Chapter 14
Evolution, Infection, and Cancer

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Lay Summary The occurrence of cancer depends on three evolutionary processes: normal cells evolve into cancer cells, humans and other species have evolved biological protections against cancer, and disease organisms have evolved countermeasures that subvert these protective mechanisms. Evolutionary thinking has led not only to the recognition of these three processes, but also to the emergence of a more balanced and comprehensive understanding of cancer, which emphasizes that causes of cancer need to be understood through the interplay among genes, germs, and the environment. This understanding is framed by a focus on the function of genes that promote oncogenesis and the effects of these genes on the environment both within and outside of the cells; cancer-promoting genes may belong to cancer cells, parasites, or both. An evolutionary perspective helps to identify the processes that most importantly contribute to cancer—and are therefore the most important to prevent—even though innumerable processes are altered during oncogenesis. It suggests that generation of cancer solely by mutations is difficult because several critical barriers must be abrogated in succession without the occurrence of other mutations that make the cell non-functional. On the other hand, although natural selection commonly moulds parasites to compromise simultaneously the critical protections against cancer, infection alone is also insufficient to bring about human cancer.

Parasites are known to contribute about 20 % of all human cancer and may play a role in much, if not most, of the remaining 80 %. Evolutionary considerations and epidemiological evidence suggest that pathogens transmitted

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by sexual contact, saliva, and hypodermic needles are disproportionately important infectious causes of human cancer. The possible influence of reducing these routes of transmission can be evaluated by comparing cancer incidences among populations in the context of the full spectrum of risk factors, as illustrated by comparisons among residents of Utah. Overall, evolutionary considerations suggest that inadequate attention has been given to possible infectious causes of cancer, and that control of infection may prove to be one of the most effective ways to control cancer.

14.1 Introduction to Evolution and Selection in Oncogenesis

Three evolutionary actions of selection are important in oncogenesis, the process by which normal cells acquire the characteristics of cancer cells. First, oncogenic selection acts through the increased survival and reproduction of cells that are genetically modified relative to normal cells in the body [1]. Second, natural selection generates adaptations in multicellular organisms that reduce their risks of cancer [2–6]. Third, natural selection also moulds infectious agents in ways that may compromise the adaptations that multicellular hosts have evolved to reduce cancer risk [1, 7, 8]. We consider each of these selective processes below.

14.1.1 Oncogenic Selection

Normal cells evolve into cancer cells in part through selection acting on genetic variation that arises from genetic mutations. This process is similar to natural selection in that genetic composition of a population changes over time as a result of differences in survival and reproduction. It is referred to as oncogenic selection [1], however, because it differs from natural selection in two distinct ways.

The most basic difference is that oncogenic selection involves the differential survival and reproduction of cells within the organism rather than that of the organism itself. Oncogenic selection results in changes in genetic composition of a population of cells within an organism rather than changes in the genetic composition of a population of organisms. Natural selection has moulded normal cells to restrict their own survival and reproduction when this regulation increases the survival and reproduction of the multicellular organism to which they belong. In contrast, oncogenic selection favours cells that lose such regulatory mechanisms when this loss increases their number relative to other cells in the body. Oncogenic selection therefore tends to involve the breaking rather than the refinement of regulatory adaptations.

The second major difference between oncogenic and natural selection involves long-term opportunities for evolutionary adaptation. Natural selection acting on an organism is open-ended, whereas selection of somatic cells within an organism is truncated by the death of the organism. Oncogenic selection therefore cannot generate the unending cumulative change and sophistication of adaptations that arises from natural selection. The reason is that cancer cells cannot, as a rule, be transmitted from one individual to another. In the rare exceptions to this rule, opportunities for future evolution become open-ended, and the cancer cells go through the transition from being cells of a multicellular organism to becoming a parasitic organism. When this transition occurs, oncogenic selection ends and natural selection begins. Two cancers that have passed through this transition have been well studied: transmissible venereal tumour of dogs and the facial tumours of Tasmanian devils [9, 10].

