CHAPTER

22

Infection Related Cancers

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Introduction

Currently information concerning the role of viruses and bacteria in the pathogenesis of human neoplasms are fragmented and incomplete. International agency for research on cancer has now confirmed seven viral or bacterial agents as carcinogens in humans. The role of these agents is rather complex and a complete understanding of the mechanism involved in the interaction with human host is still evolving.

The fact that viral infections can cause cancer has been suspected for over a 100 years, beginning with the observed connection between cervical cancer and multiple sexual partners. In 1911 JAMA had reported an association between viruses and cancers in animals. Schistosoma hematobium was linked with bladder cancer as early as in the middle of 19th century. Human tumor viruses contribute to atleast 15% of all human cancers. The mechanisms by which they contribute to development of associated cancers have illuminated non viral causes of human cancer. Understanding to the modes of transmission of tumor viruses led to public health measures to stop the spread of the viruses and development and use of effective vaccines and antiviral agents. The etiology and mechanisms of infection based cancers have been important study areas generating several Nobel prizes in recent years. Unfortunately good animal virus models do not exist for exploration of viruses causing human diseases.

Cancer of the stomach, liver and cervix rank among the most prevalent ones with a viral or bacterial origin; e.g. – virtually every cervical cancer case is positive for the presence of one or more types of Human Papilloma Viruses. Several parasitical worms or flukes (helminths) have been added to the list of proven or probable carcinogens. Improved serological techniques may eventually reveal an even greater role for infections in the phenomenon of carcinogenesis.

Table 1 represents the list of infection associated cancers. Table 2 indicates the relative contribution of individual infections attributable to various cancers. The data in developed world states that about 7% of total cancer incidence has been attributed to one or more infectious agents and is expected to be attributable for much higher incidence of cancers in the developing countries (though exact figures are not available). Globally it may be 1.2-1.5 million new cases per year. Understanding the pathogen is very important to identify and evaluate the interventions available at various stages of exposure and disease development. These include:

Early Primary Prevention

Limiting exposure to the pathogens.

Table 1 : Infectious Agents Associated with Cancer

Agent	Type of cancer
Human papillomavirus (HPV)	Cervix, vulva, anus, penis, head and neck
Hepatitis B virus (HBV)	Liver
Hepatitis C virus (HCV)	Liver
Helicobacter pylori	Stomach
Epstein-Barr virus (EBV)	Nasopharynx, Hodgkin's disease, non-Hodgkin's lymphoma
Human herpes virus type 8 (HHV-8)	Kaposi's sarcoma
Human immunodeficiency virus type 1 (HIV-1)	Kaposi's sarcoma, lymphoma
Human T-cell lymphotrophic virus type I (HTLV-I)	Leukemia/lymphoma
Schistosomes	Bladder
Liver flukes	Bile duct

Table 2 : Attribution of Infection to Cancers

Agent	Associated Cancer	Proportion Attributable to Infection
Human Papilloma Virus		
Hepatitis B/ C Virus	Liver	80%
Helicobacter Pylori	Stomach	70%
Epstein Barr Virus	HD;NHL	30-90%
HIV-1 as Co-factor	Kaposi's Sarcoma	_
HTLV-1	Leukemia	7%
HHV-8 Probable	Kaposi's Sarcoma	_

Primary Prevention

Stopping establishment of infection (through prophylactic vaccination)

Secondary Prevention

Interrupting development of cancer once the infection is present(e.g. Therapeutic vaccination,/ Autivivab)

