How Cancer Arises Based on Complexity Theory

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Executive summary

1. Cancer is an inevitable tradeoff of human biologic design. It will always be with us, particularly as life expectancy increases. However, we can often prevent it, we can detect it earlier and we can treat it more effectively.

2. Chronic cellular stress is the underlying cause of most cancer, by disturbing the delicate balance that exists in our interconnected biologic networks. In the correct microenvironment, it pushes susceptible stem or progenitor cells into increasingly dysregulated and unstable network trajectories that are ultimately associated with cancer. It is foreseeable that some chronic cellular stressors will cause cancer but which stressors will be important, where the cancers will arise and what their molecular and histologic features will be is not predictable.

3. There are nine important sources of chronic cellular stress which cause cancer, which often interact to provide the multiple “hits” that produce malignancy:

* Chronic inflammation (due to infection, infestation, autoimmune disorders, trauma, obesity and other causes)
* Exposure to carcinogens
* Reproductive hormones
* Western diet (high fat, low fiber, low vegetable consumption)
* Aging
* Radiation
* Immune system dysfunction
* Germ line changes
* Random chronic stress / bad luck

These sources of chronic stress typically create a field effect, because they affect cells throughout an organ or organ system.

4. Complexity theory helps us better understand how cancer arises:

A. To understand cancer, it is important to think about how life arose from cellular networks, because the same principles guide the pathophysiology of cancer. Focusing too much on specific details of the networks ignores the overriding theme, namely that the emergence of generic network features is independent of these details.

B. Living systems require delicately balanced cellular networks to enable major transitions from fertilization to embryogenesis to maturity to reproduction; to respond to environmental threats (infection, infestation, external and internal trauma); to physiologic threats (chronic inflammation and internal system errors) and to maintain homeostasis. Living systems must also have enough flexibility to promote and tolerate evolutionary change.

C. We can acquire new insights about malignancy by analyzing patterns of network behavior, which are more uniform than changes to downstream oncogenes.

D. Self-organized criticality describes how enormous transformations (“catastrophes”) occur over short time scales. Malignant change does not occur through gradualism but by bursts of activity.

E. Malignancies arise due to a build up of hierarchies, in which combination of agents (biomarkers and networks) at one level become agents at the next level. Hierarchies are identifiable by patterns of molecular changes; in some but not all cases there are accompanying histologic changes called intermediate states.

Introduction

This paper proposes a model of how cancer arises based on complexity theory. Chronic cellular stress is the underlying cause of most cancers by disturbing the delicate balance that exists in cellular networks necessary for the major functions of the organism: homeostasis; transition from fertilization to embryogenesis to maturity to reproduction; response to environmental changes; repairing external or internal damage; and providing genetic flexibility to allow evolutionary change. It is foreseeable that cancer will occasionally arise from these chronic cellular stressors although the site of disease and its histologic and molecular features are not *a priori* predictable. Future papers will discuss the top 20 causes of cancer death in the U.S. and the chronic stressors which cause them.

In his 1971 State of the Union address, President Richard M. Nixon announced the beginning of the “war on cancer” in the United States (see **President Nixon's 1971 State of the Union** at 15:03). Despite U.S. government expenditures of more than $100 billion on related research (**Kolata: Grant System Leads Cancer Researchers to Play It Safe, New York Times, 27Jun09**) and

testimonials that the war on cancer "did everything it was supposed to do" (NCI: National Cancer Act of 1971, accessed 2Nov17), cancer is still the #2 cause of death in the U.S. and is projected to be #1 by 2020 (Centers for Disease Control and Prevention: Heart Disease and Cancer Deaths - Trends and Projections in the United States 1969–2020, 2016), with high mortality from common cancers of the lung, colon, pancreas and breast (Cancer Facts and Figures 2017). This suggests an underlying flaw in our understanding of the disease.

The limits of reductionism

Traditional biology relies on the reductionist approach, which assumes that for all systems, including human physiology, the behavior of the whole is equal to the sum of the behavior of the parts. This means that sophisticated systems are merely combinations of simpler systems, which can themselves be reduced to simpler parts (Mazzocchi 2008), and disease is just due to flawed parts or systems. We reject reliance on reductionism, and believe that principles of complexity theory and self-organization create a more robust framework for understanding the origins and dynamics of cancer. We previously summarized the laws of complexity and self-organization as they relate to neoplasia, the process of abnormal tissue growth which includes cancer (Pernick 2017):

The Laws of Complexity and Self-Organization as a Framework for Understanding Neoplasia

1. In life, as in other complex systems, the whole is greater than the sum of the parts.
2. There is an inherent inability to predict the future of complex systems.
3. Life emerges from non-life when the diversity of a closed system of biomolecules exceeds a threshold of complexity.
4. Much of the order in organisms is due to generic network properties.
5. Numerous biologic pressures push cellular pathways towards disorder.
6. Organisms resist common pressures towards disorder through multiple layers of redundant controls, many related to cell division.
7. Neoplasia arises due to failure in these controls, with histologic and molecular characteristics related to the cell of origin, the nature of the biologic pressures and the individual's germ line configuration.

These seven "laws" shift the emphasis on understanding cancer from cataloging a list of molecular alterations towards focusing on biologic stressors (pressures) that transform essential physiologic networks into lethal pathways.

Complexity theory

A system is considered complex if the properties of the entire system are greater than the sum of the properties of each part of the system. This is due to emergence of novel properties which cannot be predicted, based on interactions between the parts. Life can be considered to be a complex adaptive system with biologic networks composed of numerous independent agents, such as genes and proteins. These agents interact with each other through many connections, and behave as a unified whole to learn from experience and adjust to changes in the environment (BusinessDictionary.com: Complex adaptive system, accessed 2Nov17).

Complex adaptive systems lack the fixed properties of planetary motion and their behavior cannot be solved with partial differentiation equations. They are best understood by analyzing patterns of behavior (Bak, How Nature Works 1999), which provides new insights into understanding pathophysiology and may ultimately lead to more effective treatment.

How life arose

To fully understand cancer, it is useful to consider how life arose, because the same principles may guide the pathophysiology of cancer. According to Kauffman, life is an emergent property of a modestly complex mix of biomolecules, confined to a small space to promote interactions, which ultimately crystallize in a phase transition and catalyze their own reproduction (Kauffman, The Origins of Order 1993, Chapter 7). In small groups, these biomolecules are relatively inert. However, as the number of biomolecules in the mix increases, there are more reactions and a greater probability that some biomolecules will catalyze the formation of other biomolecules (Kauffman, The Origins of Order 1993, page 309). Above some threshold of complexity, a network of biomolecules with catalytic closure is likely to arise (i.e. the formation of each biomolecule is catalyzed by other network members).

Kauffman and others have demonstrated that order is a common emergent property of molecular networks, based on structural network properties not dependent on details of the particular biomolecules (Kauffman 1993). These properties include the localization of cell networks to a small subset of their possible state space, and the stabilization of networks by genes with canalyzing Boolean functions (Pernick 2017). In addition natural selection produces redundant control systems which further constrain network behavior. Chronic cellular stress can overcome these controls but typically requires years or decades to do so. The impact of chronic stressors may be countered by evolution but only if they are relatively common, affect reproductive capacity and have persisted for at least 1 million years (Uyeda 2011).

Life as a complex adaptive system embraces the principle of universality, that the formation of necessary structures is not sensitive to particular details (Bak, How Nature Works 1999, Holland, Complexity: A Very Short Introduction 2014). Many alternative pathways are possible to produce these results but only one is necessary (Kauffman, The Origins of Order 1993, Chapter 8). Focusing too much on details ignores the overriding theme, that life has generic features even if details are not predictable (Kauffman, At Home in the Universe, page 18). As Bak notes, "The theory of life is likely to be a theory of a process, not a detailed account of utterly accidental details of that process (Bak, How Nature Works 1999, page 10). Similarly, the emergence of intermediate states and ultimately cancer is predictable but does not depend on particular details although those details may be important for individualized treatment.

Self-organized criticality

Cancer is an assault on the order typically maintained in cells. There are two overlapping theories that explain how disorder arises in biologic systems - self-organized criticality and the "edge of chaos". Self-organized criticality was first described by Danish physicist Per Bak in 1987 as the tendency of large systems with many components, living or non living, to evolve into a critical state or "tipping point" (Bak, How Nature Works 1999). The evolution to this delicate critical state arises spontaneously, without interference from an outside agent, due to dynamic interactions among individual elements of the system. Remarkably, without any manager

tuning the network elements, “a system that obeys simple, benign local rules can organize itself into a poised state…” (Bak, How Nature Works 1999, page 33). Although the precise mechanism of the self-organization is unknown, it is based on local interactions between many components in an open system (Krink and Thomsen 2001). At this critical state, minor disturbances cause events whose impact and frequency follow a power law distribution, with a high frequency of minor impact events and a small tail of major impact events. Rarely, an apparently trivial event triggers a large scale systemic response, leading to a major reconfiguration of the system (Bak, How Nature Works 1999).

Self-organized criticality is illustrated by dropping one grain of sand at a time on the center of a table to create a sand pile. Initially, the grains stay where they land. As the slope increases, a single grain is likely to cause other grains to topple. At this point, the system has been transformed from one in which individual grains cause predictable patterns to one where the dynamics are global, a self-organized critical state. Although a single grain of sand may cause an avalanche affecting the entire pile, we are incapable of predicting its impact, because it is contingent on extensive knowledge of minor details of the sand pile’s configuration (Bak, How Nature Works 1999, page 59). The emergence could not have been anticipated based on properties of the individual grains (Bak, How Nature Works 1999, page 51). This system cannot be understood by focusing on isolated parts, because the dynamics observed are due to the entire system as a whole. The sandpile itself is the functional unit, not the individual grains, so reductionism is illogical in this context. The configuration of the sandpile does not change gradually but by means of large avalanches (Bak, How Nature Works 1999, page 61). Thus, self-organized criticality may be nature’s mechanism of making large transformations over short time scales, an approach which is useful in understanding how cancer arises.

Hierarchies

Living systems arise based on hierarchies, in which combination of agents (genes, proteins, processes) at one level become agents themselves at the next level. Hierarchies include the transcription and translation of DNA to produce proteins, proteins interacting to form organelles, clustering of organelles to create cells, cells combining to form tissues, tissues forming organs, organs forming systems, systems working together to form individuals, and individuals interacting to form communities (Holland, Complexity: A Very Short Introduction 2014, page 32). In a similar way, a biologic network can be considered to have a specific purpose, such as phosphorylating a protein moiety. Multiple networks working together contribute to a more general biologic purpose, such as metabolizing a substance. Networks with these purposes then cooperate to create important cell functions, such as mitosis, apoptosis and morphogenesis, which can then work together, at a higher level, to form cells or create an organism.

Hierarchies explain how malignant change occurs through bursts of activity, not through gradualism. Tumors characterized by multistep progression (Vogelstein 1993) appear to arise through the formation of increasingly unstable hierarchies (hyperplasia, dysplasia) that may lead to malignancy. However, the process is not necessarily linear, and the formation of the hierarchies themselves may be discontinuous. For example, it appears that breast cancer does not typically progress continuously from hyperplasia to low grade DCIS to high grade DCIS to invasive carcinoma; instead, multiple parallel, genetically distinct pathways may be present (Tang 2006). Similarly, malignancy in the prostate does not progress continuously from low grade to high grade prostatic intraepithelial neoplasia to adenocarcinoma (Bostwick 2004, Braun 2011).

The origin of cancer begins with isolated network alterations, which may be mutations or simply changes in a network’s “rhythm” (i.e. how it associates with other networks). These changes are often in response to chronic stressors which find or create “weak spots” in a network to cause it to deviate from its usual physiologic state. These local network changes may interact to create, within the context of other chronic stressors, a hierarchy of new biologic properties, which may be identifiable by altered patterns of molecular expression. Kauffman describes how cells maintain a stable phenotype, called an attractor, through large numbers of mutually regulating genes (Kauffman, The Origins of Order 1993, page 467). Similarly, hierarchies may have their own version of stability due to “cancer attractors” (Huang 2009), and be identifiable as an intermediate state. Intermediate states may interact with each other and with chronic stressors to create new hierarchies of more chaotic networks with new patterns of molecular expression, and eventually lead to malignancy. The intermediate state is defined by patterns of molecular or network expression but there need not be an associated histologic change. This explains why some malignancies, such as well differentiated pancreatic adenocarcinoma, have molecular properties distinct from benign conditions, such as chronic pancreatitis, even though they are similar morphologically (Hruban 2007, Logsdon 2003).

The edge of chaos

Disorder can also be understood based on the concept of human biologic networks being at the edge of chaos, a self-organized critical state between order and chaos, which represents a state of biologic tension, analogous to a transition state in physics, although the details differ. Positioning networks in this manner: (a) provides flexibility to coordinate complex activities such as transcription, translation, mitosis and apoptosis, (b) helps coordinate global functions such as fertilization, embryogenesis and response to environmental and physiologic threats (Kauffman, At Home in the Universe, page 86) and (c) maximizes an organism’s evolutionary advantages, because rigid order would doom species that could not adapt to a changing and competitive environment (Kauffman and Johnsen 1991, Langton 1990).

Part of the tradeoff for maintaining a self-organized critical state is that catastrophic systemic failure is predictable. This failure has been described for man made and natural systems (Clearfield 2013, Rietkerk 2004, Scheffer 2001), as well as for human physiology and cancer (Hogenboom, BBC Earth 2016, Simpson 1998, Maley 2017). Thus, we believe that cancer is an inevitable feature of human biologic design, and will always be with us. We can prevent many cases of cancer by targeting chronic stressors and risk factors, we can diagnose it earlier and we can treat it more effectively but the mission of the American Cancer Society for a “world without cancer” will never be achieved.

Chronic cellular stress is the underlying cause of most cancers

This paper proclaims that chronic cellular stress is the underlying cause of most cancers. It disturbs the delicate balance that exists in biologic networks involving susceptible stem or progenitor cells and pushes them into dysregulated and unstable network trajectories associated with increased and relatively uncontrolled cell division. These new network states are based not only on gene changes but altered cellular processes, which may be difficult to reverse:

“Because the cell must be inherited, and because its processes cannot always be constructed de novo from genetic instructions (Cavalier-Smith 2004), genes often manipulate ongoing cellular behavior. DNA is the cell's information-storage device, but only some information is stored. The basic mechanisms of life must be inherited as ongoing processes. Thus, if life evolved as a coupled set of interconnected processes, then it has remained so ever since (Nicolis and Prigogine 1977, Kauffman, The Origin of Order 1993, Newman et al. 2006). Therefore, the perspective on evolution that focuses solely on shuffling genes propagating through time is limited because the cell propagates as a whole and its processes are the engines of life” (Johnson and Lam 2010, The Nobel Prize in Chemistry 1977 Award Presentation Speech, accessed 16Nov17).

These sources of chronic stress typically create a field effect, because they affect cells throughout an organ or organ system.

This paper deemphasizes the importance of oncogenes in understanding how cancer initially arises (The Nobel Prize in Physiology or Medicine 1989, Press Release, accessed 26Nov17), because alterations in their control or function are foreseeable downstream effects of the chronic cellular stress. In contrast to Emmanuel Farber (Farber 1984), we consider permanent DNA damage to typically be a late effect, not cancer’s initiating event.

We have identified nine chronic cellular stressors which act in combination to destabilize networks and cause cancer:

* Chronic inflammation (due to infection, infestation, autoimmune disorders, trauma, obesity, diabetes and other causes)
* Exposure to carcinogens
* Reproductive hormones
* Western diet (high fat, low fiber, low vegetable consumption)
* Aging
* Radiation
* Immune system dysfunction
* Germ line changes
* Random chronic stress / bad luck

If time limited, these stressors typically have little malignant potential, for several reasons. First, as complex adaptive systems, cells have inherent stability. Control of cell networks tends to be highly dispersed, so a single alteration is typically insufficient to produce marked network changes (Waldrop, Complexity: The Emerging Science at the Edge of Order and Chaos, page 145). Second, inactive genes in biologic networks can be considered to be “frozen” and resistant to minor perturbations (Kauffman, At Home in the Universe, pages 87-90, Pernick 2017). Third, to add biologic sophistication, evolution has added intricate control systems to existing genes and pathways, which are not easily disrupted (Molecular Biology of the Cell (4th Ed), How Genomes Evolve, accessed 3Nov17, Glassford 2015). However, when the stress continues for years or decades, pummeling weak spots in the network similar to ocean waves hitting the shore, there is an increased probability of disrupting networks in susceptible cells. A simple network change may provide a niche for other changes, which may further increase network instability, and under the proper circumstances, this may push the cell towards a malignant phenotype.

Due to the complex, nonlinear interactions which characterize living systems, one typically cannot predict which types of chronic stress will be associated with malignancy at all, what malignant patterns will arise, which cells will be affected and what molecular pathways or gene products will be altered.

This model of cancer as due to chronic cellular stress is an extension of current views about DNA damage and repair. Cells exposed to ionizing radiation, ultraviolet light or chemicals are prone to acquire multiple sites of bulky DNA lesions and double strand breaks. This induces activity in multiple genes, cell cycle arrest and inhibition of cell division, with the ultimate goal of macromolecular repair and bypass of lesions that stall transcription or apoptosis. Similar to HIV infection, this process may reflect a dynamic between destabilizing forces (the chronic cellular stress) and stabilizing (repair) forces (Nowak and McMichael 1995, Goulder 1997), and ultimately, the magnitude of DNA damage or its chronic nature may overtake the organism’s repair capacity (Friedberg 2003). Cofactors include germ line changes which limit the effectiveness of repair or make damage more likely, cell states that are particularly susceptible to these changes and deficiencies in the immune system. These processes also apply to malignancy.