14.1.2 Natural Selection on Multicellular Organisms

Natural selection has led to adaptations that guard against oncogenesis. Barriers are defined as adaptations that block oncogenesis when they are in place [1]. The four main barriers are cell cycle arrest, apoptosis, telomerase regulation, and cell adhesion [1]. The presence of barriers may vary according to cell type, resulting in different vulnerabilities to oncogenesis [1]. Restraints inhibit but do not block oncogenesis [1]. Regulation of division rate of a dividing cell, for example, is a restraint, which retards rather than prevents oncogenesis, because even a slowly replicating cell can proceed down the path of oncogenesis. Alterations that compromise barriers are defined as essential causes of cancer; those that interfere with restraints are exacerbating causes [1]. Understanding whether a target is part of an essential or exacerbating cause is important for determining whether an intervention could be preventive, curative, or just ameliorative.

14.1.3 Natural Selection on Infectious Agents of Cancer

Approximately 20 % of human cancers are caused by parasites [11], here defined as self-replicating entities (e.g. viruses, bacteria, protozoa, or multicellular organisms) that live in or on a host organism and harm it. The extent to which infection contributes to the remaining 80 % of human cancer is not known, because a causal role for parasites can be ruled out for very few of these cancers.

Natural selection moulds infectious agents to exploit their hosts in ways that increase their own evolutionary fitness. When an infectious agent contributes to oncogenesis, it is important to determine the extent to which this contribution compromises restraints or barriers. If a parasite compromises one or more barriers, then prevention or cure of the infection may prevent oncogenesis.

Barriers to cancer can also be barriers to persistence within a host, particularly for intracellular parasites such as viruses. Breaking cell cycle arrest allows the viral genome within the cell to replicate in concert with cellular replication. By relaxing control of the synthesis of telomerase, the viral genome removes the cap on the total number of divisions a cell can undergo. By inhibiting apoptosis, a virus can reduce the chance that it will be destroyed by cellular self-destruction. By altering cell adhesion, viruses allow infected cells to disperse to new locations in the body. Together, these compromises of barriers to cancer enhance persistence because they allow a virus to replicate its genome with less exposure to the immune system than would occur through the release of virions from cells. By favouring viruses that subvert the host barriers to persistence, natural selection may lead to the evolution of increased oncogenicity in viruses.

Several cancer-causing viruses of humans have been sufficiently well investigated to evaluate whether they compromise these barriers: Epstein Barr virus (EBV), Kaposi's sarcoma-associated herpes virus (KSHV), hepatitis B virus (HBV), hepatitis C virus (HCV), human papillomavirus (HPV), and human T-cell lymphotropic virus type 1 (HTLV-1). Each of these viruses compromises all four barriers (reviewed by [8]). Each virus therefore contributes to four essential causes of cancer. This simultaneous compromising of four barriers to cancer is important for oncogenesis because it can generate large populations of infected, dividing cells, within which a relatively small number of additional mutations are needed to complete the progression to cancer.

This emerging understanding of oncogenic viruses contrasts markedly with earlier presumptions about the ways in which infectious agents contributed to oncogenesis. When parasites were first associated with oncogenesis, it was generally presumed that they exacerbated the mutation-driven process of cancer. Infection results in inflammation, which can increase rates of cellular proliferation [12] and generate reactive compounds that cause mutations. Through these effects, infection would generally contribute exacerbating rather than essential causes of oncogenesis, because most mutations would tend to occur in genes other than the few that maintain barriers. In contrast, oncogenic viruses contribute to multiple essential causes of oncogenesis, because from the onset of infection they are abrogating multiple barriers to cancer.

14.2 Research Findings

14.2.1 The Triad of Disease Causation

There are three general categories of disease causation: genetic, parasitic, and non-parasitic environmental causes. Diseases are often referred to using other adjectives, such as developmental, endocrinological, or neurological, but to explain aetiology more deeply, one must invoke at least one of the three general categories of causation. The triad of disease causation (Fig. 14.1) emphasizes that different aetiologies