Infectious Agents

Helicobacter pylori

Helicobacter pylori (HP) is ranked top amongst various infectious agents and represents approximately 5 per cent of new cancer cases in the world.[1] For their discovery of *H. pylori* and its role in gastric ulcer formation, Marshall and Warren were awarded the 2005 Nobel Prize in Medicine. These cancers are important from a public health point of view because they are potentially preventable by treatment with antibiotics. Helicobacter pylori infection is very common (80-90 percent) in populations with high risk for stomach cancer. It contains 2 groups of polymorphic genes, receptors to HP lipopolysaccharide (LPS) and a cell wall component which elicits immediate proinflammatory responses. Some evidence also links *H. pylori* infection to gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and perhaps pancreatic cancer.[2] In 2001, a combined analysis of 12 *H. pylori* and gastric cancer studies estimated that the risk of non-cardia gastric cancer was nearly six times higher for *H. pylori*-infected people than for uninfected people**.** In addition, one study found that out of 92 pancreatic cancer patients, 65 per cent tested positive for *H. pylori*, while only 45 per cent of non-cancer control participants tested positive.[3,4] Although the study group was small

and patients were not tested for *H. pylori* until after they were diagnosed with cancer, this study concluded that a positive association exists between *H. pylori* and pancreatic cancer. Nearly all patients with gastric MALT lymphoma are infected with *H. pylori*, and the risk of developing this tumor is over six times higher in infected people than in uninfected people.[5] Furthermore, up to 80 per cent of patients with gastric MALT lymphoma achieve complete remission of their tumors after treatment with *H. pylori*-eradicating triple therapy or bismuth. The exact incidence of gastric MALT lymphoma in *H. pylori*-infected persons is unknown, but these tumors occur in less than one per cent of infected individuals.[6]

H. pylori bacteria use a needle-like appendage to inject CagA, a toxin produced by cytotoxin-associated gene A, into the junctions where two stomach lining cells meet. Not all strains of *H. pylori* carry the CagA gene; those that do are classified as CagA-positive. This toxin alters the structure of stomach cells and allows the bacteria to attach themselves more easily. Long-term exposure to CagA causes chronic inflammation. That infection with CagA-positive strains of *H. pylori* further increases the risk of gastric cancer above the risk associated with CagA-negative strains.[7] Laboratory studies show that CagA-induced cellular changes can lead to accumulation of genetic mutations involved in the development of malignancies This link is supported by a combined analysis of 16 studies that found a two-fold increase in the risk of non-cardia gastric cancer associated with CagA-positive *H. pylori* as compared to Cag A-negative *H. pylori*. In the pancreatic cancer study, infection with Cag A-positive *H. pylori* strains were associated with an approximately two-fold increase in risk for the disease over people in the study who were not infected.[8,9]

Human Papilloma Virus (HPV)

Globally cancer of the cervix is the 2nd most common cancer in females and there is a virtually one-to-one connection between carcinoma cervix and HPV DNA detection.[10] Cervical cancer strikes nearly half a million women each year worldwide, claiming a quarter of a million lives. Studies also suggest that HPVs may play a role in cancers of the anus, vulva, vagina, and some cancers of the oropharynx (the middle part of the throat that includes the soft palate, the base of the tongue, and the tonsils). Some types of HPV are referred to as "low-risk" viruses because they rarely develop into cancer. Both high-risk and low-risk types of HPV can cause the growth of abnormal cells, but generally only the high-risk types may lead to cancer. Sexually transmitted, high-risk HPVs include types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, and possibly a few others. These high-risk types of HPV cause growths that are usually flat and nearly invisible, as compared with the warts caused by types HPV–6 and HPV–11.[11]

Having many sexual partners is a risk factor for HPV infection. Other factors that may increase the risk of cervical cancer in women with HPV infection include smoking and having many children.[12]

The surest way to eliminate risk for genital HPV infection is to refrain from any genital contact with another individual. HPV infection can occur in both male and female genital areas that are covered or protected by a latex condom, as well as in areas that are not covered. Although the effect of condoms in preventing HPV infection is unknown, condom use has been associated with a lower rate of cervical cancer.