This concept of chronic cellular stress triggering cancer has similarities to the paradigm of a pathogenic stimulus, followed by chronic inflammation and the ultimate development of a “cancer cell” (Brücher and Jamall 2014), as well as the concept of an etiologic field effect (Lochhead 2015).

Modeling cancer as due to chronic stressors may provide an alternative approach to classify and treat cancer. Conceptually, it may make sense to group malignancies together if they are due to the same stressor even if they have different morphologies, comparable to how tumors are considered similar if arising from the same cytogenetic translocation.

Focusing on the chronic stressors also alters our consideration of treatment, which should not only target the tumor’s morphologic and molecular patterns and microenvironment but also its chronic stressors or macro environment, to the extent possible. Even when treatment eradicates most or all existing disease, the continued presence of these chronic stressors makes it more likely that residual tumor cells will grow or a new tumor will arise. In addition acknowledging the role of complexity in cancer pathophysiology suggests that targeting some of its features may be helpful, as described below.

Exclusions from model

This model specifically excludes acute types of cancer - when tumor cells are close to their genetic events, such as childhood tumors due to known germ line changes (Childhood Cancer Genomics (PDQ®), accessed 25Nov17), which are not due to chronic stressors. In these cases, treating only the existing tumor is often curative. In contrast, adult tumors may also require minimizing the chronic stressors to prevent recurrence or relapse. This echoes the view of Savage, who argues that malignancies can be functionally divided into 2 groups: those that arise in cells with naturally heightened apoptotic potential due to their proximity to unique genetic events, which are generally chemotherapy curable, and those that arise in cells of standard apoptotic potential, that are not curable with classical cytotoxic drugs (Savage 2015, Savage 2016).

Of note, even apparently “straightforward” pediatric malignancies such as retinoblastoma do not follow a reductionist model; its development involves oxidative stress, additional mutations and appears to occur in a nonlinear manner (Kandalam 2010, Vandhana 2012).

The chronic stressors that cause cancer and their mechanism of action

We describe nine chronic stressors that cause cancer, recognizing that most malignancies are due to interactions of multiple stressors. Although the mechanisms of these stressors are distinctive enough to be described separately, some risk factors have features of multiple stressors (e.g. infections trigger chronic inflammation but also carry mutagenic proteins) and some stressors are related to each other (e.g. diet influences obesity, which triggers chronic inflammation).

Remarkably, chronic stressors which can cause cancer only do so in a small percentage of those exposed, and only at a limited number of sites. The explanation may be that the sources of order described above make networks resilient to many stresses, and that cancer requires not only chronic stress but the appropriate amount and type of stress, the correct context (organ / tissue / microenvironment), an inadequate immune response and a suitable germ line configuration to overcome a network’s inherent stability.

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Section 1.0 Chronic inflammation

In this section, we describe how chronic inflammation associated with microorganisms (bacterial and viruses), parasites, autoantigens, trauma and excess weight contributes to malignancy. The chronic inflammation affects existing cells by pressuring networks to veer towards malignant pathways and by creating a more supportive microenvironment for malignant change (Mbeunkui 2009). This process is not reductionist - it involves complex combinations of germ line variations of numerous genes and multiple alterations to interacting networks of susceptible cells. It is also affected by the existing microenvironment and immune response, which it also manipulates.

Prevention and treatment are described below, and include drugs to treat infectious organisms, behavioral changes to reduce excess weight and trauma, and anti-inflammatory agents; these measures are typically more useful for premalignant than aggressive invasive disease, which is treated in a traditional manner with surgery, chemoradiation therapy and immunotherapy. For autoimmune disorders other than celiac disease, watchful waiting is recommended, as treatment side effects are too severe.

Additional discussion of chronic inflammation related effects appears in sections 4.0 (proinflammatory diet) and 7.0 (immune system dysfunction).

Section 1.1 General

Chronic inflammation has long been considered a major cause of cancer. In 1863, Virchow noted that cancer occurs at sites of chronic inflammation, speculating that some irritants enhance cell proliferation via tissue injury and associated chronic inflammation (Balkwill 2001, Schottenfeld 2006). The current paradigm is that cancer is also accompanied by DNA damaging agents and occurs in the context of a permissive microenvironment that contains growth factors (cytokines, chemokines) and activated stroma (Coussens 2002).

Inflammation associated cancer, described at most body sites (Kanda 2017, Table 1), is considered the seventh hallmark of cancer (Colotta 2009), in addition to self-sufficiency in growth signals, insensitivity to inhibitory growth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis and tissue invasion and metastasis (Hanahan 2000).

Cancer may arise when the chronic inflammatory process persists over years. Tumors have been described as wounds that do not heal (Dvorak 1986, Drovak 2015). In typical wounds, tissue injury causes inflammation and cell proliferation which induce network changes resulting in less stable states. When the trauma ceases and the repair is complete, the inflammation also subsides and the microenvironment returns to its initial, more stable condition. However, when the inciting cause persists, the inflammation also persists with its pro-carcinogenic production of reactive oxygen and nitrogen species, growth factors, pro angiogenesis factors and attenuation of local cell mediated immunity (Kanda 2017, Figure 3, Rasch 2014). When mutated cells arise, this microenvironment nurtures them, helps them escape immune surveillance (Dalgleish 2006) and ultimately promotes invasion by subverting physiologic “invasion” of wounded epithelium through the extracellular matrix (Bleaken 2016, Coussens 2002).

Germ line variations in inflammatory mediators, such as macrophage migration inhibitory factor (Zhang 2015), interleukin 1A, interleukin 4, NFκB1 and protease activated receptor 1 may also promote inflammation associated cancer (Amador 2016).

Section 1.2 Infections

Infections are a major contributor to chronic inflammation related cancer. In 2012, 15.4% (2.2 million) of the 14 million new cancer cases worldwide were attributed to infections, including *Helicobacter pylori* (770,000 cases), human papillomavirus (640,000 cases), hepatitis B virus (420,000 cases), hepatitis C virus (170,000 cases) and Epstein-Barr virus (120,000 cases). In sub-Saharan Africa, Kaposi sarcoma was the second largest contributor to new cancer cases (Plummer 2016). The attributable fraction for cancers due to infection varies from less than 5% in the United States, Canada, Australia, New Zealand and some countries in western and northern Europe, to more than 50% in some countries in sub-Saharan Africa (Plummer 2016, Oh 2014, Schottenfeld 2015).

The International Agency for Research on Cancer (IARC), the specialized cancer agency of the World Health Organization (WHO), has classified numerous infectious agents as Group 1 carcinogens, meaning there is sufficient evidence of carcinogenicity in humans. They include bacteria: *Helicobacter pylori,* parasites: *Clonorchis sinensis, Opisthorchis viverrini, Schistosoma haematobium* and viruses: Epstein-Barr virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus type 1 (HIV1), human papillomavirus (HPV) (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59), human T cell lymphotropic virus type 1 (HTLV1) and Kaposi sarcoma herpesvirus (HHV8) (IARC Monograph on the Evaluation of Carcinogenic Risks to Humans 2017, Ohnishi 2013). Bacteria and parasites which promote carcinogenesis primarily through chronic inflammation are described in this section. Viruses other than Hepatitis C are described in sections 2.3 and 2.4 because they promote carcinogenesis primarily through oncogenic proteins.

Chronic infections promote the continuous release of inflammatory mediators, including the NFκB family of transcription factors. Epithelial cells also produce reactive oxygen species and nitric oxide in response to inflammation, which promote mutations (Nath

2010). Bacterial toxins also modify cellular processes that control DNA damage, proliferation, apoptosis and differentiation (Nath 2010, Table 2), and are discussed in section 2.2.

Section 1.3 Antigen driven lymphoproliferation - infections

We describe four chronic bacterial infections and one viral infection which typically cause MALT lymphoma or other low grade non Hodgkin lymphoma through a process called antigen driven lymphoproliferation. This mechanism appears to account for a high percentage of MALT lymphoma arising in the stomach (92% have *H. pylori* infection, Wotherspoon 1991) and ocular adnexae (up to 80% contain *C. psittaci* DNA, Ferreri 2004), and occasional cases in the skin, small intestine and other sites. However, these microorganisms are not a major cause of lymphoma, as only 8% of all non Hodgkin lymphoma is MALT subtype (The Non-Hodgkin's Lymphoma Classification Project 1997).

In general, chronic infection is not associated with malignancy. Antigen driven malignancy requires a specific type of infection, with a response by susceptible cells, within the correct tissue context. For example, *M. tuberculosis* infects 2 billion people worldwide (Centers for Disease Control and Prevention 2017), and if untreated, typically persists as a chronic infection but does not induce B cell proliferation or other malignancy. Bacterial or mycobacterial infections may induce proliferation of neutrophils, macrophages or inflammatory cells other than B cells but these inflammatory cells have a limited potential to attain clonality and malignancy.

Gastric MALT lymphoma due to chronic *Helicobacter pylori* infection

Gastric MALT lymphoma due to chronic *Helicobacter pylori* gastritis is the paradigm of antigenic driven lymphoproliferation, with these features: (a) the persistence of bacteria that cannot be killed by the immune system causes chronic immune stimulation, which ultimately directs cellular networks affecting B lymphocytes towards a less stable state, which over years may become clonal and overtly malignant, (b) the immune stimulation is directed at countering the bacteria, and is not a generalized proliferation, (c) these network changes are typically not permanent, (d) removal or antagonism of the bacterial stimuli by antibiotics may cause reversion towards the original non malignant state (Suarez 2006).

Gastric MALT lymphoma is rare, with an incidence of 0.2 to 3.8 per 100,000, and is declining due to reductions in the incidence of *H. pylori* infection (Luminari 2010, Khalil 2014). *H. pylori* induces chronic gastritis, which causes ongoing stimulation of antigen presenting T cells, leading to a reactive B cell infiltrate. In a small percentage of patients, it promotes B cell clonal expansion through a multistage process. Although the stomach is normally devoid of organized lymphoid tissue, marginal zone lymphocytes are attracted by the presence of *H. pylori*, mediated through chemokine BCA1 (CXCL13) and its chemokine receptor CXCR5 (Mazzucchelli 1999, Winter 2010). These lymphocytes are anatomically positioned in the spleen, lymph nodes and mucosa associated lymphoid tissue to constitute a first line of defense against invading pathogens, with a low activation threshold (Suarez 2006). The immune system cannot destroy *H. pylori* (Bende 2009), leading to chronic lymphoid proliferation, which makes these inherently unstable lymphocytes more prone to additional network alterations, and increases the risk of transformation of clones that are dependent on antigenic stimulation (Suarez 2006). MALT lymphoma is considered to arise at a relatively late stage in lymphocyte development, when the lymphocyte is responding to antigenic stimulation by modifying diversity within its antigen receptors (Malcolm 2016). These changes are mediated by high levels of cytokines and chemokines produced by infiltrating macrophages induced by *H. pylor*i and *H. pylori* specific T cells (Russo 2016, Munari 2011, Kuo 2010).

Both B and T lymphocytes have distinctive traits: (a) they repeatedly rearrange their DNA to produce a unique and functional antigen receptor, (b) via this receptor or its precursor, they can undergo massive clonal expansion, and (c) they can be extremely long lived as memory cells. These traits are fundamental to their role in the adaptive immune response to infectious agents, but also make these cells unstable and vulnerable to transformation (Malcolm 2016).

Antibiotics directed against *Helicobacter pylori* (“eradication therapy”) lead to long term regression in 75-80% of low grade gastric MALT lymphoma (Nakamura 2012), apparently due to elimination of the bacterial driven lymphoproliferative signals. Surprisingly, antibiotics also cause regression of some low stage *H. pylori* negative cases of MALT lymphoma (Raderer 2006, Park 2010, Asano 2012, Asano 2015), which is attributed to: (a) their association with antibiotic sensitive *Helicobacter heilmannii* (Morgner 2000, Joo 2007), (b) false negative *H. pylori* testing (Gisbert 2006) or (c) the antiproliferative effect of macrolide antibiotics which are part of the eradication therapy, such as clarithromycin (Ohe 2013, Van Nuffel 2015). Eradication therapy may also be useful for other *H. pylori* associated lymphoma. For example, some patients with *H. pylori* positive gastric diffuse large B cell lymphoma, either with or without histological evidence of MALT lymphoma, have achieved long term complete remission after first line *H. pylori* eradication therapy (Kuo 2013, Kuo 2012, Paydas 2015).

Helicobacter pylori infection may also cause gastric MALT lymphoma by translocating its cytotoxin associated gene A (CagA) protein into B cells, which stimulates their proliferation (Wang 2013, Krisch 2016) and promotes a more potent inflammatory response (Zucca 2014). In addition germ line variations of the TNF alpha T 857 allele (Hellmig 2005) and Interleukin 22 (Liao 2014) are associated with an increased risk of gastric MALT lymphoma.

Immunoproliferative small intestinal disease due to chronic Campylobacter infection

In the small intestine, persistent infection by *Campylobacter jejuni* (Lecuit 2004) or less commonly *Campylobacter coli* (Criscuolo 2014) or *H. pylori* (Dutta 2010) cause immunoproliferative small intestinal disease (IPSID), an antigen driven lymphoproliferative disorder with features similar to *H. pylori* associated gastric MALT lymphoma. IPSID, also known as alpha chain disease, was first described in 1968 (Seligmann 1968). It is most prevalent in the Middle East and Africa, particularly in developing countries where *C. jejuni* infection is hyperendemic due to environmental and food contamination (Coker 2002).

The WHO considers IPSID a variant of MALT lymphoma that arises in small intestinal mucosa associated lymphoid tissue due to infiltration by plasma cells which secrete a monotypic truncated immunoglobulin alpha heavy chain lacking both the light chain region and the first constant domain (Al-Saleem 2005). The corresponding mRNA lacks the variable heavy chain and the constant heavy chain 1 sequences and contains deletions as well as insertions of unknown origin. Cytogenetic studies demonstrate clonal

rearrangements involving predominantly the heavy and light chain genes, including a t(9;14) translocation involving the *PAX5* gene (Al-Saleem 2005).

Chronic *C. jejuni* infection can elicit a strong IgA mucosal response, which leads to sustained stimulation of the mucosal immune system. This may eventually cause expansion of IgA secreting clones, and selection of a clone which secretes alpha heavy chains and eludes antibody antigen Fc dependent down regulation (Lecuit 2004), due to the absence of variable region determinants.

As with gastric MALT lymphoma, IPSID is often eradicated by antibiotics, which appear to stop the proliferative signals to lymphocytes. Early stage disease is treated by tetracycline, possibly with the addition of metronidazole (Pervez 2011), with 30-70% complete remissions. In cases refractory to antibiotics, or in advanced disease such as diffuse large B cell lymphoma, CHOP chemotherapy is indicated (Economidou 2006).

C. jejuni also secretes CDT (cytolethal distending toxin), the first bacterial genotoxin described, which hijacks the control system of eukaryotic cells (Ohara 2004) to induce cytoplasm distention and cell cycle arrest, which may ultimately promote malignant change (Lara-Tejero 2000).

Ocular adnexal MALT lymphoma due to chronic *Chlamydia psittaci* infection
In the ocular adnexa, chronic *Chlamydia psittaci* infection is variably associated with MALT lymphoma. Ocular adnexal lymphoma (OAML) accounts for 1 to 2% of non Hodgkin lymphoma cases, and 80% are MALT subtype. They show a mature B cell phenotype, derived from post germinal center B cells. *C. psittaci is* an obligate intracellular bacterium responsible for psittacosis (ornithosis) in birds; humans are infected by inhaling aerosolized bacteria when exposed to infected birds, contaminated feathers, fecal material or carcasses. *C. psittaci* infection is typically asymptomatic with repeated infection cycles in humans, but mainly involves the respiratory tract (Perrone 2016).

Chlamydia psittaci infections have more geographic variability than *Helicobacter pylori* and *Campylobacter* infections. An international study detected *C. psittac*i DNA in biopsies of 89% of newly diagnosed stage I OAML patients from Chile, Italy, Spain and Switzerland (results were not reported separately by country, Ferreri 2012) but another international study showed lower rates in Germany (47%), the U.S. east coast (35%), The Netherlands (29%), Italy (13%), U.K. (12%), and Southern China (11%) (Chanudet 2006). Studies focusing on single countries showed prevalence rates varying from 80% in Italy (Ferreri 2004), Korea 79% (Yoo 2007), Austria 54% (Aigelsreiter 2008) to 0% in Kenya (Carugi 2010), Florida (Rosado 2006) and China (Cai 2012). These variable rates may be due to differing prevalences of *Chlamydia psittaci* as well as EBV coinfection, differences in genetics or other host factors (Mosleh 2011a, Moslehi 2011b, Perrone 2016).

Chronic antigenic stimulation by *Chlamydia psittaci* may lead to clonal expansion and proliferation of post germinal center memory B cells (Coupland 1999). This process, initially dependent on ongoing antigenic stimulation, may eventually progress to genetic instabilities with successive chromosomal abnormalities, causing transformation of a clone of normal lymphoid cells to MALT lymphoma (Stefanovic 2009, Suarez 2006).

Antibiotic treatment, primarily doxycycline, is often effective, with response rates of 45% (Kiesewetter 2013) to 65% (Ferreri 2012). Due to the geographic variability of the association, blanket antibiotic therapy is advised only when there is proof of *Chlamydia psittaci* involvement (Cohen 2009). As with gastric MALT lymphoma, some OAML cases not associated with *Chlamydia psittaci* nevertheless respond to doxycycline (Ferreri 2006).

Primary cutaneous lymphoma due to chronic *Borrelia burgdorferi* infection
Primary cutaneous lymphoma is associated with *Borrelia burgdorferi* infection but the association is much weaker than with the prior three infectious agents. It is strong in areas endemic for Lyme disease, including the Scottish Highlands (Goodlad 2000), Austria (Cerroni 1997) and Yugoslavia (Jelić 1999). However, no association was found in Asia (Li 2003), Central Italy (Goteri 2007) and Northern Italy (Ponzoni 2011). Reports from the U.S. show varied results (association present: de la Fouchardiere 2003, association not present: Takino 2008, Wood 2001).