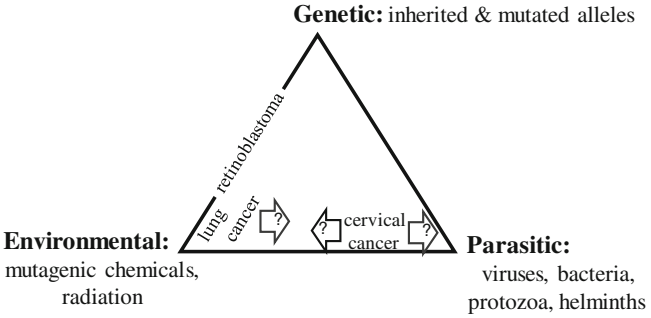

Fig. 14.1 The triad of disease causation: a visual aid for thinking about the spectrum of causation and the interplay between different causes. Placement of a cancer corresponds to the degree to which the cause compromises barriers (i.e. adaptations that block oncogenesis) as opposed to restraints (i.e. adaptations that hinder oncogenesis)

co-occur and interact. Genetic causes of cancer can be inherited or can arise because of mutations that are generated by parasitic or nonparasitic environmental causes. Parasitism can contribute to oncogenesis by compromising barriers and restraints but rarely if ever generate cancers without contributions from mutations. In addition, genetic variation in resistance to parasitism is ubiquitous and therefore must also influence contributions of parasites to oncogenesis.

The precise placement of a cancer within the triangle is almost always tentative and corresponds to the extent to which each of the three categories encompasses essential causes. Retinoblastoma is the best example of a cancer for which evidence implicates inherited alleles and additional mutations without contributions from an infectious agent [1]; it is therefore placed directly on the genetic-environmental axis in Fig. 14.1. Cervical cancer is placed close to the parasitic vertex because the causal agent, HPV, encodes proteins that compromise four barriers to cancer. Current evidence indicates that the frequencies of mutations in genes that maintain barriers tend to be relatively low in cervical cancer; these mutations therefore are not necessary for oncogenesis when viruses are present [13]. The arrows containing a question mark in Fig. 14.1 are inserted to acknowledge the remaining uncertainty about the overall contribution of environmentally induced mutations (e.g. by compounds in tobacco smoke and the overall net effect of mutations).

Inherited vulnerability to cervical cancer contributes to the placement of cervical cancer above the environmental/parasitic axis. Much of this contribution involves variation in immunological defences against viral infection [14–16] and therefore represents exacerbating causes of cervical cancer.

Consideration of the triad of causation guards against the error of overextending one category of explanation. The strong association between tobacco smoke and lung cancer, for example, has led to the sense that infection does not contribute to lung cancer, even among experts who recognize a broad role for infectious causation of cancer (e.g. [17]). It is well known that smoking can increase the probability of pulmonary infections; yet until recently there has been little investigation

of the possible involvement of infectious agents in lung cancer. The few studies that have addressed this issue have reported associations with JC virus, merkel cell polyomavirus, EBV, and HPV [18–20]. Each of these viruses compromises three or more barriers to cancer [8, 19].

14.2.2 The Extended Phenotype in Oncogenesis

Oncogenesis involves not only the evolution of cancer cells, but also modifications of their microenvironments, including alterations of extracellular molecules and effects on non-cancerous cells [21, 22]. Although these modifications may be complex and diffuse, the role of the microenvironment can be grasped by applying the concept of the extended phenotype, which is defined as the effects of a genetic variant on its environment [23]. The extended phenotype of a cancer cell, for example, includes elevated metalloproteases, which may degrade cell adhesion molecules and influence proliferation, angiogenesis, and metastasis [24, 25]. Viral effects on barriers to oncogenesis are part of the extended phenotype of the virus.

An important aspect of the extended phenotype of oncogenic viruses involves epigenetic changes: alterations in gene expression that are not associated with changes in DNA sequence but can be stable from one cellular generation to the next. These modifications can be associated with tumour initiation and progression. Tumours infected with oncogenic viruses have shown distinct epigenetic alterations relative to non-cancerous patient tissue [26] and to uninfected cancers that are of the same type [27]. Methylation of gene promoter regions has been shown to silence genes involved in barriers to cancer; investigators have found this category of epigenetic alteration associated, for example, with HPV-positive cervical cancer [13], HPV-positive oropharyngeal carcinoma, [28], and EBV-positive cancers [29]. Telomerase expression is often up-regulated in virally associated cancers. HPV type 16 can increase telomerase expression in infected cervical carcinoma cell lines by decreasing methylation of the promoter for the hTERT subunit of telomerase [30]. In addition, epigenetic modifications at gene loci associated with cell adhesion have been identified in cervical cancer, HPV-positive oropharyngeal carcinomas, and EBV-related nasopharyngeal carcinoma [27, 31, 32]. Importantly, because gene expression abnormalities associated with epigenetic modifications are not mutations, they are potentially reversible; for example, experimental knock down of the E6 protein of HPV types 16 and 18 in cervical cancer cell lines restored silencing of telomerase [30].