Recently, the U.S. Food and Drug Administration (FDA) approved a vaccine that is highly effective in preventing infection with types 16 and 18, two "high-risk" HPVs that cause most (70 per cent) cervical cancers, and types 6 and 11, which cause most (90 per cent) genital warts.[13]

Laboratory researchers at National Cancer Institute (NCI) have indicated that HPVs produce proteins known as E5, E6, and E7, which interferes with anticancer proteins like human protein p53.[14]

Prevention

A. *HPV Vaccine :* Vaccination is primary prevention. Whom and when to be given is controversial. There are 2 schools of thought – (i) girls before they get sexually active, (ii) as it causes cancer in male and female so vaccinate every one. The polyvalent vaccine is widely used in public health. It reduces cancer risk by 83% if vaccinated against 16, 18, 31, 33, 45 strains. Adverse events are very low. The vaccine also seems to prevent " it's causative agent" from residing in the genital tract where it can infect new sexual partners. The vaccine however does not appear to reverse infection or cervical neoplasia.[15]

B. *Secondary prevention :* A Pap test is the standard way to check for any cervical cell changes. Because the HPV test can detect high-risk types of HPV in cervical cells, the FDA approved this test as a useful addition to the Pap test such as colposcopy and biopsy of any abnormal areas. Although there is currently no medical cure for papillomavirus infection, cryosurgery (freezing that destroys tissue), LEEP (loop electrosurgical excision procedure, the removal of tissue using a hot wire loop), and conventional surgery are being tried. Some drugs may be used to treat external genital warts.

Epstein - Barr Virus

About 100 Human Herpes Viruses (HHV) have been identified out of which only 8 of them infect human. Epstein Barr Virus (HHV-4) was the first human virus to be directly implicated in carcinogenesis, identified in 1964 from children of Africa by Burkitt in common lymphoma. It infects > 90% of the world's population. Although most humans coexist with the virus without serious sequelae, a small proportion will develop tumors. Normal host populations can have vastly different susceptibility to EBV-related tumors as demonstrated by geographical and immunological variations in the prevalence of these cancers. EBV has been implicated in the pathogenesis of Burkitt's lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, nasopharyngeal carcinoma, as well as leiomyosarcomas arising in immunocompromised individuals.

The presence of this virus has also been associated with epithelial malignancies arising in the gastric region and the breast, although this remains disputed. EBV uses its viral proteins, the actions of which mimic several growth factors, transcription factors, and antiapoptotic factors, to usurp control of the cellular pathways that regulate diverse homeostatic cellular functions.[16] 2 sub types are prevalent among them, most important being EBV-1. Once infected the individual becomes carrier for life. Transmission mainly is via saliva contact because it primarily infects squamous epithelium and lymphoid tissue (esp. B cell) of oro-pharynx and causes shedding in saliva after primary infection. Most of individuals are asymptomatic. Some develop infectious mononucleosis (kissing disease). Infectivity rates go up to 95% when associated with AIDS. Systemic lymphomas demonstrate EBV in 30-90% of cases. There are effusion lymphomas in visceral cavity which demonstrate EBV frequently. These infect mainly B-cell, but can infect T-cell of NHL.

Recent advances in antiviral therapeutics, application of monoclonal antibodies, broad spectrum antiviral agents are beginning to show promise in the treatment of EBV-related disorders.[16] Primary prevention is difficult. Summing up the progress it must be acknowledged that what ever the presence of immunotherapy and anti viral therapy be, the prevention and management of EBV related morbidity remains only in the "nascent stage".

Hepatitis Virus

The name traditionally are for those viruses which are hepato-trophic, that is they have an affinity for liver. The hepatitis B virus belongs to Hepadnaviridae family and hepatitis C virus to Flaviviridae family. Neither of these viruses are singular agents. Each of them exhibit multiple genotypes, which may in turn represent variation in natural history and response to treatment. A further complication is the fact that several viruses

can be implicated in a particular case of liver disease, including HepB and Hep C interacting together, as well as EBV and HIV. More than 8% of the African and Asian population are chronic carriers of HBV. In North America, Australia and Western Europe it is less than 2%. Prevalence of HCV is under 2% in developing countries[17] whereas incidence in developed countries is higher. The risk of development of HCC in the setting of Hepatitis – B related cirrhosis is approximately 0.5% per year, whereas in hepatitis C related cirrhosis is 5% per year.[18]

