<br>lividuals. JC, John Cunningham; <i>C. neoformans, Cryptococcus neoformans; S. pneumonia, Streptococcus</i><br>, <i>Haemophilus influenza; M. pneumonia, Mycoplasma pneumonia; L. pneumophila, Legionella pneumophila;</i><br>irus. <i>Source</i> : Refs 86, 87 |

which acts as potent mitogen for quiescent cells and as inducer of anchorage-independent growth, may activate cyclooxygenase-2 (COX-2), an enzyme involved in different stages of carcinogenesis, including the suppression of apoptosis<sup>97</sup>. Histological alterations (e.g., metaplasia) have been observed before the onset of gastric cancer in individuals with HP infection<sup>98</sup>. The presence of bacteria could be utilized as a diagnostic marker for cancer: for example, high salivary levels of Capnocytophaga gingivalis, Prevotella melaninogenica and Streptococcus mitis, have been found in cases of oral squamous cell carcinoma, showing diagnostic sensitivity and specificity  $\geq 80$  per cent<sup>99</sup>. The link between bacteria and cancer could be further explained by the regression of lesions after antibiotic treatment, as observed after eradication of HP in patients with gastric cancer<sup>100</sup>. The association between bacteria and different types of cancer is reported in Table V.

# Helicobacter pylori (HP)

Although gastric malignancies may have multifactorial causes (*e.g.*, use of tobacco, low vegetable intake, high dietary salt and nitrate intake), but HP plays a main role in the carcinogenesis as shown by the increased risk of developing gastric cancer in infected individuals<sup>106</sup>. In 1994, the International Association for Research on Cancer classified HP as Group 1 carcinogen<sup>107</sup>. The duration of infection and the type of bacterial strain may influence the risk of cancer,

and the presence of cagA-positive strains of HP is associated with an increased risk of gastric carcinoma. The cagA gene encodes for one of the major HP virulence proteins, and infection from cagA-positive strains is characterized by increased virulence and inflammation<sup>108</sup>. The combination of environmental factors, bacterial factors and host immune response may drive the initiation and progression of carcinogenesis (Fig. 3). The precancerous cascade is a progressive process that usually lasts for several decades, but the mechanisms underlying initial DNA damage are still not known. The most plausible hypothesis is that cancer onset could be the result of oxidative stress, as represented by inducible NOS expression due to HP infection<sup>109</sup>. A reduction in the incidence of gastric cancer and a regression of precancerous lesions have been observed in patients with HP infection after treatment with antioxidant supplements (such as  $\beta$ -carotene, vitamin E and C and selenium)<sup>110</sup>. Other antioxidants showed protective effects on cancer inhibiting reactive oxygen species production and MAPK signal transduction pathways<sup>111,112</sup>.

COX-2 is a regulator in immune response and it is often over-expressed in many cancers, especially in colorectal cancer. Chronic induction of COX-2 could favour the survival of transformed cells that otherwise would become apoptotic and die. Therefore, cancer invasiveness could be reduced by inhibition of COX-2 activity<sup>113</sup>. The use of non-steroidal anti-

| Table V. Association between bacterial infections and cancer |                    |  |  |
|--|--------------------|--|--|
| Bacteria   | Tumour             | Odds ratio (OR)  |  |
| Helicobacter pylori  | Gastric cancer     | Non-cardia cancers: OR=3.0; 10+ yr before cancer diagnosis OR=5.9 Cardia cancer: OR= $1.0^{101}$ |  |
| Streptococcus bovis (Biotype 1)                              | Colorectal cancer  | OR=5.1 <sup>102</sup>  |  |
| Chlamydia trachomatis  | Cervical cancer    | OR=2.21 <sup>103</sup>   |  |
| C. pneumonia   | Lung cancer        | OR=1.30 <sup>104</sup>   |  |
| Salmonella Typhi   | Gallbladder cancer | OR=4.0 <sup>105</sup>  |  |
|  |                    |  |  |



Fig. 3. Role of *Helicobacter pylori* in the pathogenesis of gastric

cancer. H. pylori infection may cause a number of diseases, ranging from superficial gastritis to gastric carcinoma. The progression to gastric cancer is mediated by cytokines, genetic polymorphisms, oxidative stress, gastric commensal organisms and alteration of epithelial cells response to acid. Source: Ref 91.