B. burgdorferi infection may cause chronic inflammation of the skin with a dense lymphocytic infiltration followed by atrophy. However, some patients have no clinical findings (Garbe 1991). *B. burgdorferi* is thought to provoke chronic antigen stimulation, similar to *H. pylori*, *C. jenuni* and *C. psittaci*, leading to primary cutaneous lymphoma.

Antibiotics are effective in many but not all cases in treating the lymphoma, apparently by reducing the stimulus for the chronic antigenic stimulation (Roggero 2000, Monari 2007). Disappearance of the microorganism, accompanied by the unequivocal decrease of most indicators of active T and B cell immune response, strongly supports a pathogenetic role for *B. burgdorferi* in sustaining an antigen driven process (Kütting 1997) even if no clinical or molecular evidence of *B. burgdorferi* is present (Kempf 2014).

Hepatic lymphoma due to Hepatitis C
Hepatitis C virus (HCV) infects 180 million people, or 3% of the global population (Forghieri 2012). Chronic HCV infection is associated with B cell lymphoma (Khoury 2014), including splenic marginal zone lymphoma (De Re 2012) and diffuse large B cell lymphoma (Bronowick 2003, Kikuma 2012). This association appears strongest in highly endemic areas such as Italy, Japan and the southern U.S. (Arcaini 2012, Khoury 2014). The etiologic fraction of non Hodgkin lymphoma attributable to HCV varies by country, and may approach 10% in Italy and other areas where HCV prevalence is high, compared with <1% in low prevalence areas (Dal Maso 2006), where the lack of an association may be due to small sample sizes of HCV positive subjects (Datta 2012).

Although no clear mechanism has consistently been demonstrated, chronic antigen stimulation of B cells by HCV appears to be important based on: (a) immunoglobulin variable region genes of non Hodgkin lymphoma B cells from HCV positive patients exhibit somatic mutations indicative of an antigen selection process, (b) the histology of these cells is often typical of germinal center (GC) and post germinal center B cells (Quinn 2001), (c) HCV infection is not associated with lymphoma subtypes that do not originate

from germinal center or post germinal center B cells, such as mantle cell, Burkitt and T cell lymphoma (de Sanjose 2008) and (d) chronic HCV infection is strongly associated with mixed cryoglobulinemia type II and vigorous polyclonal B lymphocyte activation due to persistent immune stimulation (Oliveira 2014, Agnello 1992), with massive clonal expansion of marginal zone B cells that recognize the HCV E2 protein of HCV (Visentini 2013). Analogous to *Helicobacter pylori* related lymphomagenesis, it is conceivable that progressive independence from the antigen driven mechanism will develop, possibly due to chromosomal translocations or other genetic aberrations (Zignego 2012). However one study found that lymphoma in HCV infected patients appears not to arise from B cells aimed at eliminating the virus (Ng 2014).

Antiviral therapy is associated with an overall response rate up to 77% in indolent B cell lymphoma associated with HCV infection (Arcaini 2014). Prospective studies demonstrate that antiviral therapy is associated with improved survival and support the current recommendation of antiviral therapy as a first line option in asymptomatic patients with HCV associated indolent non Hodgkin lymphoma (Michot 2015, Merli 2016).

Section 1.4 Antigen driven lymphoproliferation - autoantigens

Antigen driven lymphoproliferation due to autoantigens

Antigen driven lymphoproliferation may also occur due to autoantigens, with a pathophysiology similar to cases due to microorganisms. Since B and T cell activation are important in the pathogenesis of autoimmunity, it is not surprising that longstanding chronic inflammation is a risk factor for lymphoma in patients with autoimmune disease (Baecklund 2014). Similar to the lymphomas described above, the B or T cell proliferations appear to be directed against the autoantigens; i.e. the lymphoma is not due to a generic stimulation of B or T cells. Various cofactors are important in these entities, some related to the primary autoimmune disorder itself, including germ line changes related to NFκB and other inflammatory mediators.

In contrast to antigen driven lymphoproliferation due to infections, treatment is directed at the lymphoma itself with various combinations of surgery or chemoradiation therapy. It typically is not directed at suppressing autoantigens, with the exception of celiac disease, because the side effects of therapy outweigh the possible benefits of preventing a primary or relapsing indolent lymphoma.

MALT lymphoma of thyroid gland due to autoimmune (Hashimoto) thyroiditis

Autoimmune (Hashimoto) thyroiditis, the most common cause of hypothyroidism in iodine sufficient regions (UpToDate: Pathogenesis of Hashimoto thyroiditis, accessed 24Nov17), is a major risk factor for primary thyroid lymphoma, including MALT lymphoma, with a relative risk of 67 to 80 times those with an uninvolved thyroid (Holm 1985, Hyjek 1988). Hashimoto thyroiditis is a T cell mediated disease characterized by lymphocytic infiltration that leads to thyroid cell loss and hypothyroidism. It has an incidence of 0.3 to 1.5 cases per 1,000 population per year, and is 15 to 20 times more frequent in women than men. It typically occurs between ages 30 to 50, but may be seen in any age group, including children (Endotext [Internet]. Hashimoto's Thyroiditis, accessed 4Nov17). Many patients need no treatment because the disease is asymptomatic and the resulting goiter is small. If the goiter causes local pressure symptoms or is unsightly, thyroid hormone is given (Endotext [Internet]. Hashimoto's Thyroiditis, accessed 4Nov17).

Primary thyroid lymphoma is rare, accounting for 1-5% of thyroid malignancies (Chai 2015). Hashimoto thyroiditis may have clonal bands with a polyclonal smear pattern (Saxena 2004), but is not considered malignant. However, the sequence similarity between the clonal bands in Hashimoto thyroiditis and subsequent thyroid lymphoma suggests that it is a precursor lesion (Moshynska 2008). This progression is not well understood, but involves the NFκB pathway (Troppan 2015), an important regulator of numerous inflammatory genes, with both pro and anti inflammatory roles (Lawrence 2009).

In the thyroid gland, MALT lymphoma is considered low grade with an excellent prognosis after treatment with various combinations of surgery or chemoradiation therapy (Chai 2015, Cha 2013, Oh 2012). As a result, no treatment for Hashimoto thyroiditis is provided prior to or even after the diagnosis of MALT, to reduce the risk of primary or recurrent disease.

MALT lymphoma of salivary gland due to lymphoepithelial sialadenitis of Sjögren syndrome

Patients with lymphoepithelial sialadenitis of Sjögren syndrome have a 44 times increased risk of developing lymphoma, 80% of which are marginal zone / MALT type, typically of salivary gland origin (Harris 1999). Sjögren syndrome is a chronic, systemic autoimmune disorder of unknown etiology with an incidence of 3.9 to 5.3 per 100,000 per year. It is nine times more common in women than men, with a peak onset during menopause (Mavragan 2014). It is characterized by marked B cell hyperactivity, hypergammaglobulinemia and serum autoantibodies, including antinuclear antibodies, rheumatoid factor, cryoprecipitable immunoglobulins and antibodies against ribonucleoprotein complexes Ro/SSA and La/SSB.

Sjögren syndrome is characterized histologically by a benign lymphoid infiltrate with lymphocytic epitheliotropism in salivary glands. Lymphoepithelial sialadenitis (LESA) is common, and exhibits markedly hyperplastic lymphoid tissue with loss of most acinar structures. Altered ducts are infiltrated by lymphoid cells, and monocytoid B cells may be prominent within the ducts themselves, even in the absence of lymphoma (Jaffe 2002). In up to 50% of cases of benign LESA, some foci of intraepithelial B cell infiltration are clonal, as demonstrated by PCR for Ig heavy chain gene rearrangement. Despite clonality, the infiltrates usually have a benign clinical course, analogous to lymphocytic gastritis associated with *Helicobacter pylori*, which can show monoclonality by PCR without overt lymphoma. Thus, clonality is insufficient to diagnose MALT lymphoma in the salivary gland in the absence of other evidence of malignancy (Jaffe 2002).

MALT lymphoma in the salivary glands typically arises due to autoimmunity associated inflammation, which causes a proliferation of B cells directed against the autoantigen, as with LESA. This occasionally leads to clonal overgrowth, and, after acquiring secondary genetic changes, to MALT lymphoma (Jaffe 2002). In contrast to gastric MALT, salivary gland cases usually have no translocations involving the MALT1 gene (Mulligan 2011, Ye 2003).

Germ line changes, such as TNFAIP3 polymorphisms in patients with primary Sjögren syndrome, are associated with an increased risk for MALT and other lymphoma. TNFAIP3 encodes the A20 protein that plays a key role in controlling NFκB activation (Nocturne 2013). Germ line abnormalities of TNFAIP3 lead to decreased control of the NFκB pathway, promoting survival of B cells and oncogenic mutations (Nocturne 2015).

LESA is routinely treated symptomatically and with surgery if nothing else works. Unlike gastric MALT lymphoma, therapy is not directed towards reducing the risk of lymphoma, because it is usually low grade and indolent (median overall survival is18.3 years, Jackson 2015), and the risk of therapy likely outweighs any possible benefit. The lymphoma is effectively treated with surgery, radiotherapy or rituximab based regimens (Matutes 2017).

Enteropathy associated T cell lymphoma due to celiac sprue
Enteropathy associated T cell lymphoma (EATL) is a rare lymphoma subtype strongly associated with celiac disease, an autoimmune disease triggered by gluten ingestion. Its incidence has increased significantly in the U.S., which may reflect an increasing seroprevalence of celiac disease or better recognition of rare T cell lymphoma subtypes. The incidence may continue to rise given the large number of undiagnosed individuals (Sharaiha 2012). EATL is aggressive, with a 5 year survival of 8-60% (Nijeboer 2015, Delabie 2011). EATL type II, now known as monomorphic epitheliotropic intestinal T cell lymphoma (Swerdlow 2016) is rarer, and has no known association with celiac disease (Sharaiha 2012).

Celiac disease has a 1% prevalence in Western populations and may have no clinical symptoms (Brito 2014). It is usually diagnosed by demonstrating gluten enteropathy in a small bowel biopsy or anti tissue transglutaminase antibodies in serum (Webb 2015).

EATL occurs in 14% of celiac disease patients. Patients have HLA-DQ2 and DQ8 haplotypes (Bao 2012) and increased immunological responsiveness to prolamins such as dietary wheat gliadin and similar proteins in barley, rye and possibly oats. In these patients, gliadin becomes cross linked to transglutaminase to create a neoantigen, which leads to an immune response and accumulation of intraepithelial cytotoxic T cells and helper T cells in the small bowel lamina propria. Chronic exposure promotes antigen driven lymphoproliferation affecting T cells, and an increased risk of EATL (Kooy-Winkelaar 2017, Kim 2015). A dysregulated microbiome may drive aberrant type 1 IFN or IL15 expression and contribute to celiac disease but the evidence is not yet definitive (Kim 2015).

Treatment of celiac disease is adherence to a strict gluten free diet for life, which is usually effective (Holmes 1989) although rare cases are refractory (Woodward 2016). EATL is an aggressive lymphoma, with a 5 year survival of 8 to 60% (Nijeboer 2015, Delabie 2011). There is no standardized treatment, and optimal therapy is unknown. Typically, local debulking is the first step, followed by anthracycline based chemotherapy, possibly followed by high dose chemotherapy and autologous stem cell transplantation (Nijeboer 2015).

Lymphoma due to rheumatoid arthritis
Rheumatoid arthritis is associated with diffuse large B cell lymphoma, as well as other subtypes of leukemia / lymphoma (Parodi 2015, Hellgren 2017, Hashimoto 2015) but the association is strongest for those with severe disease (Baecklund 2006). The risk does not appear to be familial (Ekström 2003). The driving force is apparently immunostimulation not immunosuppression (Baecklund 2006, Gridley 1994). Treatment with methotrexate is associated with lymphoma in some (Kamel 1983, Mariette 2002), but not all studies (Hellgren 2017). The lymphoma itself may be effectively treated with methotrexate withdrawal or steroid pulse therapy; however some lymphomas require aggressive chemotherapy (Ikeda 2016, Tokuhira 2017).

Hepatic lymphoma due to autoimmune disease
Although primary hepatic lymphoma is rare (0.016% of non Hodgkin lymphoma), persistent inflammatory processes associated with Hepatitis B or C infection or autoimmune disease (primary biliary cholangitis, Sjögren syndrome and autoimmune hepatitis) may play independent roles in the lymphomagenesis of hepatic B cells (Kikuma 2012). Other risk factors are chemical exposure, cirrhosis (Ugurluer 2016) and gastric *Helicobacter pylori* infection (Nagata 2015, Iida 2007). Occasionally, no risk factor is found (Shiozawa 2015). The most common subtype is diffuse large B cell lymphoma.

Chronic antigenic stimulation due to primary biliary cholangitis or other disorders may induce the accumulation of reactive lymphoid hyperplasia (Okada 2009, Ishida 2010, Higashi 2015), leading to various subtypes of lymphoma (MALT: Prabhu 1998, diffuse large B cell: Kanellopoulou 2011, lymphoplasmacytic: Koumati 2011).

Treatment is typically CHOP-like (cyclophosphamide, doxorubicin, vincristine and prednisone) or radiotherapy (Ugurluer 2016), and is not directed at the antigen driven lymphoproliferation.

Section 1.5 Bacterial driven carcinoma

Carcinoma due to chronic bacterial infection
Chronic bacterial infections promote cancer of epithelial cells through changes associated with chronic inflammation as well as via bacterial mutagenic toxic proteins (Cummins 2013, Table 1). This process has similarities to antigen driven lymphoproliferation in that the bacteria and associated inflammation induce chronic stress, which leads to unstable states in the stem / progenitor cells of the epithelium. Elimination of the bacteria reduces this stress. However, unlike lymphocytes which undergo apoptosis when no longer triggered by antigen, the stem / progenitor cells persist and may accumulate additional mutations due to their increasing instability.

Gallbladder cancer due to chronic *Salmonella typhi* infection
Gallbladder carcinoma, projected to cause 3,830 deaths in the U.S. in 2017, is associated with chronic carriage of *Salmonella typhi,* the cause of typhoid fever, with an increased risk compared with non carriers of 4.3 to 14 (Nagaraja 2014, Gonzalez-Escobedo 2013). The association is strongest among women in Southeast Asia and South America, including Delhi, India (21.5 per 100,000

women), Karachi, Pakistan (13.8) and Quito, Ecuador (12.9), compared with low rates (<3) in Northern Europe and North America (Randi 2006, Nath 2010). In contrast, no association between *S. typhi* and biliary cancer was found in Shanghai, China, attributed to the very low prevalence of chronic *S. typhi* carriers in this population (Safaeian 2011). PCR may be the most sensitive diagnostic tool for *S. typhi* infection (Tewari 2010), because the bacterial culture isolation rate is very poor in the gallbladder (Nath 2010).

Bile is typically sterile (Ikeda 1990, Suna 2014) but in typhoid fever, 3-5% of patients become chronic carriers of *S. typhi*. The bacteria typically persist in the liver and are excreted intermittently into the gallbladder (Nath 2010). *S. typhi* bacteria may survive in the gallbladder niche by forming biofilms on cholesterol gallstones. Chronic infections can persist for decades and although highly contagious through fecal spread, patients are typically asymptomatic (Gonzalez-Escobedo 2013). Recommended follow up consists of careful monitoring with ultrasound or cholecystectomy.

S. typhi appears to mediate gallbladder carcinogenesis through both chronic inflammation and direct bacterial genotoxins. Persistent bacterial infections cause chronic inflammation with production of cyclooxygenase 2, which can cause molecular disturbances in the cell cycle of gallbladder mucosa. The bacteria also metabolize primary bile acids to produce potentially carcinogenic toxins and metabolites, including bacterial β glucuronidase, a glycosidase which produces cytolethal distending toxin, described previously under IPSID, as well as mutagenic intermediates and other primary and secondary bile acid metabolites (Nath 2010).

Other bacterial species associated with gallbladder cancer include *Helicobacter bilis* and *Helicobacter hepaticus*, *Escherichia coli* (Nath 2010) and non typhoidal Salmonella species (Iyer 2016), some of which produce their own toxins (Nath 2010). Other risk factors associated with chronic inflammation in the gallbladder include chronic cholelithiasis, chronic infection and obesity (Nath 2010).

Gallbladder carcinoma has been linked with genetic disorders including multiple familial polyposis / Gardener syndrome, Peutz-Jegher syndrome, porcelain gallbladder and anomalous pancreaticobiliary ductal union (Nath 2010).

Gallbladder cancer has a five year survival rate of less than 5%. Prevention is based on treating typhoid fever, as well as diagnosis and management of non typhoidal Salmonella species to reduce the chronic carrier state (Gonzalez-Escobedo 2013).

Colorectal carcinoma due to chronic *Escherichia coli* infection
A diet high in saturated fats (Reddy 2002) and low in fiber, coupled with obesity, a sedentary lifestyle and germ line susceptibility, may lead to a change in the gut microbial community to promote carcinogenesis (Cho 2016, Mehta 2014). Dietary fiber undergoes bacterial fermentation in the colon to yield butyrate, a short chain fatty acid and histone deacetylase inhibitor that may protect against colorectal tumorigenesis (Bultman 2016, O'Keefe 2016).