Chronic hepatitis B virus (HBV) infection is a major global cause of hepatocellular carcinoma (HCC). Blumberg and his colleagues demonstrated a striking association between HBV, antibodies to it's antigens, and hepatocellular carcinoma.[19] HBV is estimated to cause 50-70% of HCC, rest being attributed to HCV. A prospective survey of 22,707 male civil servants in Taiwan was initiated at the end of 1975.[20] Of these 3454 were found to be H BsAg positive. By the end of 1986, 152 of the 3454 H BsAg positive men had HCC, whereas 9 out of 19, 253 H BsAg negative men had it. This epic study clearly demonstrated correlation between HBV infection and HCC. Individuals who are chronic carriers have a greater than 100-fold increased relative risk of developing the tumour. Several mechanisms of HBV-induced HCC have been proposed. Integration of HBV DNA into the genome of hepatocytes occurs commonly, although integration at cellular sites that are important for regulation of hepatocyte proliferation appears to be a rare event. Several studies have implicated that the x gene product(s) of HBV are important to the pathogenesis of HCC. There is a hypothesis that immunohistochemical detection of hepatitis B x antigen (HBxAg) is closely associated with HCC.[21] Functions of the HBx protein are potentially oncogenic. These include transcriptional activation of cellular growth regulatory genes, modulation of apoptosis and inhibition of nucleotide excision repair of damaged cellular DNA.[22] Necroinflammatory hepatic disease, which often accompanies chronic HBV infection, may contribute indirectly to hepatocyte transformation in a number of ways, including by facilitating HBV DNA integration, predisposing to the acquisition of cellular mutations and generating mutagenic oxygen reactive species.

Recently investigators at MD Anderson Cancer Center the pathway by which the hepatitis B virus (HBV) leads to development of hepatocellular carcinoma (HCC) and found that it "turns off" an enzyme known as GSK-3ß, which acts to suppress tumor formation as well as inhibit the spread of cancer. HBX shuts down GSK-3ß, whose role is to degrade the beta catenin proteins that enter the interior of a cell. Therefore, GSK-3ß functions as a tumor suppressor, and when it is inactive, beta catenin accumulates in the cell cytoplasm and nucleus. They also resolved a puzzle regarding the relationship between GSK-3ß and Erk, a well-known enzyme frequently activated in human cancers. Erk interacts with and phosphorylates GSK-3ß at a specific amino acid residue Thr 43, resulting in degradation and thus inactivation of GSK-3ß.[23]

The Hepatitis C virus has been evolving over thousands of years and has 6 genotypes and many subtypes. Their distribution varies throughout the world. Several investigators have found significant differences in virus load associated with infection with different genotypes of HCV and it had been argued that this could be one of the factors involved in genotype-specific differences in the outcome of interferon therapy. In particular, genotypes 1 and 4 are not as responsive to treatments based on interferon compared with the others. Alcohol, cirrhosis, NIDDM, perhaps obesity, exposure to afla toxins in poorly stored grains, combined infections are co-factors. These cases are less responsive to interferon. HCV is a common co infection with HIV, a unique challenge, as HAART is itself hepatotoxic. The HCV core protein has oncogenic potential. The pathway responsible is cell proliferation through stimulation of mitogen activated protein kinase (MAPK). Its transforming potential depends

on activating STAT 3 (signal transduction and activator). The hyperproliferative state induced by chronic hepatitis and cirrhosis is argued to lead to accumulation of genetic changes and to contribute to the onset of liver cancer.

Primary Prevention: Vaccination: HBV vaccination is given to all babies just after birth, to all individuals upto the age of 18 who have not been vaccinated before and all individuals who are at risk. HBV vaccine has been seen to reduce incidence of child hood liver cancer in endemic areas. Although HCC is a malignancy with a poor prognosis, the availability of an effective vaccine against HBV infection, and its inclusion in the Expanded Programs of Immunization of many countries, augurs well for the eventual elimination of HBV-associated HCC. *HCV vaccine development on the other hand is at early stage. Pegylation of interferon with ribavirin improves response rate compared to standard interferon only in HCV. Effective ongoing programs include sexually transmitted disease, health education, syringe and needle exchange programs, counseling for intravenous drug users (IVDU).*