inflammatory drugs (NSAIDs) is associated with a reduced risk of gastric cancer, through both inhibition of COX-2 and NF-KB activity. These findings underlined the role of NF-kB activation as a crucial component in bacteria-associated cancer formation<sup>114</sup>. Treatment of HP infection may reduce mucosal inflammation, DNA damage and cell turnover and improve gastric acid secretion in patients with previous hypochloridia<sup>115</sup>. The detection of high levels of HP DNA in liver biopsies of patients with liver chronic diseases, such as HCC, biliary cirrhosis and sclerosing cholangitis, suggested a promoting role of HP in hepatic carcinogenesis<sup>116</sup>.

# Streptococcus infantarius (formerly S. bovis II/1)

Streptococcus infantarius is commonly reported in infections of the central nervous system, osteomyelitis, endocarditis and colon cancer<sup>117</sup>. However, the link between S. infantarius and cancer is still not clear; the bacterium is occasionally detectable in the normal colonic bacterial flora, but it is increased in faecal material of patients with colorectal cancer. A high percentage of patients with S. infantarius infection also show colorectal adenomatous polyps or carcinoma<sup>118</sup>. IL-8, a neutrophil and T-cells chemoattractant cytokine, plays a key role in the immune response to S. infantarius and other bacteria. IL-8 can lead to mucosal damage through the production of free radicals and proteolytic enzymes from neutrophils<sup>119</sup>. S. infantarius infection could be involved in the development of many cancers such as metastatic melanoma lymphoma, pancreas, endometrium, oesophagus, stomach and colon cancer<sup>117</sup>. However, further research is needed to clarify the link between S. infantarius infection and carcinogenesis.

# Chlamydia trachomatis

The consequences of genital C. trachomatis infection are generally represented by urethritis, cervicitis, ectopic pregnancy, infertility, pelvic inflammation, epididymitis, prostatitis and increased risk of HIV infection<sup>120</sup>. Chlamydial infection causes chronic inflammation with epithelial damage, cytologic cervical atypia and consequent metaplasia, which in turn can increase the risk of cervical cancer<sup>121</sup>. Invasive squamous cervical cancer has been shown to be associated with serum detection of chlamydial antibodies<sup>121</sup>.

# Chlamydia pneumoniae

Infection with C. pneumoniae, a Gram-negative bacillus, has been associated with an increased risk of lung carcinoma<sup>122</sup>. A case-control study of chronic C. pneumoniae infection as lung cancer risk factor in smokers showed a significant difference between male patients and their controls for specific C. pneumoniae antibodies, but there were no significant differences between female patients and their control groups<sup>123</sup>. Chronic C. pneumoniae infection was significantly higher among male patients with lung carcinoma below age 55 than controls, and even in this case, there were no age-related variations to the female sex<sup>123</sup>. Impairment of lung and bronchial immunity, increased levels of IL-4 and suppression of cellular immunity could facilitate C. pneumoniae lung localization and invasion in smoking subjects. IL-8, also produced by smokers, along with IL-1 $\beta$  and TNF- $\alpha$ , may cause genetic damage<sup>124</sup>.

# Salmonella Typhi

Chronic *Salmonella* Typhi infection has been found to be strongly associated with gallbladder cancer. Lazcano-Ponce *et al*<sup>125</sup> observed that individuals who became carriers of *S*. Typhi showed more than eight-fold increased risk of developing gallbladder carcinoma as compared to those who had acute typhoid and cleared the infection. Strom *et al*<sup>126</sup> reported a 12-fold increase in risk of gallbladder cancer in patients with a history of typhoid fever (CI 95% 1.5-598), which unfortunately could not be supported with serological assays. Data from the epidemics of typhus in 1922 in New York and in 1964 in Aberdeen showed that people who contracted typhoid, but did not become carrier, were at lower risk for cancer and chronic typhoid carriers died of hepatobiliary cancer six times more often than the matched controls<sup>127</sup>.

#### Parasitic infections and cancer

*Opisthorchis viverrini* and *Schistosoma haematobium* can cause liver cholangiocarcinoma and urinary bladder cancer, respectively<sup>128</sup>. Other reported associations include *Clonorchis sinensis* and cholangiocarcinoma<sup>129</sup>, *Schistosoma japonicum* and HCC or colorectal cancer and *Schistosoma mansoni* and HCC<sup>130</sup> (Table VI).