The gut microbiota exist in a balanced community which maintains homeostasis through symbiotic interactions with intestinal epithelium (Sheflin 2014) but alterations to the microbiome (dysbiosis) caused by diet and infection can promote colorectal carcinoma (Gagnière 2016, Sun 2016). Specifically, subclinical colorectal mucosal colonization with *Escherichia coli* and other Proteobacteria is associated with and may be a risk factor for colorectal carcinoma (Swidsinski 1998, Yang 2014, Jobin 2013). Alteration in bacteria flora may contribute to an expanded community of “alpha bugs” which harbor virulence traits that drive colon cancer development (Elinav 2013, Grivennikov 2013, Schwabe 2013, Coleman 2016). The alpha bug hypothesis proposes that some microbiome members can remodel the colonic bacterial community to enhance induction of alpha bugs, which coopts other members of the microbial community (Sears 2011) and may “crowd out” cancer protective microbial species (Yang 2014). The alpha bugs include *E. coli* harboring the polyketide synthase (pks) island (Arthur 2012, Bonnet 2014, Cougnoux 2014, Raisch 2014), enterotoxigenic *Bacteroides fragilis* (Wu 2009) and *Fusobacterium nucleatum* (Kostic 2014, Rubinstein 2013).

The proposed pathophysiology is: (a) persistent asymptomatic bacterial infection of the colon leads to bacterial penetration of the inner mucus layer, which may induce chronic inflammation and generate a pro carcinogenic microenvironment (Dejea 2013), (b) inflamed epithelial cells under the stress of bacterial toxin exposure or chronic bacterial infection generate reactive oxygen species and nitric oxide, which induces mutations (Dejea 2013), (c) microbial activation of innate immune pathways can also promote cancer development (Schwabe 2013).

The change in microbiome, associated chronic inflammation and exposure to bacterial toxins induce local network changes that slowly produce changes identified morphologically as steps in the dysplasia to carcinoma pathway (Sears 2014). Initially, bacteria may induce increased permeability of tight junctions (Soler 1999, Grivennikov 2012), allowing delivery of bacterial toxins directly to the epithelium (Sears 2014), which may ultimately lead to a new hierarchy of adenomatous epithelium. Dysplastic mucosa is usually goblet cell depleted, lacks overlying mucus and has sparse underlying glycocalyx, which facilitates bacterial contact with the mucosal surface to induce additional network and molecular alterations, leading to malignancy (Prorok-Hamon 2014).

Human host polymorphisms modulating the inflammatory response may affect microbiota influence on colorectal carcinoma pathogenesis (Dejea 2013). In addition polymorphisms within DNA repair process genes can decrease their efficiency and promote increased susceptibility to resident *E. coli* producing genotoxins (Buc 2013).

Treatment of colorectal carcinoma is based on stage (American Cancer Society, accessed 20Nov17), and includes surgery, chemoradiation therapy, immunotherapy and targeted therapy. A diet high in vegetables, fruit and whole grains is recommended to minimize recurrence and maintain optimal health although this diet may not have any specific antitumor properties (Mehra 2017).

Gastric carcinoma due to chronic *Helicobacter pylori* infection
Chronic gastric infection by *Helicobacter pylori* is a major cause of gastric carcinoma, the world’s fourth largest cause of cancer death (after lung, liver and colorectal cancer, World Health Organization 2017 accessed ???). *Helicobacter pylori,* discovered by Marshall and Warren (Marshall 1984), is classified by the IARC as a group 1 (definite) carcinogen in relation to gastric carcinoma (IARC 1994). A 2001 prospective study demonstrated that only patients with *H. pylori* infection develop gastric carcinoma (Uemura 2001).

H. pylori has a prominent chronic inflammatory component that is considered necessary but insufficient to cause gastric carcinogenesis. *H. pylori* gains access to the gastric mucosa and triggers the production of cytokines that recruit acute inflammatory cells, probably involved in tissue damage. Infection triggers a cascade of proinflammatory signals, including activation of NFκB and AP1 and release of IL8 and tumor necrosis factor α (Hoffmann 2015). Chronic inflammation also promotes a tumor microenvironment favoring angiogenesis and recruitment of inflammatory mediators and inflammatory cells which generate reactive oxygen and nitrogen species. This leads to inflammatory related histologic changes (gastric atrophy, intestinal metaplasia, dysplasia) that may lead to cancer (Zabaleta 2012, Castaño-Rodríguez 2014).

In addition *H. pylori* has a direct oncogenic effect on gastric epithelium; it induces mutations in mitochondrial DNA and the nuclear genome (Machado 2010) including mismatch repair (Fishel 1995) and deficient MutYH DNA glycosylase activity (Raetz 2012, Kidane 2014).

Cofactors that increase the risk of gastric carcinoma include *cag* PAI strains of *H. pylori* (Hanada 2014) which disrupt cell polarity (Osman 2013, Zhang 2016) and a proinflammatory diet (Shivapp 2016). In addition 10-15% of diffuse histology cases are hereditary (Zanghieri 1990), often due to mutations in *CDH1* (E cadherin) (Hansford 2015, van der Post 2015) or other genes (Huang 2015, Gaston 2014).

The American College of Gastroenterology and others recommend *H. pylori* eradication confirmed by the carbon 13 labeled urea breath test for patients with endoscopic resection of early gastric cancer, as well as gastric MALT lymphoma (Chey 2007, Howden 2014). Eradication therapy reduces recurrence in early gastric cancer treated with endoscopic resection in some (Fukase 2008), but not all studies (Kim 2016a, Kim 2016b, Tahara 2016). In addition eradication therapy is recommended for atrophic gastritis, metaplasia or dysplasia although it may be only partly effective at reversing these high risk conditions (Rokkas 2007, Ohba 2016).

Other chronic bacterial infections
Other chronic bacterial infections are associated with cancer, but are not risk factors. As noted, to overcome the sources of order within cells requires not only chronic stress, but a microenvironment sensitive to this stress. *Streptococcus gallolyticus subsp gallolyticus* endocarditis is not common, but is so strongly linked to colorectal cancer (McCoy 1951, Klein 1997, Boleij 2013, Paritsky 2015, Cummins 2013) that its presence may warrant colonoscopic examination. This association may be due to disruption of tight junction permeability (Boleij 2011). *Bartonella henselae,* a facultative intracellular pathogen, causes bacillary angiomatosis and bacillary peliosis, two vasculoproliferative but non neoplastic disorders. The bacteria may induce production of vascular endothelial growth factor, an angiogenic factor leading to endothelial cell proliferation (Kempf 2001).

Section 1.6 Parasite driven carcinoma

Gallbladder carcinoma due to infestation by liver flukes
Three trematode parasites, *Opisthorchis viverrini, Clonorchis sinensis* and *Schistosoma haematobium* are classified as Group 1 biological carcinogens (IARC 1994, IARC Monograph on the Evaluation of Carcinogenic Risks to Humans 2017). However, infestation with their phylogenetic relatives, also major human pathogens, is not carcinogenic (Brindley 2015), perhaps because the correct chronic combination of chronic stressors in the proper microenvironment are needed to push physiologic networks onto malignant pathways.

Cholangiocarcinoma due to liver flukes
Liver fluke infestation is strongly associated with cholangiocarcinoma, the most common biliary tract malignancy, which has a relatively poor prognosis (Yusoff 2012, Buettner 2017). Incident rates are markedly elevated in Thailand (84.6 per 100,000) compared with Korea (7.4 per 100,000), Japan (2.8), Singapore (1.0) and Western countries (0.2 to 0.7) (Lim 2011). The tradition of eating ground, raw freshwater and salt fermented fish on a daily basis, particularly in Thailand, results in repeated exposure to liver flukes and nitrosamine contaminated food beginning in childhood (Pairojku 1991), and more commonly in men (Haswell-Elkins 1994).

Opisthorchis viverrini and *Clonorchis sinensis* live in bile ducts and damage bile duct epithelia via several mechanisms. First, the feeding parasites cause mechanical damage. Second, their presence leads to chronic inflammation, including recurrent suppurative cholangitis and bile duct stones (Lim 2011), with release of cytokines and generation of reactive oxygen intermediates and nitric oxide (Ohshima 1994). Third, fluke secreted proteins directly induce proliferation of biliary progenitor ("oval") cells and inhibit DNA repair and apoptosis (Lee 1997).

Nitrosamines may be necessary for the development of cholangiocarcinoma (Pairojku 1991). Syrian golden hamsters developed cholangiocarcinoma only with dimethylnitrosamine plus fluke infestation; either alone was insufficient (Lee 1993). Other established risk factors include alcohol (Miwa 2014) and biliary tract stone disease (Cai 2011, Chang 2013). Germ line polymorphisms appear to be important, specifically those with a proinflammatory phenotype (Sripa 2012) such as IL6R (Prayong 2014).

Treatment of liver fluke infestation by praziquantel has been very successful but this is dependent on early accurate diagnosis and correct species identification (Huang 2012) . Community wide prevention programs are also helpful (Sripa 2015).

Bladder squamous cell carcinoma due to *Schistosome haematobium*
Infestation by *Schistosoma haematobium,* a blood fluke which resides in venules and capillaries of the bladder and other pelvic organs, is strongly associated with bladder squamous cell carcinoma (Khaled 2013). First identified in 1851 by Theodor Bilharz, *S. haematobium* infestation is endemic in Africa and the Middle East, including Egypt. In one study from Egypt, 82% of patients with bladder carcinoma had *S. haematobium* eggs in the bladder wall (El-Bolkainy 1981). In 1994, the IARC confirmed that *S. haematobium* was carcinogenic (IARC 1994).

The mechanism of carcinogenesis in *S. haematobium* is similar to liver flukes - the parasite causes chronic inflammation, leading to epithelial metaplasia. The presence of nitrosamines (exogenous in liver flukes, endogenous with schistosomiasis) acts as a cofactor. Adult *S. haematobium* commonly invade the venous plexus around the urinary bladder. The adult worms release eggs which cause chronic granulomatous inflammation in the bladder mucosa and submucosa, leading to squamous metaplasia of the urothelium. Chronic granulomatous inflammation also leads to bladder fibrosis, which causes urine stasis and bacteria superinfection. The bacteria convert dietary nitrates and nitrites into nitrosamines, which are then excreted in the urine. These nitrosamines are carcinogenic and act on the metaplastic epithelium, with subsequent progression to squamous cell carcinoma (Sheweita 2004).

Schistosomiasis is not implicated in the etiology or pathogenesis of any other malignant disease (Khaled 2013). Despite endemics in 52 countries causing 206 million people to receive preventative treatment in 2016 (World Health Organization, Schistosomiasis Fact Sheet, accessed 26Nov17), less than 25 cases of Schistosomiasis have been reported to be associated with prostatic adenocarcinoma (Figueiredo 2015, Mazigo 2010).

Bladder cancer is still the most common malignant tumor among men in Egypt and some African and Middle East countries. However, its frequency has declined significantly during the last 25 years due to control of Schistosomiasis (Khaled 2013).

Treatment is discussed in section 2.5 (tobacco).

Section 1.7 Trauma related

Trauma, whether physiologic or external is associated with inflammation and repair and occasionally with malignancy, particularly in the esophagus (due to reflux and hot beverages), skin (burns, sinuses / fistulas and various dermatoses), stomach (wood dust, iron files) and bladder (stones).

Esophageal adenocarcinoma due to gastroesophageal reflux

Gastroesophageal reflux is the major cause of esophageal and gastric cardia adenocarcinoma (Yang 2016). Its pathophysiology is dominated by functional and anatomic defects at the gastroesophageal junction (Ness-Jensen 2016). Initially it causes Barrett esophagus (Barrett metaplasia), which results in replacement of esophageal stratified squamous epithelium with columnar epithelium, with a high rate of progression to dysplasia and then adenocarcinoma (Goldblum 2003). In the U.S., the incidence of esophageal cancer has been stable for many years (American Cancer Society - Key Statistics for Esophageal Cancer, accessed 6Nov17) but as with lung carcinoma, the incidence of esophageal adenocarcinoma has been markedly increasing while rates for squamous cell carcinoma have been decreasing.

Esophageal adenocarcinoma, a classic example of inflammation associated cancer (O'Sullivan 2014), is typically caused by cytokine mediated inflammatory injury, not caustic chemical (acid) injury. Refluxed acid and bile stimulate the release of inflammatory cytokines from esophageal squamous cells, recruiting lymphocytes first to the submucosa and later to the luminal surface (Souza 2016). Healing of reflux esophagitis may lead to Barrett metaplasia, a process facilitated by reflux related nitric oxide production and Sonic Hedgehog secretion by squamous cells (Souza 2016). Barrett esophagus is an intermediate step or a hierarchy between the common reflux esophagitis and the rare esophageal adenocarcinoma.

Other risk factors for esophageal adenocarcinoma include cigarette smoking, obesity (Long 2014, Zakaria 2017) and diet (high fat, low vegetables and fruit, Neto 2016). A high fat diet may produce changes in the esophageal microbiota (Kaakoush 2017) as it does in the colon; it is also associated with obesity which directly causes reflux (see section 1.8).

The risk of Barrett esophagus and esophageal adenocarcinoma is influenced by many germ line genetic variants of small effect (Ek 2013), including *VSIG10L* (Fecteau 2016) and *MGST1* (Buas 2017).

Prevention is particularly important due to the poor prognosis of esophageal adenocarcinoma (O'Sullivan 2014) and focuses on early detection and treatment of premalignant lesions. Lifestyle modifications include increasing physical activity, consumption of vegetables and fruits, losing weight and reducing smoking, alcohol and meat consumption (Yang 2016), which reduce the risk of gastroesophageal reflex and subsequent adenocarcinoma (Ness-Jensen 2016).

Esophageal squamous cell carcinoma is also associated with chronic inflammation but via a different mechanism, see the discussion in sections 2.5 (tobacco), 2.7 (alcohol) and 4.2 (diet). Its highest incidence occurs in the “Asian esophageal cancer belt”, from Iran east to China and north to Russia. The degree of chronic inflammation correlates with esophageal precursor lesions. Persistent chronic inflammation may trigger oxidative DNA damage (Lin 2016), which may be mediated by COX2 (Zhang 2011, Yang 2005).

Cutaneous squamous cell carcinoma due to chronic inflammation

Rarely, cutaneous squamous cell carcinoma arises at the site of chronic inflammation due to various types of tissue trauma, including ulcers, sinus tracts, osteomyelitis (Horvai 2006, Li 2015), radiation dermatitis and others (Alam 2001).

Marjolin ulcer is a well described squamous cell carcinoma which develops after a prolonged latent period in posttraumatic scars and chronic wounds, including deep burns (Saaiq 2014). Although the precise mechanism of malignant transformation is unknown, these lesions are chronically inflamed and undergo continuous mitotic activity due to regeneration and repair, which leads to unstable network states which may eventually overcome growth controls and trigger malignant transformation. Impaired healing in chronic wounds occurs secondary to flaws in blood supply, angiogenesis and matrix turnover, as well as infection and continued trauma, which themselves disturb the intricate balance of cytokines, growth factors, proteases and cellular and extracellular elements necessary for proper wound healing (Saaiq 2014, Pekarek 2011). In addition scar tissue may have impaired immunologic reactivity to tumor cells due to obliterated lymphatics (Visuthikosol 1986).

Treatment is early excision and grafting. Radiotherapy has an important adjunctive role due to the tumor's aggressive clinical behavior (Saaiq 2014).

Section 1.8 Excess weight related

Being overweight (BMI of 25 or more) or obese (BMI of 30 or more) causes an estimated 20% of cancer cases, with the increased risk influenced by diet, weight change, body fat distribution and physical activity. According to the IARC and World Cancer Research Fund, the malignancies with the strongest association with excess weight are adenocarcinoma of the esophagus, colorectum and postmenopausal breast, and carcinoma of the endometrium and kidney (De Pergola 2013, Ramos-Nino 2013).

In the U.S. in 2012, being overweight or obese caused 3.5% of new cancer cases in men (28,000) and 9.5% in women (72,000) (National Cancer Institute: Obesity and Cancer, accessed 6Nov17), compared with worldwide figures of 1.9% of new cancer cases in men and 5.4% of new cancer cases in women; attributable fractions vary from 6% for rectal cancer to 33% for esophageal adenocarcinoma in men and 4% for rectal cancer to 34% for endometrial cancer and esophageal adenocarcinoma in women (Arnold 2015).

Obesity, defined physiologically as abnormal excess accumulation of fat in adipose tissue, is a chronic low grade inflammation associated with a high risk of developing type 2 diabetes, metabolic syndrome (Reaven 1988, Zhang 2014) and cardiovascular disease, as well as various types of cancer (Divella 2016). Obesity is associated with diet (see section 4.0), sedentary behavior (Sugiyama 2016) and lack of physical activity (Siddarth 2013).

The low grade inflammation tends to occur in white adipose tissue due to chronic activation of the innate immune system, which can lead to insulin resistance, impaired glucose tolerance and even diabetes. Adipose tissue hypoxia may also lead to insulin resistance, infiltration of macrophages, adipocyte death and mitochondrial dysfunction (Divella 2016). These changes are associated with alteration of other factors which directly or indirectly drive tumor progression, including insulin, glucose, free fatty acids, insulin-like growth factor 1 and 2, adipose tissue derived proinflammatory factors, adipokines (adiponectin and leptin), vascular endothelial growth factor, sex hormones, gut microbiota and secondary bile acids (Ungefroren 2015, Tilg 2014, Bastard 2006). Obesity is also associated with altered estrogen levels (Engin 2017), a chronic stressor described in section 3.1.

Breast cancer due to obesity

The World Cancer Research Fund estimates that 17% of U.S. breast cancer cases could be prevented by maintaining a healthy weight (World Cancer Research Fund: Second Expert Report: Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective 2007), which is important because two thirds of U.S. women are overweight or obese (Matthews 2016). Postmenopausal women who are metabolically unhealthy or have central adiposity may be at increased risk for breast cancer even with a normal BMI (Park 2017). Obesity is also a risk factor for breast cancer in men (Brinton 2014). Regular use of NSAIDs appears to reduce breast cancer risk, particularly among overweight women (Cui 2014).