Without the conceptual structure provided by the extended phenotype, the vast collection of microenvironmental and intracellular alterations during oncogenesis could be overwhelming. Together with the concepts of barriers and essential causes, the extended phenotype maintains the emphasis on a relatively small number of processes that result directly or indirectly from oncogenic genes in the genomes of the cancer cell and oncogenic parasites.

14.2.3 Transmission of Oncogenic Parasites

An evolutionary perspective suggests that selection for persistence of viruses, and hence potential oncogenicity, will be especially strong when opportunities for transmission are widely spaced over time. This condition applies to sexual transmission because opportunities for sexual transmission depend on changes in sexual partnerships, which tend to occur less frequently than, for example, opportunities for transmission by sneezing or coughing. Similarly, pathogens transmitted by intimate kissing should be subject to strong selective pressure for persistence because new intimate kissing partnerships tend to be temporally spaced. Selection for persistence will also be strong when pathogens are maintained across generations by transmission through milk, because such transmission requires persistence within a host from infancy until adulthood and is augmented by extended persistence over periods that encompass successive births. Opportunities for needle-borne transmission through intravenous drug use or blood donation are also relatively infrequent. Because molecular mechanisms for persistence often compromise critical barriers to oncogenesis (as discussed in Sect. 14.1.3), evolutionary considerations lead to the expectation that oncogenic capabilities should occur disproportionately among pathogens transmitted by sex, saliva, needles, and milk. This prediction is particularly applicable to viral pathogens because viruses infect intracellularly.

This evolutionary logic accords with the transmission routes of viruses that are accepted causes of human cancer. Among oncogenic viruses, the predominant route of transmission is sexual, with needle-borne and salivary transmission being present to a lesser extent (Table 14.1). In contrast, these routes apply to only about one-quarter of all known human viruses. HTLV-1 is the only accepted tumour virus that is known to be maintained substantially in humans across generations through transmission by milk (Table 14.1). Candidate oncogenic viruses are transmitted largely by these routes (Tables 14.1 and 14.2).

Two unicellular pathogens are also accepted infectious causes of cancer: *Plasmodium falciparum* and *Helicobacter pylori* (Table 14.1). Oncogenic mechanisms are less well understood for these pathogens than for oncogenic viruses. Burkitt's lymphoma can be caused by EBV in the absence of *P. falciparum*, which apparently contributes to this cancer by enhancing EBV [33–36]. *P. falciparum* therefore appears to be an exacerbating rather than an essential cause. *H. pylori* enhances telomerase activity [37–39] but has complex and sometimes contradictory effects on other barriers [40, 41]. One of its proteins exerts anti-apoptotic effects that counter the host cell's apoptotic responses to the bacterium [42]. *H. pylori* also stimulates pro-inflammatory and growth factor signalling [43, 44], and is associated with increased telomerase expression [45] as well as with reduced adhesion and abrogation of cell cycle arrest [46]. *H. pylori* therefore can compromise the four barriers to oncogenesis that are abrogated by oncogenic viruses. *H. pylori* can infect intracellularly [47] and thus may benefit directly from the replication of its host cell.