Human T-Lymphotropic Virus

Human T-lymphotropic virus (HTLV) is a human, single-stranded RNA retrovirus that causes T-cell leukemia and T-cell lymphoma in adults and may also be involved in certain demyelinating diseases, including tropical spastic paraparesis. There are 4 types. HTLV-I is a virus that has been seriously implicated in several kinds of diseases including HTLV-I-associated myelopathy, Strongyloides stercoralis hyper-infection, and a virus cancer link for leukemia (see adult T-cell leukemia/lymphoma). As estimated 10-20 million people are infected with HTLV type 1. HTLV was discovered in 1977 in Japan.[24] It was the first identified human retrovirus. Infection with HTLV-I, like infection with other retroviruses, probably occurs for life and can be inferred when antibody against HTLV-1 is detected in the serum.[25] Transmission of HTLV-I is believed to occur from mother to child via breastfeeding; by sexual contact. Through exposure to contaminated blood, either through blood transfusion or sharing of contaminated needles. The importance of the various routes of transmission is believed to vary geographically. The virus activates a subset of T-helper cells called Th1 cells. The result is a proliferation of Th1 cells and overproduction of Th1 related cytokines (mainly IFN-gamma and TNF-alfa). Feedback mechanisms of these cytokines cause a suppression of the Th2 lymphocytes and a reduction of Th2 cytokine production (maily IL-4, IL-5, IL-10 and IL-13). The end result is a reduction in the ability of the infected host to mount an adequate immune response to invading organisms that require a predominantly Th2 dependant response (these include parasitic infections and production of mucosal and humoral antibodies).

Human Herpes Virus TYPE 8

Human herpesvirus 8 or Kaposi's sarcoma associated herpesvirus (HHV-8/KSHV) was recognized to be a novel gamma-2 herpesvirus of the rhadinovirus genus closely related to the human gamma -1 herpesvirus, Epstein-Barr virus (EBV).[26] Kaposi's sarcoma (KS) is a highly and abnormally vascularized tumor-like lesion affecting the skin, lymphnodes and viscera, which develops from early inflammatory stages of patch/plaque to late, nodular tumors composed predominant of spindle cells (SC).[27] These SC are infected with the Kaposi's sarcoma-associated herpesvirus or human herpesvirus-8 (KSHV/HHV-8). KS is promoted during HIV infection by various angiogenic and pro-inflammatory factors including HIV-Tat. The latency associated nuclear antigen type 1 (LANA-1) protein is well expressed in SC, highly immunogenic and considered important in the generation and maintenance of HHV-8 associated malignancies**.** Various studies favor an endothelial origin of the KS SC, expressing "mixed" lymphatic and vascular endothelial cell markers, possibly representing hybrid phenotypes of endothelial cells.

Human Immunodeficiency Virus

AIDS-Defining Cancers

People infected with HIV are 100 to 300 times more likely to have KS**.** In the presence of HIV, KS is

associated with human herpes virus 8. The risk and severity of KS increase in the presence of low CD4 T cell counts and people with intact immune systems tend not to develop KS when infected with HHV-8**.** Studies have unequivocally demonstrated significant declines in the incidence of KS following the introduction of HAART**.**

The risk of ***non-Hodgkin's lymphoma*** (NHL, also referred to as AIDS-related lymphoma) is substantially increased in the HIV-infected population, with risks ranging from approximately 40 to 400 times that of the general population, depending on the specific study and the type of NHL. NHL encompasses several types of lymphoma, including systemic NHL, primary central nervous system NHL (PCNSL, also referred to as primary brain lymphoma or cerebral lymphoma), and primary effusion lymphoma (PEL) or body cavity-based lymphoma, a rare and aggressive form of NHL. Some studies have demonstrated significant decreases in incidence of NHL following the introduction of HAART, however, other studies fail to show any substantial change, and even suggest modest increases in incidence. Nevertheless, studies routinely show that incidence of PCNSL has decreased considerably following the introduction of HAART**.** Patients with systemic NHL who received and responded to HAART were significantly more likely to achieve a complete response.