Colorectal carcinoma due to obesity

In Europe, 11% of colorectal cancer cases have been attributed to excess weight (Bardou 2013). Obesity is associated with a 30-70% increased risk of colon cancer in men but the association is less consistent in women. Abdominal obesity seems to be more important than subcutaneous fat obesity. The underlying mechanisms are not straight forward, but metabolic syndrome, insulin resistance and modifications in levels of adipocyte cytokines seem to be important, as is cross talk between pre neoplastic epithelial cells and immune cells (Riondino 2014), most likely by destabilizing associated networks. Sedentary behavior is also associated with colon carcinoma risk, and may be mediated through obesity (Schmid 2014).

Esophageal adenocarcinoma due to obesity

Abdominal visceral obesity is a risk factor for gastroesophageal reflux although the mechanism is unknown (El-Serag 2008). Visceral obesity increases the risk of Barrett esophagus and adenocarcinoma via reflux dependent and independent mechanisms (Long 2014). In Canada in 2010, an estimated 42% of cases of esophageal adenocarcinoma were attributable to excess body weight (Zakaria 2017). Weight loss, in addition to the combined use of a statin, aspirin or another cyclooxygenase inhibitor, is associated with a significantly reduced cancer incidence in patients with Barrett esophagus (Long 2014).

Hepatocellular carcinoma due to obesity

The current obesity epidemic has caused an increase in nonalcoholic fatty liver disease (NAFLD), found in 75-100% of obese and overweight adults and children. The most severe form of NAFLD is nonalcoholic steatohepatitis (NASH), which is associated with cirrhosis and hepatocellular carcinoma (Ip 2013, Page 2009), as well as carcinoma of the colon, esophagus, stomach and pancreas, renal cell carcinoma in men and breast carcinoma in women (Sanna 2016).

NAFLD progression from steatosis to NASH to hepatocellular carcinoma is a multistep process, beginning with hepatocyte damage, followed by inflammation and cycles of necrosis and regeneration (Sun 2012). Hepatic inflammation and injury in NASH activate hepatic stellate cells, which promote cirrhosis by replacing hepatocytes with scar tissue rich in type I collagen. This creates an environment permissive to genetic modulations, leading to malignant transformation.

Green tea catechins and branched chain amino acids may prevent obesity related hepatocellular carcinoma by improving metabolic abnormalities. Acyclic retinoid, a pharmaceutical agent, may also reduce risk (Sakai 2016).

It has been suggested that weight loss strategies should consider disparities in genetic and environmental factors, focusing on the specific ancestry of each population and the convenience of consuming traditional ethnic food (Roman 2015).

Pancreatic adenocarcinoma due to obesity

Pancreatic ductal adenocarcinoma is projected to become the second most common cause of cancer related death by 2030 due to an epidemic in obesity and metabolic syndrome (Rahib 2014). Obesity, particularly android obesity (central obesity or fat excess

primarily in the abdominal wall and visceral mesentery) and pancreatic fatty infiltration are risk factors for pancreatic precancerous lesions. This risk may be mediated through insulin resistance and an altered adipokine milieu, or through its associated chronic low grade inflammation with production of inflammatory mediators (Rebours 2015).

Other risk factors for pancreatic adenocarcinoma in addition to chronic inflammation and tobacco (discussed in section 2.5) include diabetes and family history (McWilliams 2016). Alcohol consumption is not a significant risk factor (Andersson 2016).

Statins may reduce pancreatic cancer risk or improve survival in patients with pancreatic cancer and metabolic syndrome, possibly by blocking the synthesis of intermediates important for both prenylation and activation of the Ras/mitogen activated protein kinase 1 signaling pathway (Gong 2017).

Section 1.9 Other

Cancer due to diabetes

Patients with diabetes have a 20% increased risk of cancer (Scappaticcio 2017), highlighted by reports of antidiabetic drugs treating (Fukumura 2016) or promoting cancer, which suggests cross talk between the multiple pathways at the interface of the diabetes-cancer link (Tudzarova 2015).

Diabetes mellitus is associated with a moderately increased risk of bladder cancer, particularly in men (Zhu 2013, Fang 2013) although some confounding by tobacco or body mass index may partly explain the association (Turati 2015). The risk may be greater in those taking oral hypoglycemics and with greater disease duration (MacKenzie 2011, Mamtani 2012). The mechanism is unknown but there appears to be an important interaction between hyperglycemia, hyperinsulinemia, peripheral insulin resistance and central adiposity, creating a low grade chronic inflammatory state (Gristina 2015).

Colorectal carcinoma due to inflammatory bowel disease

Patients with long standing ulcerative colitis and Crohn disease have an increased risk of colorectal cancer although the incidence has been decreasing in western countries (Kim 2014). The risk increases with greater duration and extent of colitis, as well as more prominent inflammation, the presence of primary sclerosing cholangitis and family history of colorectal cancer (Triantafillidis 2009). Histologic changes apparently progress from no dysplasia to indefinite dysplasia, low grade dysplasia, high grade dysplasia and finally to invasive adenocarcinoma although steps can be skipped (Triantafillidis 2009). As noted above, the changes appear to be due to establishment of new hierarchies of molecular patterns, which may not have associated histologic changes.

Host inflammation affects the composition and functional capabilities of gut microbiota (Arthur 2013). Inflammatory mediators TNF, IL17A and IL23 and byproducts such as reactive oxygen and nitrogen species produce genetic and epigenetic modifications that may lead to carcinogenesis although it may be difficult to establish if specific bacteria are a cause or effect of the intestinal inflammation (Arthur 2013).

During intestinal inflammation, some bacteria adjust to and exploit the inflamed environment to gain a growth advantage (see the alpha bug discussion in section 1.5), which may lead to marked alterations in gut microbial composition (Yang 2014, Kostic 2014). Key epigenetic mechanisms also link chronic inflammation to colitis associated cancer (Däbritz 2014).

Pancreatic adenocarcinoma due to chronic inflammation

The risk of pancreatic cancer is significantly elevated in patients with chronic pancreatitis, with a standardized incidence ratio of 26.3 The cumulative risk of pancreatic cancer in subjects is 1.8% at 10 years and 4.0% at 20 years (Lowenfels 1993), which persists after adjusting for tobacco and alcohol use (Ling 2014). However, the population attributable fraction of chronic pancreatitis is only 1.3% (Duell 2012). In autoimmune pancreatitis, the incidence of subsequent pancreatic cancer ranges from 0 to 4.8% (Ikeura 2016).

Possible mechanisms are: (a) inflammation related reactive oxygen species and reactive nitrogen intermediates, enhanced by growth factors and cytokines, may induce malignancy through DNA damage and abortive repair (Ling 2014), (b) in response to macrophage secreted inflammatory cytokines, pancreatic acinar cells undergo acinar to ductal metaplasia, which induces differentiation to a duct-like phenotype and contributes to pancreatic intraepithelial neoplasia and pancreatic adenocarcinoma (Guerra 2007, Strobel 2007), mediated by NFκB and matrix metalloproteinases (Liou 2013), (c) the inflammatory process creates a tumor microenvironment in which the immune response is actively suppressed (Evans 2012), (d) chronic inflammation is associated with epithelial to mesenchymal transition and possibly pancreatic cancer cell dissemination prior to pancreatic tumor formation (Rhim 2012) although this process is not well understood (McDonald 2012).

Regular use of aspirin may reduce the risk of pancreatic cancer (Streicher 2014, Risch 2017 but see Amin 2016), possibly mediated through its inhibition of COX1 and COX2.

Lung carcinoma due to chronic inflammation

The overwhelming contribution of smoking to lung cancer makes it difficult to determine additional risk factors but a prior history of chronic obstructive pulmonary disease or pneumonia is associated in most studies with an increased risk (smokers and nonsmokers: McHugh 2013, Shen 2014, Koshiol 2009, Ho 2017; smokers only: Wang 2012; never smokers: Brenner 2011). Additional risk factors are recurrent pneumonia in AIDS patients (Shebl 2010, Hessol 2015 but see Koshiol 2010), tuberculosis in male smokers (Shiels 2011), *Chlamydia pneumonia*e infection (Zhan 2011), and elevated acute phase reactants, including C reactive protein (Zhou 2012, Chaturvedi 2010) and others (Shiels 2013, Keeley 2014). There are variable conclusions on whether NSAIDs protect against lung cancer risk (yes in smokers - Harris 2002, yes in women - Van Dyke 2008 but see Jiang 2015).

Section 2.0 Exposure to carcinogens

In this section, we describe how exposure to carcinogens, whether from bacteria, parasites, viruses, tobacco, alcohol or work related, is associated with malignancy. Although these substances may directly be mutagenic, the malignant process is not

straightforward and reductionist; it requires additional chronic stressors and indirect methods of overcoming network controls and the immune response. Prevention and treatment are described in each section.

Section 2.1 General

Carcinogens are substances or exposures that lead to cancer; their mechanisms of action are described below. Due to network stability (see below), we cannot predict in advance which carcinogens will induce change in which networks, and whether or not this will propel stem or progenitor cells along a malignant pathway. Cellular networks do exhibit marked changes over time in response to signals from each other, accounting for the marked differences in activity and the phenotypic changes associated with progression from a fertilized egg through embryogenesis, fetal development, prepubertal and pubertal growth and adult activities, with further changes due to inflammation and repair and other internal or external signals. Some pathways are more sensitive to disruption than others, and some disruptions, while damaging to the cell, will dampen out, and are unlikely to influence interacting networks to promote cancer.

Predicting the effect of changes to any particular gene or network is difficult for several reasons. First, based on self-organized criticality, we can predict that some network changes will reverberate and be catastrophic (Bak, How Nature Works 1999) but we cannot identify them in advance. Second, complex organisms tend to reuse genes and networks and to increase sophistication via small changes and additional controls (Mattick 2001, Glassford 2015), which makes it extremely difficult to follow the flow of activity, even in an isolated network. Third, evolution has taken advantage of physical laws that promote nonlinear results. For example, rapid cell growth is associated with dedifferentiation, whether during embryogenesis or malignancy, because the shorter interphase and lack of mitotic gap phases prevents the relatively time consuming polymerization of lengthy transcripts. This activates numerous other networks in a manner that can be evaluated conceptually but is difficult to follow specifically.

Section 2.2 Carcinogens associated with bacteria and parasites

Numerous bacterial or parasitic toxins are associated with carcinogenesis (Nath 2010, Table 2), often as cofactors with antigen driven lymphoproliferation or other chronic inflammation. For example, *Helicobacter pylori* infection promotes gastric MALT lymphoma by translocating its cytotoxin associated gene A protein (CagA) into B cells. After tyrosine phosphorylation, it deregulates intracellular signaling pathways, stimulates B cell proliferation (Wang 2013, Krisch 2016) and promotes a more potent inflammatory response (Zucca 2014). *Campylobacter jejuni* secretes the CDT toxin, whose DNase activity produces chromosomal DNA damage (Lara-Tejero 2000, Méndez-Olvera 2016). *Salmonella typhi* metabolizes primary bile acids to produce bacterial β-glucuronidase, which then produces CDT, mutagenic intermediates and bile acid metabolites that promote gallbladder carcinogenesis (Gonzalez-Escobedo 2013, Nath 2010).

In the colon, alpha bugs that promote intestinal carcinogenesis in animal models include: (a) *E. coli* harboring the polyketide synthase (pks) island that encodes a putative genotoxin called Colibactin (Arthur 2012, Bonnet 2014, Raisch 2014), (b) enterotoxigenic *Bacteroides fragilis* (Wu 2009) and (c) *Fusobacterium nucleatum* (Kostic 2014, Rubinstein 2013). Colibactin may promote tumorigenesis by inducing DNA damage and genomic instability (Arthur 2012).

In *Schistosomiasis haematobium*, chronic granulomatous inflammation in the urinary bladder produces urine stasis and bacterial superinfection, which produces nitrosamines that act on metaplastic epithelium (Sheweita 2004). Soluble antigens from *S. haematobium* eggs may also promote malignancy (Botelho 2013).

As described in sections 1.3, 1.5 and 1.6, treatment is directed against the bacteria and parasites, not the possible toxins. When not effective, treatment is directed against the malignancy itself.

Section 2.3 Viral carcinogens causing lymphoma

Viruses often drive lymphomagenesis directly by activating proliferation pathways. Of particular importance are Hepatitis C, Epstein-Barr virus, HTLV1 and HHV8.

Hepatic lymphoma due to Hepatitis C

Although Hepatitis C virus promotes hepatic B cell lymphoma indirectly by antigen directed lymphoproliferation (see section 1.3), HCV can also directly activate B cells by: (a) reducing the threshold of B cell activation through the binding of HCV E2 to CD81 on B cells (Forghieri 2012), (b) inducing permanent damage to tumor suppressor genes and proto-oncogenes due to a transiently intracellular virus infection that may quickly leave the cell (“hit and run” theory, Forghieri 2012, Rossotti 2015), (c) directly activating antiapoptotic pathways within B cells (Agnello 1992, Mele 2003) and (d) activating proinflammatory cytokines (de Sanjose 2008). As Hepatitis C virus lacks reverse transcriptase or oncogenes, immediate malignant transformation of B or T cells is unlikely (Pozzato 1994). When present, Sjögren syndrome may a cofactor in HCV lymphomagenesis (Ramos-Casals 2007).

Antiviral treatment with interferon induces regression of indolent lymphoma in 75% of cases, particularly marginal zone lymphoma, with loss of serum HCV RNA and complete remission of lymphoma (Hermine 2002, Merli 2016, Arcaini 2012, Vallisa 2005). Chemotherapy is necessary for associated high grade lymphoma (Tasleem 2015).

Lymphoma due to Epstein-Barr virus

Epstein-Barr virus (EBV) is a ubiquitous γ herpes virus which infects 95% of the adult population worldwide through oral secretions and is also associated with an astounding 2% of cancer deaths worldwide, primarily gastric cancer (48% of EBV cancer deaths) and nasopharyngeal carcinoma (44% of EBV cancer deaths) (Khan 2014). It has an important role in almost all cases of endemic Burkitt lymphoma, lymphomatoid granulomatosis, extranodal NK/T cell lymphoma nasal type, pyothorax associated lymphoma, angioimmunoblastic T cell lymphoma and post transplant lymphoproliferative disorder. It is associated with Hodgkin lymphoma (80% of mixed cellularity and 30% of nodular sclerosis cases, Houldcroft 2015) and sporadic Burkitt lymphoma (30% of cases). Its role in post transplant lymphoproliferative disorder, diffuse large B cell lymphoma associated with chronic inflammation, Hodgkin lymphoma and Burkitt lymphoma (sporadic) is discussed in section 7.0.

EBV is a potent growth transforming agent for primary B cells through stimulation of the NFκB pathway and increased expression of antiapoptotic genes (Rowe 2014). After primary infection, it remains in a latent state within resting B cells for the lifetime of the host. Cytotoxic T cells (CTL), both CD8+ and CD4+, and natural killer (NK) cells are primarily responsible for containing the infection. If the host cellular immune system fails to control EBV activity, infected B cells can transform from their latent state into malignant cells, which are typically aggressive (Roschewski 2012). EBV also plays a complex and multifaceted role in T/NK cell lymphoma by promoting Th2 skewed T cell responses and increasing the expression of immune checkpoint ligand PDL1 (Gru 2015).

EBV has three distinct patterns of latency. Type I has selective expression of EBNA1 and is seen in Burkitt lymphoma. Type II expresses EBNA1, LMP1 and LMP2 and is seen in Hodgkin lymphoma and peripheral T cell lymphoma. Type III expresses all nine latent cycle EBV antigens and is commonly seen in post transplantation lymphoproliferative disorder (Roschewski 2012).

Typically the treatment approach for these tumors is similar whether they are EBV positive or negative (Kanakry 2013) although for immunodeficiency related EBV tumors, treatment aims to restore the host immune response to EBV and may include specific cytotoxic T cell therapy (see section 7.4). There is no specific anti-EBV medication.

Burkitt lymphoma-endemic due to EBV
EBV appears to be actively involved in all stages of endemic Burkitt lymphoma development. In a Ugandan prospective study, children who subsequently developed Burkitt lymphoma had significantly higher titers of EBV-VCA IgG antibodies up to 6 years before lymphoma onset; chronic rather than acute EBV infection appears to be relevant to lymphomagenesis (de-Thé 1978, van den Bosch 2012).

EBV potentiates lymphomagenesis by directly stimulating and maintaining B cell proliferation, which increases the size of the B cell pool and the risk of translocation or other cytogenetic changes (van den Bosch 2012). EBV-LMP1 acts as an oncogene by mimicking the CD40 ligand and binding the B cell CD40 receptor, causing constitutive activation of the NFκB pathway and providing a growth signal to B cells (Roschewski 2012). EBV also promotes genomic instability by inducing oxidative stress (Kamranvar 2007) and protects cells damaged by mutations from destruction by apoptosis (Mancao 2005).

Although EBV is widespread in all human communities, only a very small number of infected individuals develop Burkitt lymphoma or any other cancer linked to the virus. Endemic Burkitt lymphoma is primarily a childhood cancer in parts of Africa and Brazil, and is associated with the t(8;14) IgH-Myc translocation (Bernheim 1981).

Malaria appears to be a common cofactor in the pathogenesis of endemic Burkitt lymphoma (Magrath 2012). In sub-Saharan Africa, 90% of children are infected with EBV by age 2 and develop immune tolerance to it. Malaria produces polyclonal B cell activation, inhibition of EBV specific cytotoxic T cells and an increase in EBV transformed B cells (Whittle 1990, van den Bosch 2012). The combination of EBV and holoendemic malaria amplifies the incidence of endemic Burkitt lymphoma in African children approximately a hundredfold, from 0.04–0.08/100,000 in Western Europe, 1-2/100,000 in Algeria to 10/100,000 in the African lymphoma belt (van den Bosch 2012). Burkitt lymphoma has a germinal center cell immunophenotype (BCL6$^+$, CD10$^+$), and persistent malarial infection may promote the hyperactivation of these germinal centers and increase the risk of somatic hypermutation and Myc translocation (Roschewski 2012).