Table 14.1 Parasites for which a causal role in human cancer has been generally accepted

Virus[a]	Mode of transmission	Cancers for which the parasite is	
		An accepted cause	A candidate cause
EBV	Saliva, sex	Burkitt's lymphoma, Hodgkin's lymphoma, gastric carcinoma, post-transplant proliferative disease, nasopharyngeal carcinoma	Breast, acute lymphoblastic leukaemia, ovarian, lung
HPV	Sex	Cervical, oropharyngeal, penile, anal, vulval, vaginal cancers	Breast, bladder, oesophagus, prostate, lung, skin
HTLV-1	Sex, needle, milk	Adult T-cell leukaemia and lymphoma	None
KSHV	Saliva, sex	Kaposi's sarcoma	Lung
HBV	Sex, needle, milk	Hepatocellular carcinoma	Cholangiocarcinoma, pancreas
HCV	Sex, needle	Hepatocellular carcinoma	Cholangiocarcinoma
MCPyV	Saliva	Merkel cell carcinoma	Lung
Helicobacter pylori	Saliva? Diarrhoea? Vomit?	Gastric carcinoma; Mucosa-associated lymphoid tissue MALT lymphoma	None
Plasmodium falciparum	Mosquitoes	Endemic Burkitt's lymphoma	None
Schistosomal and opisthorchid trematodes	Water contact, fish consumption	Cholangiocarcinoma, bladder	Colorectal

[a]*EBV* Epstein Barr virus = Human Herpes virus 4; *HPV* Human papilloma virus; *HTLV-1* Human T lymphotropic virus type 1 = human T-cell leukaemia/lymphoma virus type 1; *KSHV* Kaposi's sarcoma-associated herpes virus = human herpes virus 8; *HBV* Hepatitis B virus; *HCV* Hepatitis C virus; *MCPyV* Merkel cell polyomavirus. For references, see [1, 7, 8, 20, 67, 68]

When infecting extracellularly, it may benefit from stimulating the replication of host cells in its immediate vicinity if they provide some protection against stomach acidity.

14.2.4 Environmental and Infectious Risk Factors: An Illustration

The predominance of sexual and salivary transmission among tumour viruses suggests that reduction in the numbers of intimate partnerships would reduce the prevalence of a variety of cancers. Evaluation of this prediction is difficult because epidemiological studies of cancer generally must rely on correlation rather than experimentation.

Table 14.2 Parasites that have been associated with cancers but are not yet accepted causes of any cancer

Pathogen[a]	Mode of transmission	Cancers for which virus is a candidate cause	References
HCMV	Saliva, sex, milk	Brain (glioblastoma), prostate, breast	[69–72]
HHSV-2	Sex	Melanoma, prostate	[73]
JCV	Unknown	Brain, colorectal, oesophageal, lung, gastric	[18, 19, 74]
BKV	Unknown	Brain, bladder, kidney, ovary, prostate	[72]
SV40	Unknown	Brain, mesothelioma	[75]
MMTV	Milk in mice	Breast	[76]
BLV	Milk in cows	Breast	[77]
XMRV	Unknown	Prostate	[72]
Mycoplasma hominis	Sex	Prostate	[72]
Propionobacterium acnes	Skin contact	Prostate	[72]
Trichomonas vaginalis	Sex	Cervical	[78, 79]

[a]*HCMV* Human cytomegalovirus = Human Herpes virus 5; *HHSV-2* Human herpes simplex virus 2 = human herpes virus 2; *JCV* JC virus; *BKV* BK virus; *SV40* Simian virus 40; *MMTV* Mouse mammary tumour virus = human mammary tumour virus; *BLV* Bovine leukaemia virus; *XMRV* Xenotropic murine leukaemia virus-like retrovirus

Measured variables may be correlated with cancer but not causally involved, and important correlates may have been unmeasured. Quantification of the number of sexual partners, for example, does not incorporate the amount of sexual contact per partner and whether the sexual partners are themselves at high risk for infection. Moreover, measured variables could be correlated with unmeasured variables in unobvious ways. Smoking, for example, could be correlated with a tendency to be more risk prone and hence with unmeasured aspects of risky sexual behaviour.

In spite of these drawbacks, comparisons of cancer in populations characterized by different risk factors may provide a sense of the extent to which changes in behaviour might reduce cancer incidence. They may also illustrate the importance of considering alternative combinations of risk factors and unmeasured variables when attempting to determine causes of cancers.