Invasive cervical cancer (ICC) is considered an AIDS-defining condition. HIV-positive women with ICC tend to have higher CD4 T cell counts compared to HIV-positive patients with other malignancies. Studies report that HIV-positive women are approximately 5 to 9 times more likely to have ICC compared to seronegative women, and this cancer accounts for 55% of AIDS-related malignancies in some settings. Moreover, the clinical course becomes even more aggressive when CD4 T cell count is low**.**

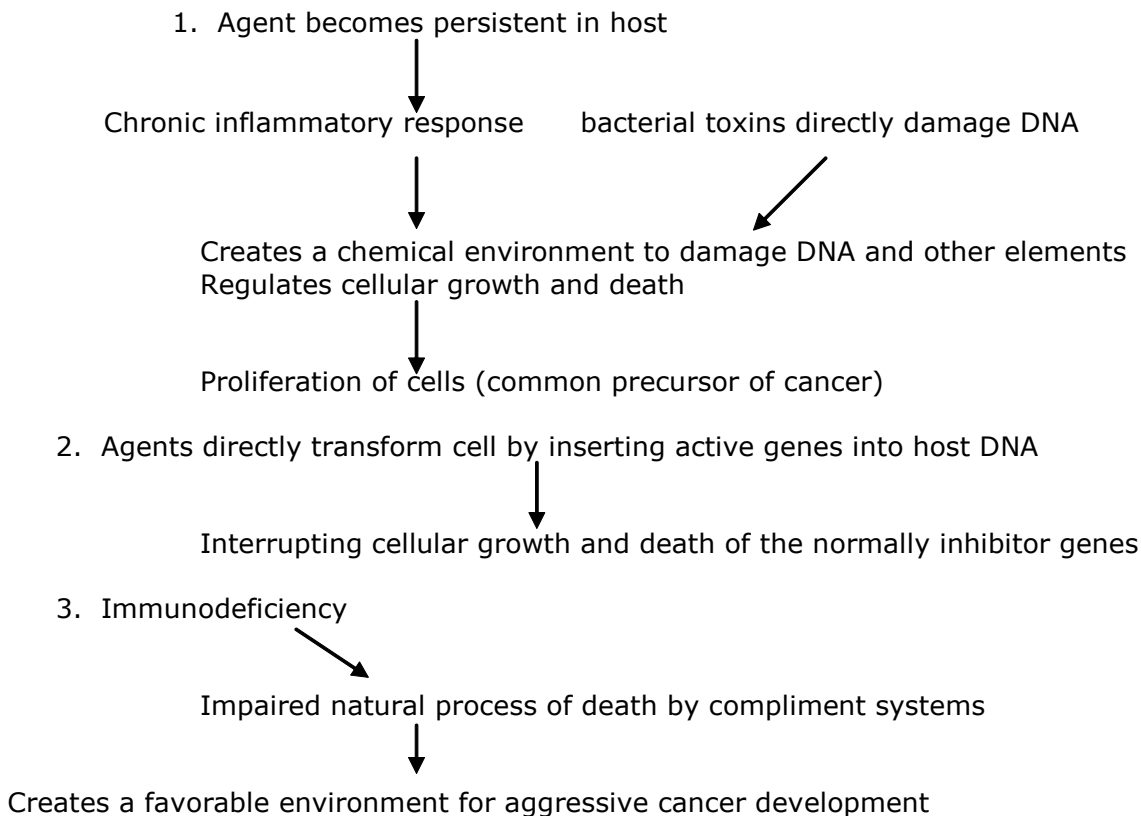
Non-AIDS-Defining Malignancies

Currently, ***Hodgkin's disease*** (**HD**) is not considered an AIDS-defining cancer. However, those infected with HIV are 7.6 to 11.5 times more likely to have HD compared to the general population. This issue is controversial. While analysis have routinely demonstrated increased risk of HD in those infected with HIV, an actual causal link between HIV and HD has not been established and studies assessing the effect of immunosuppression on incidence of HD are conflicting. A positive correlation between immunosuppression and increased incidence of HD has been demonstrated in some analyses Few studies have looked at the effect of HAART on incidence of HD. However, those that have assessed this relationship reported no difference in rates when comparing patients who had received HAART with that us treatment-naïve patients**.**