Although EBV and malaria are the most common infections associated with endemic Burkitt lymphoma, other cofactors have been described including infections with HIV, human herpesvirus 5, human herpesvirus 8 (Abate 2015) and Chikungunya virus and the presence of the EBV activating plant *Euphorbia tirucalli* (van den Bosch 2012, MacNeil 2003).

Treatment of Burkitt lymphoma is highly effective in the West and cure rates are >90% using short, intensive, rotational multiagent chemotherapy including rituximab (Dozzo 2016). In Africa, long term cure rates have remained at 25-30% due to limited resources and poor patient compliance (Mbulaiteye 2013).

Lymphomatoid granulomatosis due to EBV
Lymphomatoid granulomatosis is a rare angiodestructive EBV driven lymphoproliferative disease comprised of atypical clonal EBV$^+$ B cells in an inflammatory background. Most patients have lung involvement (Chavez 2016).

Typically there is no known immunodeficiency at diagnosis but there may be defective immune surveillance of EBV infected B cells, particularly by CD8+ T cells (Roschewski 2012). As a result, the EBV infection leads to uncontrolled growth of infected B cells. Treatment with interferon (grades 1/2) or dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (grade 3 disease) improved progression free survival to 56% for grades 1/2 (median followup 5.1 years) and to 44% for grade 3 disease (median followup 32 months) (Song 2015).

Extranodal NK/T cell lymphoma, nasal type due to EBV
Extranodal NK/T cell lymphoma, nasal type is an aggressive extranodal non Hodgkin lymphoma most commonly found in East Asia and Latin America but increasing in the U.S., where it is more common among Asian Pacific Islanders and Hispanics (Haverkos 2016). It accounts for 15% of all non Hodgkin lymphoma in southwest China, 7.8% in Guatemala, 6.1% in Korea, 2.8% in Taiwan, 2.6% in Japan, 2.6% in Chile, 2.4% in Peru and less than 0.1% in Europe and North America (Gru 2015). EBV is associated with virtually all cases and is the only factor implicated in its pathogenesis although Asian and South American patients often have antecedent lymphoproliferative disorders (Haverkos 2017). If in situ hybridization for EBV is negative, one should question the diagnosis. EBV viral load detected by polymerase chain reaction is intimately tied to prognosis, clinical course and disease relapse (Roschewski 2012).

Although the precise mechanism of action of EBV in this tumor is unknown, important factors appear to be the microenvironment, cross talk with surrounding cell types and clinically unapparent immune dysregulation (Haverkos 2016).

Pegaspargase, gemcitabine and oxaliplatin combined with radiotherapy produced a 94% response rate in one study (Wei 2017). Another study recommended combined chemotherapy and radiotherapy for stage I/II disease and non anthracycline regimens containing L-asparaginase for stage III/IV disease. Up to 90% of "good risk" stage I/II patients may achieve durable remission but treatment of high risk stage I/II and stage III/IV patients remains challenging (Tse 2017).

Pyothorax associated lymphoma due to EBV
Pyothorax associated lymphoma is a distinct type of diffuse large B cell lymphoma associated with chronic inflammation which develops in patients who received an artificial pneumothorax for pulmonary tuberculosis 30 to 40 years previously (Nishiu 2004) although lymphomas with similar features are also recognized in other chronic inflammatory conditions (Xie 2015). EBV is detected in lymphoma cells of most cases (Nakatsuka 2002). Patients often have a very large tumor (>10 cm) confined to the thoracic cavity, which helps distinguish it from primary effusion lymphoma (Roschewski 2012).

Pyothorax associated lymphoma tumor cells typically derive from crippled post germinal center cells at the differentiation stage, before antigen selected maturation has occurred, which differs from most B cell lymphomas (Miwa 2002). EBV appears to induce B cell transformation and escape from cytotoxic T cells (Roschewski 2012, Takakuwa 2008).

Prognosis is poor, with a 5 year survival (as of 2007) of only 35% (Narimatsu 2007).

Angioimmunoblastic T cell lymphoma due to EBV
Angioimmunoblastic T cell lymphoma (AITL) is a distinct peripheral T cell lymphoma associated with EBV infection in almost all cases (Roschewski 2012). It originates from the follicular T helper cell, a CD4+ T cell of germinal center origin and is characterized by the RHOA G17V mutation together with genetic alterations in *TET2* (Lemonnier 2017), *DNMT3A* and *IDH2* (Cortés 2016), which most likely promote T cell differentiation and malignant transformation (Wang 2017). AITL is the second most frequent peripheral T cell lymphoma worldwide after peripheral T cell lymphoma not otherwise specified.

The exact role of EBV in AITL lymphomagenesis is not completely understood. Of note, it is the background B cells that are partially infected by EBV, not the malignant T cells (Roschewski 2012). AITL tissues are characterized by massive infiltration of B cells partially infected by EBV, follicular dendritic cells and high endothelial venules, promoted by cytokines and chemokines released from tumor cells (Sakata-Yanagimoto 2016). EBV+ B cells may upregulate CD28 ligand, which leads to activation of follicular T helper cells and production of CXC13 and other chemokines. Chronic stimulation of the follicular T helper cells through this mechanism may eventually lead to an antigen independent clone (Roschewski 2012).

Outcomes with anthracycline containing regimens are poor; autologous transplantation at first remission is recommended (Broccoli 2017, Lunning 2017).

Lymphoma due to Human T cell Lymphotropic virus type 1 (HTLV1)
HTLV1 is a type 1 carcinogen associated with lymphoproliferative diseases collectively termed adult T cell leukemia / lymphoma (Morales-Sánchez 2014). It is endemic in Japan, the Western African coast, Central America and the Caribbean, with 15 million to 25 million people infected worldwide. Transmission is by sexual contact, breast feeding or intravenous exposure. The virus infects T and B lymphocytes and dendritic cells and binds to their GLUT1 receptor (Maeda 2015).

Most HTLV1 infected patients carry tens of thousands of clones of HTLV1 infected T lymphocytes, each distinguished by a unique integration site of provirus into the host genome. However only 5% of those infected develop adult T cell leukemia / lymphoma, typically those infected by breast feeding and usually more than 50 years after becoming infected (Bangham 2015). Compared with HIV1, HTLV1 varies little in sequence, and the genotypes of patients with adult T cell leukemia / lymphoma, HTLV1 associated myelopathy or HTLV1 associated tropical spastic paraparesis are similar to those from asymptomatic carriers. The efficiency or "quality" of the specific cytotoxic T lymphocyte (CTL) response to HTLV1 is a major determinant of the HTLV1 proviral load and the risk of disease. The chief factors that determine a high quality anti-HTLV1 CTL response are the host genotype in HLA Class 1 and killer immunoglobulin-like receptor loci (Bangham 2015).

The HTLV1 viral oncoprotein Tax directly leads to leukogenesis and immortalization of T lymphocytes by: (a) inducing NFκB activity, which stimulates cytokine expression, which triggers T cell proliferation and may amplify the pool of HTLV1 infected cells (Morales-Sánchez 2014), (b) transcriptionally repressing DNA polymerase β, involved in base excision repair (Jeang 1990) and (c) independently suppressing the nucleotide excision repair mechanism, which together lead to faulty chromosomal segregation and aneuploidy in HTLV1 infected cells. In addition Tax can also modulate the host innate immune response to favor virus replication and oncogenesis (Hyun 2015).

Prognosis is poor, with 4 year overall survival rates of 11%, 16%, 36% and 52% for the acute, lymphoma, chronic and smoldering types (Ishitsuka 2017).

Primary effusion lymphoma due to HHV8
Primary effusion lymphoma is a rare, aggressive B cell lymphoma universally associated with HIV infected patients and human herpesvirus 8 (HHV8), the oncogenic virus associated with Kaposi sarcoma. It typically presents in adults with a median age of 41 years (El-Fattah 2016) as a malignant serous effusion of the pleura, pericardium or peritoneum with no tumor mass although solid variants have been described (Pielasinski 2014, Guillet 2011). Cases are occasionally observed in transplantation and elderly patients in areas where HHV8 is endemic, such as the Mediterranean and sub-Saharan Africa (Kaplan 2013).

HHV8 may promote lymphomagenesis through viral IL6, a lytically produced cytokine capable of mediating paracrine signaling to promote cell growth and survival in addition to proinflammatory and angiogenic responses (Chen 2014). There is no effective treatment, and the overall median survival is 6 months (Kaplan 2013).

Multicentric Castleman disease, plasmablastic variant, due to HHV8

Human herpesvirus 8 also causes multicentric Castleman disease (MCD) in immunocompromised individuals, such as HIV infected patients, although >50% of MCD cases are negative for HIV and HHV8 (Yu 2017, Kaplan 2013).

Multicentric Castleman disease is often referred to as human interleukin 6 syndrome, since overproduction of IL6 is present (Carbon 2015). In idiopathic MCD, defined as HHV8 negative disease, numerous mechanisms increase IL6 (Wang 2016); rarely it is caused by immune reconstitution inflammatory syndrome (Siegel 2016).

Treatment with rituximab with or without chemotherapy results in significantly better overall survival (Kaplan 2013). Siltuximab, an anti-IL6 monoclonal antibody, has also demonstrated durable tumor responses (van Rhee 2015, Sarosiek 2016).

Section 2.4 Viral carcinogens causing carcinoma or sarcoma

Hepatocellular carcinoma due to Hepatitis B and Hepatitis C

Hepatocellular carcinoma (HCC) is a leading cause of cancer related death worldwide (Forner 2012, Baumert 2017), and the fastest growing cause of cancer related death in the U.S. (El-Serag 2011). In the U.S., in persons age 68 or older, population attributable risks for HCC are diabetes / obesity (37%), alcohol related disorders (24%), hepatitis C virus (22%), hepatitis B virus (6%) and rare genetic disorders (3%) (Weizel 2013).

Most HCV infected patients are unaware of their status, and 85% progress to chronic HCV infection and cirrhosis. The risk of HCC for patients with HCV related cirrhosis is 2-6% per year (de Oliveria Andrade 2009). HCV is a RNA virus with no ability to integrate into the host genome (Goossens 2015). It promotes malignancy by activating liver fibrogenic pathways and by interacting with immune and metabolic systems. Germ line changes are also important in immune system, metabolic and growth signaling pathways (Goossens 2015).

Direct acting antivirals have improved the HCV hepatitis cure rate to above 90% although this is limited by high cost. Due to under diagnosis among baby boomers, inmates and injection drug users, HCC incidence even in high resource countries is predicted to increase (Baumert 2017, El-Serag 2002).

In Africa and East Asia, 60% of HCC cases are attributable to hepatitis B, compared with 20% in the developed Western world (Di Bisceglie 2009). HBV encoded X protein (HBx) plays a pivotal role in the pathogenesis of viral induced HCC by modulating transcription, cell cycle progression, DNA damage repair, cell proliferation and apoptosis (Ali 2014). Universal hepatitis B immunization is effective in reducing HCC incidence due to HBV (Chang 2003).

Gastric adenocarcinoma due to EBV

EBV associated gastric cancer is the largest group of EBV associated malignancies, primarily because gastric cancer is the third leading cause of cancer related mortality worldwide, after lung and liver cancer. Ten percent of gastric carcinoma cases worldwide contain EBV; in these cases, typically all tumor cells harbor the clonal EBV genome (Nishikawa 2014). EBV associated gastric cancer is one of four subtypes based on gene expression profiles; the others are microsatellite unstable, genomically stable and chromosomal instability (Cancer Genome Atlas Research Network 2014). EBV associated gastric carcinoma occurs predominately in younger men, typically with a diffuse histology rich in lymphocytes (Nishikawa 2014).

Gastric cancer arises due to dysregulated differentiation of stem and progenitor cells caused by a chronic inflammatory environment. However, the situation in the stomach is considered rather complex, consisting of two types of gastric units which show bidirectional self renewal from an unexpectedly large variety of progenitor / stem cell populations (Hoffmann 2015). Genetic and epigenetic changes characteristic of EBV associated gastric cancer alter gene expression related to cell proliferation, apoptosis, migration and immune signaling, and include mutations in *PIK3CA* and *ARID1A*, amplification of *JAK2* and *PDL1/L2* and global CpG island hypermethylation, which induces epigenetic silencing of tumor suppressor genes (Shinozaki-Ushiku 2015).

Cofactors for EBV associated gastric carcinoma include salty food and exposure to wood dust or iron filings, which may induce mechanical injury to the gastric epithelia (Nishikawa 2014).

EBV subtype of gastric carcinoma has favorable survival compared with other subtypes, especially in Asians (Liu 2015). To date, treatment for gastric carcinoma is similar for EBV positive and negative cases although new therapies based on epigenetic regulation (Nishikawa 2017), immunotherapy (Tashiro 2017) and developing lytic induction therapy (Kraus 2017, Kenney 2014) are being explored.

Nasopharyngeal carcinoma due to EBV

Nasopharyngeal carcinoma is a squamous cell or undifferentiated carcinoma caused by a combination of EBV infection, environmental influences and heredity. In Guangdong (Canton) in Southern China, it accounts for 18% of all cancers and has an incidence of 25 cases per 100,000, 25 times higher than the rest of the world (Wang 2013). It is also quite common in Taiwan. The regional differences may be due to the Southeast Asian diet of salted vegetables, fish and meat. Salt preservation is inefficient, leading to partially putrefied foods, which may accumulate significant levels of nitrosamines, a known carcinogen (Li 2016, Tan 2014).

The etiological role of EBV in the pathogenesis of nasopharyngeal carcinoma is unknown but involves attacks on networks in different cells at multiple points. Possible mechanisms are: (a) defective immune system presentation of EBV antigens to host immune cells based on the HLA locus at chromosome 6p, preventing an appropriate immune response, (b) clonal expansion of an EBV infected cell, (c) multiple somatic mutations of regulators of NFκB signaling, which drive the transformation of pre-invasive nasopharyngeal epithelial cells to cancer cells, (d) nitrosamine consumption may drive networks toward malignancy via other mechanisms (Tsao 2014, Tsao 2017).

Germ line variants in *MST1R* (Dai 2016) or *MLL3* (Sasaki 2015) are associated with nasopharyngeal carcinoma. Other studies show individuals with a first degree family history have a greater than fourfold increased risk of nasopharyngeal carcinoma but no excess risk of other malignancies (Liu 2017), which suggests a strong genetic predisposition or efficient cultural transmission of environmental exposures (Rottenberg 2017).

Radiation therapy is the mainstay of treatment, with chemotherapy used in advanced cases (He 2017, Chapman 2017). In a recent study, estimated 5 year overall survival and disease free survival (DFS) rates for all patients were 87.5% and 70.1%, respectively (Li 2017). Future treatments may also incorporate EBV DNA testing (Kim 2017) or dietary plant products such as grape seed proanthocyanidins (Yao 2016).

Cervical cancer due to HPV
Virtually all cervical cancers are associated with human papilloma virus (HPV) (Brianti 2017). As of 2012, cervical cancer was the fourth leading cancer in women worldwide and the seventh overall, with an estimated 528,000 new cases and 266,000 deaths, 87% of which occur in less developed regions. Mortality rates range from less than 2 per 100,000 in Western Asia, Western Europe and Australia / New Zealand to 22.2 per 100,000 in Middle Africa and 27.6 per 100,000 in Eastern Africa (IARC: Globocan 2012, accessed 8Dec17). In the U.S., cervical cancer is the 20th most common cause of cancer deaths, with 4,210 deaths projected in 2017 (Cancer Facts and Figures 2017).

Papillomaviruses were first identified in 1933 from rabbits as a transmissible, filterable cause of benign papilloma. In 1956, human papillomavirus (HPV) was first identified. It causes multiple human cancers including anogenital cancer, and its discovery by Harald zur Hausen led to his winning the 2008 Nobel Prize in Medicine (zur Hausen 1974, Dürst 1983).

Persistent HPV infection is the main cause of anogenital cancer, including cervical cancer, which is typically due to high risk HPV types 16 and 18. Their *E6* and *E7* genes immortalize human keratinocytes. The E6 protein binds p53, which promotes its ubiquitination and subsequent proteolysis, which diminishes its tumor suppressive and transcriptional properties. The E7 protein interacts with the retinoblastoma susceptibility gene product pRb and related proteins, releasing the transcriptional activator E2F from a complex with Rb, allowing E2F to activate genes engaged in cell cycle progression (The Nobel Prize in Physiology or Medicine 2008: Advanced Information, accessed 26Nov17).

HPV appears to be necessary but insufficient for developing cervical carcinoma. Although 65-100% of sexually active adults have been exposed to HPV (Pytynia 2014), most women with HPV do not develop cervical cancer (World Cancer Research Fund International, accessed 9Nov17); other cellular, immunological, genetic, epigenetic or environmental cofactors are required (Pedroza-Torres 2014). Cofactors include smoking, passive smoking (Roura 2014, Zeng 2012), *Chlamydia trachomatis* infection (Zhu 2016), burning wood in kitchen stoves or ovens (Ferrera 2000) and tar based vaginal douching (historically, Rotkin 1967).

Although the immune system typically clears HPV, organ transplant recipients and HIV infected patients have more severe and recalcitrant disease, higher viral loads, infections with unusual HPV genotypes and a greater propensity for HPV related malignancies (The Nobel Prize in Physiology or Medicine 2008: Advanced Information, accessed 26Nov17). Worsening immunodeficiency, even with only moderately decreased CD4+ cell counts, is a significant risk factor for cervical cancer (Clifford 2016). Specific HLA alleles are associated with an increased or reduced risk of cervical cancer (Hu 2014, Zhao 2013).