Among the best-studied subjects for such assessments are members of the Church of the Latter Day Saints (LDS). LDS members have fewer sexual partners than non-LDS comparison populations [48]. Accordingly, cervical cancer among LDS women was about half as frequent as among non-LDS women [49–52]. Multivariate analyses indicated that about 40 % of this reduction was associated with fewer sexual partners [51]. Among LDS women who regularly attended church, the prevalence of cervical cancer was about 80 % lower, with just over

one-third of the reduction being attributable to fewer sexual partners [51]. About 10 % of the lower prevalence of cervical cancer among LDS women was independently correlated with lower rates of smoking. Tobacco smoke contains carcinogenic compounds and is immunosuppressive [53, 54], and might therefore increase cancer rates by increasing mutation rates or reducing immunological control of precancerous lesions. Alternatively, as suggested above, smoking could be correlated with unmeasured variables that cause the differences in cancer rates.

The difficulties in interpreting smoking-associated risk of cervical cancer were addressed a quarter century ago. Two of the researchers involved with this debate [55] wrote:

> Definitive clarification of whether this association is causal will likely have to await definitive identification of the sexually transmitted agent which is probably the most important cause of cervical cancer. Only then will it be possible to clarify the contributions of risk factors with weaker associations with cervical cancer, such as cigarette smoking and socioeconomic status.

HPV was in the process of being recognized as the main cause of cervical cancer at about the time their paper was published. A few years later, a multifactorial analysis of the associations of smoking with cervical HPV infection showed that smoking was not significantly associated with HPV infection once sexual behaviour and other life-style variables were accounted for, leading the authors to conclude that smoking, alcohol, and drug use were correlates but not causes of HPV infection [56].

Most cancers are less prevalent among LDS members [49–52]. The lower rates of smoking-associated cancers (e.g. lung, cervical, bladder, colon, and laryngeal) among LDS members could be interpreted as a direct effect of lower exposure to tobacco smoke. Indeed when these reductions are discussed, the smoking-associated cancers are often grouped together implying that their lower rates result from lower exposure to tobacco smoke [50, 52]. An association with smoking, however, does not weaken the hypothesis that infectious causes are also involved, as illustrated by the associations of sexual behaviour with cervical cancer. The associations of sexually transmitted pathogens with smoking-associated cancers (e.g. lung, bladder, colon, and laryngeal in Tables 14.1 and 14.2) raise the possibility that infectious agents may be causally involved in more cancers than previously thought.

14.3 Implications for Policy and Practice

The control of infectious diseases through the use of vaccines, anti-infective agents, and interventions that block transmission has been among the most significant accomplishments in the history of medicine. Although the control of cancer remains largely an unfulfilled goal, control of infectious causes rank among the most successful interventions against cancer. These interventions include vaccination against

HPV and HBV (for cervical and liver cancers), prevention of transmission of HBV and HCV (for liver cancer), and control of *H. pylori* by improvements in hygiene and antibiotic treatment (for stomach cancers) [57–62].

Evolutionary considerations suggest that the relative importance of infectious causation is being underestimated, in part because pathogens evolve to compromise multiple barriers to cancer. To induce cancer without infection, multiple mutations (or epigenetic changes) must compromise several critical barriers in succession without making the cell non-functional [1].

Infectious causation has been accepted for about 20 % of all human cancer, and associations with infectious agents have been reported for most of the remaining 80 %. It is critically important to determine whether pathogens cause these cancers by compromising barriers. If so, their prevention should prevent the cancers they cause.

Many cancers may be controllable with the same interventions that are already in place but are being restricted to a particular cancer. The recent prophylactic vaccines against cervical cancer, for example, probably provide protection against other cancers induced by HPV, such as oropharyngeal, penile, and rectal cancers, and may provide protection against other cancers for which HPV is at present just a candidate cause, such as bladder cancer (Table 14.1).

Standard approaches of vaccination and prevention of transmission will undoubtedly contribute much to the future control of pathogen-induced cancers, once the causal pathogens are identified. Because pathogens differ from human cells in their biochemical make-up, discovery of infectious causes of cancer also offers new approaches to cancer prevention and control. Antivirals are becoming more effective and may soon provide anti-cancer benefits that mirror the effects of antibiotic treatment of stomach cancers. For example, researchers have identified cytomegalovirus (CMV) in a majority of glioblastoma (brain tumours) samples, and adjunctive treatment with antiviral therapy has shown a significantly extended patient survival rate relative to non-treated individuals [63].