# Strongyloides stercoralis

*Strongyloides stercoralis* infection is estimated to affect around 100 million people per year worldwide and remains often neglected<sup>135</sup>. A case–control study showed a high prevalence of *S. stercoralis* infection in the patients with biliary tract cancer compared to controls<sup>136</sup>. The presence of *S. stercoralis* in the duodenum, including the duodenal papilla, may induce various patterns of inflammation, while chronic inflammation of the biliary tract is associated with invading larvae<sup>137</sup>.

# Future treatment and prevention

The focus of research has now moved towards the development of anti-tumour therapeutic vaccines using recombinant viruses such as retroviruses, adenoviruses, (including HIV-1). lentiviruses poxviruses. herpesviruses and adeno-associated viruses. These viruses could be used to transform cells genetically, activate the expression of cancer-specific antigens and infect APCs to increase anti-tumour immune response or for transgene delivery in many cancers<sup>138</sup>. Some antibiotics and antifungals, able to target specific pathways and genes implicated in cancer, could lead to possible treatment benefit. Antibiotics act trough several mechanisms that include inhibition or regulation of cell wall synthesis, cell metabolism and protein synthesis. Ampicillin, streptomycin sulphate and puromycin dihydrochloride are molecules that specifically target and kill cells. Other anti-tumour antibiotics include bleomycin, enediynes and mitomycin. After oral administration, cefazolin, ciprofloxacin, nitrofurantoin or trimethoprim-sulphamethoxazole showed significant dose-dependent cytotoxicity against bladder cancer cells<sup>139</sup>. Compounds from filamentous fungi such as Aspergillus, Penicillium and Talaromyces, Macrocyclic trichothecenes, Argemone mexicana L. and a phenazine

| Table VI. Parasitic infections and cancer |                          |  |  |
|---|--------------------------|--|--|
| Parasites                                 | Tumour                   | Odds ratio (OR)  |  |
| Opisthorchis viverrini                    | Cholangiocarcinoma       | OR=4.39 <sup>131</sup>   |  |
| Schistosoma haematobium                   | Urinary bladder cancer   | OR=From 2 to 14 <sup>106</sup>   |  |
| Clonorchis sinensis                       | Cholangiocarcinoma       | $OR=6.12^{131}$  |  |
| S. japonicum                              | HCC, colorectal cancer   | Rectal cancer relative risk=8.3 <sup>132</sup><br>HCC: OR=3.7; Colon cancer: OR=3.3 <sup>133</sup> |  |
| Strongyloides stercoralis                 | Gastrointestinal cancers | OR=6.7 <sup>134</sup>  |  |
| HCC, hepatocellular carcinoma             |                          |  |  |

compound produced by *Lactococcus* BSN307 showed both antifungal and antitumoural activities. The anti-cancer properties are due to a number of different mechanisms including inhibition of protein, DNA and RNA syntheses, impairment of mitochondrial function and effects on cell division and membranes<sup>140</sup>.

#### Conclusions

In general, acute infections may antagonize the development of malignant diseases, whereas chronic infections may induce specific cell changes in the host, increasing the risk of cancer. Mechanisms of carcinogenesis due to infections include cell growth and DNA replication by MAPK pathway, abnormal cell proliferation, inhibition of apoptosis and production of toxins that affect the cell cycle. Acute infectious diseases of childhood were associated to a reduced risk of future development of many types of cancer. Moreover, spontaneous regression associated with bacterial, fungal, viral or protozoan infections has been observed in many types of cancers such as breast cancer, melanoma, neuroblastoma, renal cancer and lymphomas. The research area is wide and further studies are needed to fill the knowledge gap on the link between the infections and the development and progression of cancer. Promising fields of investigation are represented by the development of anti-tumour therapeutic vaccines using recombinant viruses and the assessment of antibiotics and antifungals as possible therapeutic options for cancer.

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For correspondence: Dr Antonio Biondi, Department of General Surgery & Medical-Surgical Specialties, University of Catania, University Hospital 'Policlinico G. Rodolico – San Marco', Via S. Sofia 78, 95123 Catania, Italy e-mail: abiondi@unict.it