The HPV vaccine is safe and effective at reducing cervical cancer (Basu 2013) and has markedly reduced infection rates (Markowitz 2016, Kahn 2016). Routine vaccination at age 11 or 12 years is recommended by the (U.S.) Advisory Committee on Immunization Practices (Meites 2016).

Cervical cancer screening is recommended beginning at age 21 (American Cancer Society Guidelines 2016, accessed 9Nov17). Since subclinical genital HPV infection typically clears spontaneously, antiviral therapy is not recommended to eradicate subclinical HPV infection (Centers for Disease Control and Prevention: 2015 STD Guidelines, HPV, accessed 26Nov17). Treatment of precancerous lesions is surgical (WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention 2013, accessed 26Nov17). Treatment of invasive cancer is surgery or chemoradiation, based on clinical stage (NCI-Cervical Cancer Treatment (PDQ®)–Health Professional Version 2017, accessed 9Nov17).

Head and neck carcinoma due to HPV
Head and neck carcinoma is projected to cause 9,700 deaths in the U.S. in 2017 (oral cavity and pharynx: Siegel 2017, Table 1). There has been a rapid rise in oropharyngeal squamous cell cancer involving the tonsil and base of the tongue in men younger than age 50 with no history of tobacco or alcohol use (Sathish 2014, Khode 2014). Although historically tobacco and alcohol use caused 75-80% of all oral cavity cancers in the U.S. (Khode 2014), HPV prevalence in oropharyngeal cancers rose from 16.3% during 1984-1989 to 71.7% during 2000-2004, with similar increases reported in many European countries. In Sweden, 90% of oral squamous cell carcinomas are HPV positive (Sathish 2014). The reasons for the increase are unknown. Transmission of HPV is primarily through sexual contact and oral-genital contact can lead to oral / oropharyngeal HPV infection (Pytynia 2014). HPV can also be transmitted by less intimate skin to skin contact. Although the increased incidence of HPV associated head and neck cancer could be attributable to increased oral sex practices and more oral sex partners, HPV positive oral squamous cell carcinoma is documented in patients reporting very few oral sexual partners and 8-40% of patients report never having had oral sex. In addition the plausible reasons for the increased incidence of HPV associated oropharyngeal cancers in men, with no substantial rise among women, are unclear (Sathish 2014).

The pathogenesis of HPV associated head and neck carcinoma appears similar to that of cervical cancer. HPV proteins E6, E7 and E5 induce cell cycle progression of differentiated oral squamous epithelial cells, causing deregulated proliferation, loss of apoptosis, genomic instability and transformation to cancer (Sathish 2014).

Other risk factors for oropharyngeal squamous cell carcinoma include smoking, HIV infection, more than 8-10 sexual partners and more than four oral sexual partners (Pytynia 2014). Vaccines prevent infection with HPV16 and HPV18 but vaccination after

development of cancer is unlikely to provide clinical benefit as expression of the capsid proteins is usually lost during transformation (Blitzer 2014).

Cutaneous squamous cell carcinoma due to HPV
HPV may be an important factor for some cutaneous squamous cell carcinomas, particularly in the immunocompromised (Nichols 2017, Wang 2014) . More than 200 HPV types have been identified and classified into five genera, α, β, γ, μ and ν (McLaughlin-Drubin 2015). HPV from the β genus, considered a commensal organism acquired shortly after birth, is suspected to play a role in the development of cutaneous squamous cell carcinoma (Farzan 2013). Although the main risk factor for nonmelanoma skin cancer is UV radiation, immunosuppressed individuals have β HPV loads 100 times higher than immunocompetent persons (Moscicki 2017). Immunosuppressive agents vary in their association with cutaneous squamous cell carcinoma - mTOR inhibitors are actually associated with a decreased risk of developing post transplant nonmelanoma skin cancers (Jung 2016). Treatment options for post transplant cutaneous squamous cell carcinoma include electrodessication and curettage, excision, Mohs surgery, systemic retinoid therapy, topical therapy and radiation therapy (Chockalingam 2015).

Epidermodysplasia verruciformis is a rare genodermatosis associated with a high risk of cutaneous carcinoma (Orth 2006) and abnormal susceptibility to cutaneous β HPV infections. Homozygous inactivating mutations in *TMC6* (*EVER1*) and *TMC8* (*EVER2*) account for 75% of affected individuals; mutations in *RHOH*, *MST1*, *CORO1A* and *IL7* cause extensive β HPV replication and an epidermodysplasia verruciformis-like phenotype (Przybyszewska 2017).

Kaposi sarcoma due to HHV8
Kaposi sarcoma, the most common malignancy in untreated HIV patients, is caused by Kaposi sarcoma associated herpesvirus (KSHV / HHV8) (Chang 1994, Ganem 2006). It is characterized by abnormal neoangiogenesis, inflammation and proliferation of spindle cells, known as Kaposi sarcoma spindle cells, which have an endothelial cell origin and are phenotypically similar to lymphatic endothelial cells but poorly differentiated (Cancian 2013). HHV8 reprograms the host endothelial cells by upregulating lymphatic vessel endothelial receptor 1 (LYVE1), podoplanin and vascular endothelial growth factor receptor 3 (Radu 2013).

HHV8 infection alone is insufficient to cause Kaposi sarcoma; progression requires host immune dysfunction and an appropriate local inflammatory milieu. Like other herpesviruses, HHV8 remains latent within cells and has developed a variety of mechanisms to evade the host immune system (Radu 2013) but infection is typically associated with immunodeficiency states, including HIV infection, iatrogenic immunodeficiency and aging (Kaplan 2013).

AIDS associated KS has declined dramatically since the introduction of combination antiretroviral therapy in 1996 but remains the most common malignancy in HIV infected individuals and is a significant problem in sub-Saharan Africa where combination antiretroviral therapy is unavailable. The classic form of Kaposi sarcoma is occasionally seen in older individuals from endemic HHV8 regions (Kaplan 2013).

Merkel cell carcinoma due to Merkel cell polyoma virus
Merkel cell carcinoma is the eponym for primary cutaneous neuroendocrine carcinoma, a dermal malignancy which is typically due to a well defined mutated form of the Merkel cell polyoma virus (Feng 2008, Moore 2014) although some cases are not viral associated (Tothill 2015). This uncommon and aggressive tumor typically occurs in the head and neck of the elderly in actinic damaged skin. It has an estimated disease associated mortality between 33% and 46% and is now the second most common cause of skin cancer death in the U.S. after melanoma, with a 333% increase in deaths from 1986 to 2011, due to increased incidence (Schadendorf 2017). It tends to recur and cause local and distant metastases; distal metastases are usually fatal (Medscape: Skin Cancer - Merkel Cell Carcinoma, accessed 10Nov17).

The Merkel cell is found in the basal layer of the epidermis, parallel to the surface. These cells function as mechanoreceptors in skin and cluster in areas of sensory perception, such as fingertips, tactile hair follicles and the tip of the nose (Halata 2003). The Merkel cell virus is part of the normal viral skin flora but is usually clinically silent. Merkel cell carcinoma, similar to Kaposi sarcoma, is sensitive to immune surveillance and occurs more frequently in AIDS and transplant recipients (Moore 2014). Increased risk for carcinoma occurs when an individual is infected (common), loses immune surveillance against MCV proteins (uncommon) and when the virus undergoes a precise set of mutations (rare) (Moore 2014).

Merkel cell carcinoma has two viral products, the large T and small T antigens, which have cellular functions and targets in addition to those of other polyomavirus T antigens. The large T antigen facilitates the viral life cycle and also disables the Rb and p53 pathways. A small T domain region is required for transformation activity and also targets eukaryotic translation (Wendzicki 2015).

Surgery and radiotherapy achieve high rates of locoregional control but distant failure rates are high (Tothill 2015).

Section 2.5 Tobacco use

The American Cancer Society indicates that smoking is the world's leading preventable cause of death; in the U.S., it causes an estimated 480,000 annual premature deaths, including 42,000 from secondhand smoke exposure (Cancer Facts and Figures 2017, page 40). Excluding secondhand smoke, it is estimated to cause 32% of all cancer deaths. In the U.S., the Centers for Disease Control and Prevention indicates that cigarette smoking caused 163,700 annual cancer deaths during 2005-2009 (Tobacco-Related Mortality, accessed 10Nov17). The World Health Organization Global Report - Mortality Attributable to Tobacco, states that tobacco use is responsible for 22% of cancer deaths worldwide (WHO Report, accessed 10Nov17).

Cigarette smoking causes cancer by: (a) exposure to carcinogens and production of reactive oxygen species, (b) methylation of CpG sites (Sayols-Baixeras 2015), (c) DNA adduct formation, (d) accumulation of permanent somatic mutations in important genes leading to clonal outgrowth, (e) promotion of autophagy and premature aging in the host stromal microenvironment (Salem 2013) and (f) cancer associated inflammation linked with immune suppression (the mechanisms are discussed in more detail below). Of

note, smoking ***decreases*** the risk of endometrial cancer, possibly due to its association with a reduced body mass, decreased estrogen levels and earlier menopause (Zhou 2008, Felix 2014).

Tobacco smoke contains more than 60 carcinogens which react synergistically with respiratory particulates to generate reactive oxygen species, leading to oxidative stress and increased production of mediators of pulmonary inflammation (Valavanidis 2013). Although protected by enzymatic and nonenzymatic antioxidant defenses, an imbalance of prooxidants and antioxidants in the cellular environment can enhance reactive oxygen species production, which induces DNA damage, inhibits apoptosis and activates protooncogenes (Valavanidis 2013). In addition, due to the numerous carcinogens present, typically acting over decades, tobacco may created marked tumor heterogeneity by activating a myriad of different pathways at multiple sites within a tissue or organ (Fisher 2013). Thus, a reductionist strategy based on countering a specific pathway is unlikely to be effective long term. In contrast, targeting multiple pathways, the instability induced by these carcinogens or the reactive oxygen species imbalances may be more effective (Crawford 2017). To date, there is no specific therapy targeting tobacco smoke itself.

Most smokers do not get tobacco associated cancer; risks vary greatly between individuals. For example, a New York study projected ten year lung cancer risks ranging from 0.8% for a 51 year old woman who smoked one pack per day for 28 years and quit 9 years previously, compared with 15% for a 68 year old man who smoked two packs a day for 50 years and continued to smoke (Bach 2003).

According to the U.S. Surgeon General, smoking cessation is the only proven strategy to reduce the pathogenic processes leading to cancer because the specific impact of many tobacco carcinogens, alone or in combination, have not been identified (How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General 2010, Chapter 5). Within 5 years of quitting, the risk of cancer of the mouth, throat, esophagus and bladder is cut in half; within 10 years of quitting, the risk of dying from lung cancer drops by half (U.S. Centers for Disease Control and Preventing: Smoking and Cancer, accessed 19Nov17).

We discuss below the major causes of cancer death due to tobacco by site, ordered by a declining population attributable fraction (Siegel 2015-Table, see also The Health Consequences of Smoking - 50 Years of Progress, A Report of the Surgeon General 2014, at Table 12.1, page 652, PDF page 737). The population attributable fraction is the projected reduction in death or disease that would occur if exposure to a risk factor were reduced to an alternative ideal exposure scenario, such as tobacco use compared with no tobacco use (World Health Organization - Metrics: Population Attributable Fraction, accessed 25Nov17, Alberg 2013).

Lung cancer due to tobacco
Lung cancer is the leading cause of U.S. cancer death in men and women, with a projected 155,870 cancer deaths in 2017, representing 25% of all cancer deaths (Cancer Facts and Figures 2017, page 4). For lung cancer, 80-85% of deaths are attributable to smoking (How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General, accessed 10Nov17, Siegel 2015-Table). The lung cancer death rate has declined due to reductions in smoking, in men by 43% since 1990 and in women by 17% since 2002, with the rate of decline increasing in recent years. From 2010 to 2014, the rate decreased by 3.5% per year in men and by 2.0% per year in women (Cancer Facts and Figures 2017, page 19).

Cigarette smoking is by far the most important risk factor for lung cancer (Cancer Facts and Figures 2017, page 19) and risk increases with quantity and duration of smoking. Cigar and pipe smoking also increase the risk. Exposure to radon gas released from soil and building materials is the second leading cause of lung cancer in the U.S. but radon exposure is synergistic with smoking, as is asbestos exposure (Ngamwong 2015).

The pathways described above are important in lung carcinogenesis. Increased lung cancer risks due to cigarette smoking have been ascribed to: (a) various carcinogens including cigarette tar (Meyers 2017), polycyclic aromatic hydrocarbons, N-nitrosamines, aromatic amines, aldehydes and volatile organic compounds (Leon 2015, Hecht 2003), (b) alterations of DNA methylation (Fasanelli 2015), (c) DNA adduct formation (Wiencke 2002), which may persist when cellular repair systems are overwhelmed or otherwise not functioning efficiently (How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General, Chapter 5), (d) the propagation of genetic damage during clonal outgrowth, consistent with the accumulation of multiple genetic changes observed in lung cancer progression (Alexandrov 2016, How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General, Chapter 5, see Figure 5.1), (e) induction of premature aging and mitochondrial dysfunction in stromal fibroblasts, which actively promote anabolic tumor growth (Salem 2013), (f) suppression of the immune system by multiple mechanisms, including by modulating the tumor microenvironment (Lee 2012, Rodriguez-Vita 2010) through tumor cells co-opting signaling molecules of the innate immune system (Valavanidis 2013).

Numerous germ line changes are associated with lung cancer risk, affecting *CRP, GPC5* (Zhang 2015, Liu 2014) and *NFKB*1 genes (Shiels 2012), as well as cytochrome P450 2A6 (CYP2A6) activity (Park 2017) and DNA methylation levels (Levine 2015).

Treatment is surgery, chemoradiation therapy and targeted therapy. It is based on histologic subtype (most commonly small cell carcinoma, squamous cell carcinoma or adenocarcinoma) and results of molecular testing (NCCN Clinical Practice Guidelines in Oncology: Ettinger 2017). Five year survival varies by histology: 21% for nonsmall cell lung cancer versus 7% for small cell lung cancer; it also varies by stage: 55% if localized (16% of cases), 27% for regional disease and 4% for disseminated disease (55% of cases, Miller 2016).

Laryngeal cancer due to tobacco
Smoking is strongly associated with laryngeal cancer, with a population attributable fraction of 76.6% (Siegel 2015-Table) and an odds ratio of 21.7 for those with 60+ pack years of smoking compared with never smokers (Lubin 2010; see also Wyss 2013: odds ratio of 8.3, Franceschi 1990: odds ratio of 4.6). Alcohol consumption and smoking synergistically increase the risk by several mechanisms (How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A

Report of the Surgeon General, Chapter 5). First, alcohol inhibits the metabolism and clearance of NDMA, a nitrosamine and carcinogen in tobacco smoke, through competitive inhibition of the liver enzyme P450 2E1 (Swann 1984). Second, for some nitrosamines, alcohol induces the production of P450, which may increase metabolic activation of nitrosamines (McCoy 1979). Third, alcohol abuse is associated with deficiencies in folate, zinc and vitamin A, which can exacerbate the effects of smoking (How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General, Chapter 5). Finally, in the mouth, alcohol acts as a solvent, increasing absorption of tobacco carcinogens (Squier 1986).

Mechanisms of tobacco induced carcinogenesis identified in the larynx include DNA adduct formation (Szyfter 1996, Flamini 1998) and frequent mutations in *TP53* with patterns resembling lung cancer in smokers (Pfeifer 2002).

Polymorphism in *GSTM1* are related to the risk of laryngeal cancer (Zhang 2017).

Treatment is surgery and chemoradiation therapy and varies by stage (Laryngeal Cancer Treatment (PDQ®), accessed 25Nov17). Overall relative 5 year survival is 61%, varying from 76% for local disease, 45% for regional disease and 35% for distant disease (Cancer Facts and Figures 2017, page 21).

Esophageal squamous cell carcinoma due to tobacco
For esophageal cancer in the U.S. in 2011, 50.7% of 14,404 or 7,307 deaths were attributed to tobacco use (Siegel 2015-Table), with total esophageal cancer deaths projected to increase to 15,690 in 2017 (Cancer Facts and Figures 2017, page 4). This disease is 3 - 4 times more common among men than women. Smoking is strongly associated with squamous cell carcinoma and adenocarcinoma, the major subtypes. Squamous cell carcinoma is the most common type of esophageal cancer worldwide (Zhang 2013) but in the U.S., adenocarcinoma is more common in whites. Esophageal cancer makes up about 1% of all cancers diagnosed in the U.S. but it is much more common in Iran, northern China, India and southern Africa, where squamous cell carcinoma predominates.

The major risk factors for esophageal carcinoma are tobacco smoking and alcohol drinking, which act synergistically (Yaegashi 2014). Dietary carcinogens and low consumption of fruit and vegetables may be important risk factors in certain areas (Yang 2016). As indicated in section 1.7, gastroesophageal reflux is the major cause of esophageal adenocarcinoma (Yang 2016).

Possible mechanisms of tobacco related carcinogenesis in the esophagus include: (a) ingestion of tobacco condensates provides direct contact of tobacco specific nitrosamines and other tobacco carcinogens with the esophageal mucosa (Zhang 2013), (b) tobacco smoke contains carcinogenic polycyclic aromatic hydrocarbons and aromatic amines, which are converted by cytochrome P450 related enzymes into DNA reactive metabolites (Ohash 2015), (c) tobacco smoke upregulates cyclooxygenase 2 (Gong 2016), which promotes the progression from esophagitis to dysplasia to carcinoma (Huang 2011), and (d) tobacco promotes chronic inflammation associated genomic instability (Lin 2016).