Similar to cervical cancer, anal cancer is strongly associated with HPV infection and the presence of precancerous anal lesions, which is referred to as squamous intraepithelial lesions (SIL) and anal intraepithelial neoplasia (AIN)**.** High-grade forms of these lesions tend to contain the oncogenic types of HPV, specifically HPV-16 and HPV-18. Most studies demonstrate that those infected with HIV are 30 to 50 times more likely to have anal cancer, with rates as high as 60 fold in HIV-positive men who are bisexual or homosexual. Progression to high-grade dysplasia is increased in the presence of HIV infection, and anal HPV infection and high-grade SIL (HSIL) are extremely common in bisexual and homosexual men, regardless of HIV serostatus**.** The possible benefits of HAART on the incidence of anal cancer and precancerous lesions have not been conclusively demonstrated. The few studies that have examined this relationship suggest that HAART has not decreased the incidence or increased the regression of these lesions.

People infected with HIV are 2.5 to 7.5 times more likely to develop *lung cancer* compared to HIV-negative people. Several studies have reported a positive correlation between rates of

Figure I



lung cancer and immune suppression. Analyses of risk behavior have reported conflicting data: one study showed that HIV-positive patients with lung cancer smoked twice as many cigarettes as HIV-negative patients with lung cancer, while another study that compared HIV-positive women to HIV-negative women with similar smoking histories showed a 2-fold increased incidence in the HIV-positive women. Long-term cigarette exposure is typically lower in HIV-positive patients because they are usually diagnosed with lung cancer at an earlier age. Before the introduction of HAART, rates of lung cancer were low, perhaps on account of early AIDS-related mortality. A recent analysis showed an almost 9-fold increase in lung cancer incidence following the introduction of HAART.

Studies assessing cancer incidence demonstrate that HIV-positive men are 1.4 to 8.2 times more likely to develop testicular cancer. While no viral oncogene has been implicated in HIV-associated, viruses such as mumps orchitis, HPV, Epstein-Barr virus (EBV), and human endogenous retrovirus K10 are associated with testicular cancer in HIV-negative men and may be involved in development of testicular cancer in the HIV-positive population. The effect of HAART on incidence rates has not been analyzed thoroughly, but one report showed no difference in incidence rates when comparing the pre-HAART and post-HAART eras.

Other Non-AIDS-Defining Cancers With Increased Incidence in the HIV-Infected Population

Leukemia	Pharynx	Pancreas
Multiple myeloma	Esophagus	Liver
Skin cancer	Lip	Kidney
Penile	Tongue	Colorectal
Vulva/Vagina	Stomach	Brain and CNS
Leiomyosarcoma	Larynx	Heart
		Angiosarcoma

Helminths

Schistosoma hematobium are endemic in 74 countries of Africa and eastern mediterranean. Greater than 200 million people per year suffer from it and it claims 1 million lives per year. It is a potentially proven cause for squamous cell carcinoma of urinary bladder and genitourinary tracts**.** Opisthorchis vivervini most common in Thailand about 9-10 million people are infected among which15% developed Cholangiocarcinoma.[29]

Conclusion

The relationship between cancer and infection is complex and supportive epidemiological data is emerging very slowly. Vaccination remains the gold standard for prevention**.**

Mechanism of Disease

There are 3 basic pathogenic mechanisms as detailed in Fig 1 on previous page.