Some possibilities capitalize on the sophistication of immune control of foreign organisms. Therapeutic vaccines based on oncogenic HPV proteins show efficacy for treatment of cervical cancer [64, 65]. EBV-specific T-cell therapy has shown promising results in the early phase clinical trials of recurrent and metastatic nasopharyngeal carcinoma, and efforts are underway to develop effective therapeutic vaccines, anti-EBV antibodies, and therapies that target viral-associated epigenetic changes [66]. Determining whether a therapeutic target is part of an essential or exacerbating cause is crucial because interference with essential causes offer promise for cures.

Concerted interventions on interacting causes of cancer have been enacted to reduce incidence of hepatocellular cancer by vaccination against HBV and reduction in exposure to aflatoxin [61]. Similar concerted efforts may help to control cancers caused by joint infections. A two-pronged attack on opisthorchid trematodes and hepatitis viruses is a promising example for the control of cholangiocarcinoma [67].

The progress and promise for controlling cancers by controlling their infectious causes warrants attention from individuals working across the spectrum of health sciences. Scientific policymakers need to weigh the benefits of funding research that attempts to identify infectious causes of cancers and development of interventions against known and candidate pathogens. Medical policymakers need to assess the appropriateness of alternative guidelines for interventions, such as vaccines, when the interventions have likely protective benefits against cancer in addition to documented benefits against other cancers (e.g. protection against oropharyngeal cancer in addition to cervical cancer for HPV vaccines) or against other diseases (e.g. vaccination against HBV for protection against hepatocellular carcinoma in addition to liver cirrhosis, or antibiotic treatment of *H. pylori* for protection against stomach cancer in addition to peptic ulcers). Similarly, practicing physicians need to be able to advise patients about possible benefits of particular interventions (e.g. protection against oropharyngeal cancer afforded by HPV vaccination in addition to protection against cervical cancer). As this research is continually developing, experts in each of these areas need to keep abreast of ongoing developments to enhance the accuracy of their decisions.

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Glossary

Aflatoxin	A toxin produced by a *Aspergillus* fungi; can damage liver cells and contribute to liver cancer
Angiogenesis	Generation of new blood vessels; can contribute to oncogenesis by increasing supply of resources to a tumour
Apoptosis	Programmed cell death; acts as a barrier to oncogenesis by terminating precancerous lineages of cells
Barrier to oncogenesis	A process that blocks oncogenesis
Cancer	A tumour with cells that are invasive or metastatic
Cell cycle arrest	The blocking of cellular replication by enforcement at a checkpoint in the cell cycle; an important checkpoint for oncogenesis is at the transition to the phase in which DNA replication occurs
Cholangiocarcinoma	A liver cancer derived from cells of the gall bladder

Epigenetic changes	Modifications to DNA that turn gene expression on or off (e.g. through methylation) and may be inherited across cellular divisions, but do not alter the DNA sequence
Essential causes of cancer	Factors that abrogate barriers to oncogenesis
Exacerbating causes of cancer	Factors that abrogate restraints on oncogenesis
Glioblastoma	An aggressive tumour that forms from glial cells of the brain or spinal cord
hTERT	The catalytic subunit of telomerase
Oncogenesis	The evolution of cancer cells from normal cells
Oncogenic selection	The differential survival and reproduction of cells during oncogenesis
Parasite	A replicating agent that lives in or on a host organism, on which it has a harmful effect
Pathogen	A parasite at or below the single-cell level of organization
Restraint on oncogenesis	A process that inhibits but does not block oncogenesis
T-cell therapy for cancer	A process in which T-cells are activated and used clinically to attack a tumour
Telomerase	The enzyme that maintains telomere length through the addition of telomere units that would otherwise be lost during each cycle of DNA synthesis; maintenance of telomeres allows the number of future cellular divisions to be unlimited
Tumour	An abnormal mass of new tissue growth
Virion	A virus particle released from an infected cell

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