References

1. Vakil N and Fennerty B. The economics of eradicating *Helicobacter pylori* infection in duodenal ulcer disease. *American Journal of Medicine* 1996;100:60S-63S.
2. Kusters JG, van Vliet AH, Kuipers EJ. Pathogenesis of *Helicobacter pylori* infection. *Clinical Microbiology Reviews* 2006;19:449-90.
3. Helicobacter and Cancer Collaborative Group. Gastric cancer and *Helicobacter pylori*: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* 2001;49:347-53.
4. Parsonnet J, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, et al. *Helicobacter pylori* infection and the risk of gastric carcinoma. *New England Journal of Medicine* 1991;325:1127-31.
5. Raderer M, Wrba F, Kornek G, Maca T, Koller DY, Weinlaender G, Hejna M, Scheithauer W. Association between *Helicobacter pylori* infection and pancreatic cancer. *Oncology* 1998;55:16-19.
6. Parsonnet, J, Hansen S, Rodriguez L, Gelb AB, Warnke RA, Jellum E, Orentreich N, Vogelman JH, and Friedman GD. 1994. *Helicobacter pylori* infection and gastric lymphoma. *New England Journal of Medicine* 1994;330:1267-71.
7. Kamangar F, Dawsey SM, Blaser MJ, Perez-Perez GI, Pirjo Pietinen, Newschaffer CJ, Abnet CC, Albanes D, Virtamo J, Taylor PR. Opposing risks of gastric cardia and noncardia gastric adenocarcinomas associated with *Helicobacter pylori* seropositivity. *Journal of the National Cancer Institute.* 2006;98:1445-52.
8. Stolzenberg-Solomon RZ, Blaser MJ, Limburg PJ, Perez-Perez G, Taylor PR, Virtamo J, Albanes D. *Helicobacter pylori* Seropositivity as a risk factor for pancreatic cancer. *Journal of the National Cancer Institute* 2001;93:937-41.
9. Ramakrishna BS. *Helicobacter pylori* infection in India: the case against eradication. *Indian Journal of Gastroenterology* 2006;25:25-28.
10. Huang JQ, Zheng GF, Sumanac K, Irvine EJ, Hunt RH. Meta-analysis of the relationship between *cagA* seropositivity and gastric cancer. *Gastroenterology* 2003;125:1636-44.
11. Munoz N, Bosch FX, de Sanjosé S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *New England Journal of Medicine* 2003; 348(6):518–527.
12. Castle PE, Wacholder S, Lorincz AT, et al. A prospective study of high-grade cervical neoplasia risk among human papillomavirus-infected women. *Journal of the National Cancer Institute* 2002; 94(18):1406–1414.
13. Koutsky LA, Ault KA, Wheeler CM, et al. A controlled trial of a human papillomavirus type 16 vaccine. *New England Journal of Medicine* 2002; 347(21):1645–1651.
14. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002. Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report* 2002; 51(RR-6):1–78.
15. National Cancer Institute. Future directions in epidemiologic and preventive research on human papillomaviruses and cancer. Proceedings of a workshop. Bethesda, Maryland, June 2002. *Journal of the National Cancer Institutes Monographs* 2003; 31:1–130.
16. Thompson M and Kurzrock R. Epstein-Barr Virus and Cancer. *Clinical Cancer Research* 2004; 10 :803-821.
17. Maddrey WC. Hepatitis B- an important public health issue. *Clinical laboratory* 2001;47(1-2): 51-55.
18. DiBisceglieAM, Simpson AH, Lotze MT, Hoofnagle JH. Development of hepatocellular carcinoma among patients with chronic liver disease due to hepatitis C viral infection. *J Clin Gastroenterol* 1994, 19:222-226.
19. Blumberg bs. Australia antigen and the biology of hepatitis B. *Science* 1977;197:17-25.
20. Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22,707 men in Taiwan. *Lancet* 1981;2:1129-1133.
21. Unsal H, Yakicier C, Marcais C, et al. Genetic heterogeneity of hepatocellular carcinoma. *Proc Natl Acad Sci USA* 1994,91:822-826.
22. Lee DK, Park SH, Yi Y, et al. The hepatitis B virus encoded oncoprotein px amplifies TGF beta family signaling through direct interaction with Smad 4. Potential mechanism of hepatitis B virus induced liver fibrosis. *Genes dev* 2001; 15: 455-466.