Genetic polymorphism associated with tobacco related esophageal carcinogenesis involve the *CYP* (Bartsch 2000), *ADH1B* and *ALDH2* genes (Cui 2009, Zhang 2013).

The overall 5 year survival for all subtypes is 20% (American Cancer Society: Key Statistics for Esophageal Cancer, accessed 19Nov17). Early stage disease, with negligible risk of nodal metastases, can be cured by endoscopic resection of tumor, radiofrequency ablation or photodynamic therapy; surgical resection or chemoradiotherapy are required for more advanced disease (Ohashi 2015). Targeted therapy using EGFR inhibitors has shown early promising results (Saumel 2017). Nutrition management is often required, not as specific antitumor treatment but as supportive care (Mak 2017).

Oral cavity and pharyngeal cancer due to tobacco
Smoking is strongly associated with cancers of the oral cavity and pharynx, with a population attributable fraction of 47.0%; smoking caused 4,032 deaths due to oral cavity and pharynx cancer in the U.S. in 2011 (Siegel 2015-Table). There is also an increased risk due to cigar and pipe smoking (Wyss 2013, Franceschi 1990), and a markedly increased risk with smoking and alcohol use (Ferreira 2013).

Cigarette smoke mediates oral carcinogenesis primarily via reactive free radicals and volatile aldehydes (Nagler 2016, Choudhari 2014); in addition increased production of matrix metalloproteinases may be important (Allam 2011).

Stage I/II cancers of the lip and oral cavity are highly curable by surgery or radiation therapy. Stage III/IV disease typically receive both surgery and radiation therapy and clinical trials are recommended to prevent local recurrence and distant metastases. Small tumors have high cure rates; even moderately advanced tumors without nodal spread have cure rates up to 65%, which varies by site (Lip and Oral Cavity Cancer Treatment (PDQ®), accessed 25Nov17). Second primaries are common but isotretinoin may reduce their incidence (Kadakia 2017).

Bladder cancer due to tobacco
Smoking is the most well established risk factor for bladder cancer (Cancer Facts and Figures 2017, page 27), accounting for 44.8% of bladder cancer related deaths in 2011 (Siegel 2015-Table). There is a linearly increasing risk of bladder cancer with increasing duration of smoking, ranging from an odds ratio of 1.96 after 20 years of smoking to 5.57 after 60 years (Brennan 2000). Smoking cessation for 10 or more years reduces the risk (Rink 2013), but not completely (Mir 2013). Recent changes in cigarette composition may have increased the risk (Freedman 2011).

The increased risk of bladder cancer in smokers is attributable to aromatic amines in tobacco smoke, which cause DNA adduction and mutagenicity (Besaratinia 2013). Cigarette smoke may also promote epithelial-mesenchymal transition (Sun 2017).

Other cofactors for bladder carcinogenesis include diet and occupational factors (Al-Zalaban 2016), prostatitis, syphilis and hormone replacement therapy (Mir 2013), pelvic radiation, cyclophosphamide and birth defects. There is no association with HPV or polyoma virus (Polese 2012).

Some authors believe bladder cancer may be due to chronic inflammation associated with calculi (Chung 2013, Vermeulen 2015), prior urinary tract infections (Kantor 1984, Shih 2014), chronic indwelling urinary catheters (Ho 2015) or urinary tuberculosis (Lien 2013) although many studies have reported no association (González 1991, Jhamb 2007, Kjaer 1989). The discrepancy has been explained by possible recall and selection biases, as well as a greater detection of bladder cancer during workup of bladder infections or calculi (Chang 2010). There may be a multiplicative interaction of urinary tract infections with smoking (La Vecchia 1991), which may distort the apparent effect of minor contributors to the disease.

Nonmuscle invasive bladder cancer (stages Ta, Tis and T1) is treated with transurethral resection of the bladder tumor, followed by intravesical chemotherapy, with followup that may include intravesical bCG or other chemotherapy. Standard curative treatment for muscle invasive bladder cancer is either neoadjuvant multiagent cisplatin based chemotherapy followed by radical cystectomy and urinary diversion or radiation therapy with concomitant chemotherapy (Bladder Cancer Treatment (PDQ®), accessed 9Dec17). The 5 year relative survival by stage is: stage 0 - 98%, stage I - 88%, stage II - 63%, stage III - 46%, stage IV - 15% (American Cancer Society > Survival Rates for Bladder Cancer, accessed 25Nov17).

Liver and intrahepatic bile duct cancer due to tobacco
Tobacco use causes 23.6% of U.S. deaths due to liver and intrahepatic bile duct cancer, estimated at 5,060 deaths in 2011 (Siegel 2015-Table). Several constituents of tobacco smoke are known liver carcinogens in humans and experimental animals (Lee 2009), including 4-aminobiphenyl and polycyclic aromatic hydrocarbons (Wang 1998, Chen 2002).

The 5 year relative survival is: localized to liver (stage I, II, IIIA, IIIB) - 31%, regional (stage IIIC, IVA) - 11%, distant (stage IVB) - 3% (American Cancer Society > Survival Rates for Liver Cancer, accessed 25Nov17). Patients with early stage disease may be cured by liver transplantation, surgical resection or radiofrequency ablation; other patients receive palliative or supportive treatment (Adult Primary Liver Cancer Treatment (PDQ®), accessed 25Nov17).

Cervical cancer due to tobacco
Tobacco use causes 22.2% of U.S. deaths due to cervical cancer, or 862 deaths in the U.S. in 2011 (Siegel 2015-Table). Smokers have an excess risk of cervical squamous cell carcinoma that persists after controlling for the strong effect of HPV, the most important risk factor for cervical cancer, and for other potential cofactors (Fonseca-Moutinho 2011).

Cervical mucus of smokers contains measurable amounts of nicotine, other cigarette constituents and their metabolites, such as aromatic polycyclic hydrocarbons and aromatic amines (Fonseca-Moutinho 2011), which may cause DNA adduct formation (Simons 1993). In addition benzo[a]pyrene, a major carcinogen in cigarette smoke, is detected in the cervical mucus and may interact with HPV to enhance viral persistence and promote carcinogenesis (Alam 2008).

Cervical cancer risk in smokers may be modified by genetic variants in activated T helper cytokine genes (Hardikar 2015) and other immune response genes (Mehta 2017). Cervical neoplasia is also associated with HLA haplotype (Leo 2017).

During treatment, women with cervical carcinoma frequently do not quit smoking or decrease tobacco consumption (Waggoner 2010) although providing counseling (Chang 2017), educational materials and staff training can be helpful (duPont 2016).

Stomach cancer due to tobacco
Tobacco use causes 19.6% of U.S. deaths due to gastric carcinoma or an estimated 2,131 deaths in 2011 (Siegel 2015-Table). Worldwide, it is estimated to cause 11% of gastric carcinoma cases or 80,000 cases annually (Trédaniel 1997). The risk of stomach cancer among smokers varies from 1.59 to 1.98 in men and 1.11 to 1.78 in women (Trédaniel 1997, Nomura 2012) with consistency across five ethnic groups, and evidence of a dose response effect in both sexes.

This increased risk may be mediated by polycyclic aromatic hydrocarbons or their metabolite 1-OHPG (Liao 2014).

Smoking may be synergistic with *H. pylori* bacterial load and virulence factors to increase the risk of intestinal metaplasia and gastric cancer (Santibáñez 2015).

Smoking cessation reduces the risk but it remains significantly increased up to 14 years after cessation (Koizumi 2004). For patients undergoing gastric cancer surgery, preoperative smoking cessation can reduce postoperative complications (Jung 2015).

Renal cell carcinoma due to tobacco
Tobacco use causes 16.8% of U.S. deaths due to renal cell carcinoma, estimated at 2,253 deaths in 2011 (Siegel 2015-Table). This increased risk applies to clear cell and papillary renal cell carcinoma but not chromophobe renal cell carcinoma, suggesting that these subtypes have distinct carcinogenic mechanisms (Patel 2015).

Metabolism of tobacco carcinogens in renal cell carcinoma include: (a) creation of highly reactive metabolites that damage DNA, such as N-nitrosamines (Kabaria 2016), (b) inducement of chromosome 3p aberrations, the most frequently identified genetic alterations in renal cell carcinoma, by benzo[α]pyrene diol epoxide, a major constituent of cigarette smoke (Kabaria 2016) and (c) nicotine induced tumor growth (Heeschen 2001).

Acute myeloid leukemia in adults, due to tobacco
Tobacco use causes 14.6% of U.S. deaths due to acute myeloid leukemia in adults, estimated at 1,317 deaths in 2011 (Siegel 2015-Table). A recent meta-analysis concluded that the relative risk was increased regardless of sex and geographical region, with

risks of 1.27, 1.36, 1.55, and 1.77 for <10, 10 to 20, 20 to 30, and >30 cigarettes per day. Relative risk also increased with duration of smoking in pack years (Fircanis 2014, Brownson 1993).

This association may be mediated through benzene in tobacco smoke, which has been strongly associated with leukemogenesis (Snyder 2012). Benzene may act by formation of DNA adducts, or through its metabolite 1,4-benzoquinone, which inhibits topoisomerase II, which typically prevents DNA mutations by annealing DNA strand breaks (Snyder 2012). This mechanism is important to understand because chemotherapy using topoisomerase II inhibitors may cause secondary leukemia which resembles benzene induced leukemia. Other possible mechanisms include an increased production of inflammatory mediators due to smoking (Zhou 2011, Fircanis 2014)

Pancreatic adenocarcinoma due to tobacco
Pancreatic cancer is the third leading cause of U.S. cancer death after lung and colon cancer (Rahib 2014). Cigarette smoking causes from 11-32% of pancreatic cancer cases / deaths (Siegel 2015-Table; Parkin 2011, Maisonneuve 2015). Cigar and pipe smoking also increase risk, as does using smokeless tobacco.

Tobacco promotes pancreatic carcinogenesis through: (a) unknown smoking compounds which inhibit apoptosis and autophagy (Park 2013), (b) nicotine, which promotes tumor growth and metastasis (Delitto 2016), (c) an increase in mutations, not in known driver genes (*KRAS, TP53*, *CDKN2A/p16*, *SMAD4*) but in less commonly mutated genes (Edderkaoui 2013), (d) induction of inflammation and fibrosis, which lead to inhibition of cell death, stimulation of proliferation and a microenvironment which supports tumor growth (Pandol 2012, Edderkaoui 2016).

Due to the tumor heterogeneity created by tobacco use, personalized treatment targeting multiple pathways might be more effective (Cros 2017).

Heavy drinkers may have an increased risk of pancreatic cancer (Yadav 2013) although it is difficult to implicate alcohol as an independent risk factor because of its close association with smoking. Heavy alcohol consumption may potentiate tobacco smoking (Rahman 2015), poor nutrition (Yellow 2017) and inflammatory pathways related to chronic pancreatitis although it may also have independent genetic and epigenetic effects. Animal and human studies of tobacco and alcohol related pancreatic carcinogenesis suggest multimodal, overlapping mechanistic pathways (Duell 2012).

In addition a proinflammatory diet, described in section 4.0, increases the risk of pancreatic cancer (Shivappa 2015d, Ilic 2016), and may be a cofactor with cigarette smoking and diabetes to increase risk beyond that of any of these factors alone (Antwi 2016).

Colorectal carcinoma due to tobacco
Tobacco use causes 9.7% of U.S. deaths due to colorectal carcinoma, estimated at 4,969 deaths in 2011 (Siegel 2015-Table), with similar increased risks in Norway (Parajuli 2014) although no association was found in Korean women (Cho 2015). Smoking is associated with an elevated risk of synchronous colorectal carcinoma, suggesting that it creates a field effect favoring multiple primary tumors (Drew 2017).

Possible mechanisms of tobacco associated colorectal carcinoma include epigenetic modification (Limsu 2010) or altering expression of cell cycle proteins, proapoptotic proteins, epithelial-mesenchymal transition markers and cathepsin D expression (Kim 2017).

Genetic variants in spindle assembly checkpoint genes, which can drive aneuploidy, can significantly interact with smoking to enhance colorectal carcinoma risk (Zhong 2015).

Section 2.6 Occupational exposure to carcinogens

Occupational exposure to carcinogens causes 4% of U.S. cancer cases although government regulations have greatly reduced occupational exposure over the past several decades (American Cancer Society: Occupation and Cancer 2016, accessed 10Nov17). Worldwide, an estimated 3-6% of cancer cases are caused by workplace carcinogen exposure (Blot 2015). Examples include chemicals (benzene, nickel compounds, vinyl chloride), dusts (leather or wood dusts, silica, asbestos), radiation (sunlight, radon gas, industrial, medical or other exposure to ionizing radiation) and industrial processes (aluminum production, iron and steel foundry work, underground mining with exposure to uranium or radon) (American Cancer Society: Occupation and Cancer 2016, accessed 10Nov17). A list of cancers associated with occupational exposure is at Institution of Occupational Safety and Health, UK 2017, accessed 10Nov17. All of these cancers are preventable through elimination of exposure.

Lung cancer due to asbestos
The 2009 IARC working group concluded that all forms of asbestos cause lung cancer while acknowledging that controversies remain regarding the potency differences for different types and dimensions of fibers. The standardized mortality ratio ranges from 1.11 to 1.96 (Hein 2007, IARC monographs - 100C - Asbestos, Field 2012). Duration of exposure was not reported.

Asbestos is not currently mined in the U.S. and its use in 2011 was similar to the level of use in 1909. However, occupational exposure still occurs in those working with asbestos insulation, automotive repair and maintenance, building maintenance and building demolition (Field 2012). The primary source of exposure for the general public is building materials, insulation, brake linings, demolition of older buildings, waste sites, asbestos related industries, contaminated vermiculite, exposure to talc containing asbestos and contact with asbestos workers or their clothes (Field 2012).

The presence of asbestos fibers in the lungs sets off responses leading to inflammation, cell and tissue damage. How asbestos causes disease is not fully understood but it is suspected that long and thin fibers are more potent than short and thick fibers (IARC monographs - 100C - Asbestos). Three hypotheses are direct interaction with cellular chromosomes, generation of reactive

oxygen species and inflammation or other cell mediated mechanisms (Agency for Toxic Substances and Disease Registry: Asbestos Toxicity How Does Asbestos Induce Pathogenic Changes?, accessed 10Nov17).

Mesothelioma due to asbestos
Malignant pleural mesothelioma (MPM) is a rare and aggressive cancer caused by asbestos exposure. Its frequency is dramatically higher in asbestos polluted areas, as exemplified by the epidemic in Casale Monferrato, Italy, caused by an asbestos cement factory (1907-1986). In this area, the average annual MPM incidence in 2009-2013 was 51.2 cases per 100K among men and 20.2 among women, 10 times higher than the national average (Betti 2017). Many with no known exposure likely had unrecognized exposure (Musk 2017). A Swedish asbestos ban in 1982 did not reduce mesothelioma incidence through 2009 (Plato 2016). In the U.S., with up to 3,000 annual deaths due to mesothelioma, the rate of asbestos associated mesothelioma is increasing among women due to better investigation into their histories of asbestos exposure, which shows bystander, incidental or take home exposures (Lemen 2016).

Asbestos induces mesothelioma by directly interfering with mitotic spindle formation, by inducing chronic inflammation and the production of cytokines and through generation of reactive oxygen species by activated macrophages. Reactive oxygen species are also generated by the iron contained in asbestos fibers (Betti 2017).

Germ line variants in several genes may increase susceptibility to pleural mesothelioma in the presence of asbestos exposure (Betti 2017).

Recommended treatment, based on extent of disease, includes radical surgery (extrapulmonary pneumonectomy or radical pleurectomy with decortication), with or without chemotherapy and radiation. However median survival typically does not exceed 2 years (NIH > NCI > Malignant Mesothelioma Treatment (PDQ®), accessed 25Nov17, Verma 2017).

Bladder cancer due to aromatic amines or other occupational toxin exposure
Approximately 7% of bladder cancer cases in men are associated with occupational exposure (Lukas 2017). The most notable risk factor is exposure to aromatic amines (2-naphthylamine, 4-aminobiphenyl and benzidine) and 4,4'-methylenebis (2-chloroaniline) found in the chemical, dye, leather, aluminum and rubber industries as well as in hair dyes, paints, fungicides, cigarette smoke, plastics, metals and motor vehicle exhaust (Letašiová 2012, Cancer Facts and Figures 2017, page 27, Medscape, Bladder Cancer, accessed 10Nov17).

Exposure to arsenic in drinking water at concentrations higher than 300 µg/l is strongly associated with bladder cancer. There may also be an effect from other sources of arsenic exposure such as air, food, occupational hazards and tobacco (Letašiová 2012).

The pathophysiology of aromatic amines in the genesis of bladder cancer is not fully understood although aromatic amines are involved in DNA adduction and mutagenicity (Besaratinia 2013).

Mechanisms of arsenic induced bladder carcinogenesis include: (a) arsenic interferes with DNA damage repair and chromosomal structure, leading to genomic instability, (b) arsenic places a high demand on the cellular methyl pool, leading to global hypomethylation and hypermethylation of specific gene promoters, which deregulates oncogenic and tumor suppressive genes, (c) arsenic causes aberrant expression of noncoding RNAs and disrupts signaling pathways (Sage 2017), (d) arsenic inhibits indirectly sulfhydryl containing enzymes and interferes with cellular metabolism such as cytotoxicity, genotoxicity and inhibition of enzymes with antioxidant function (Letašiová 2012).

Bladder cancer risk is also associated with polymorphisms in the *GSTM1* and *UGT1A* genes (Lukas 2017).

Section 2.7 Alcohol
The America Society of Clinical Oncology recently stated:

"The importance of alcohol drinking as a contributing factor to the overall cancer burden is often underappreciated. In fact, alcohol drinking is an established risk factor for several malignancies. As a potentially modifiable risk factor for cancer, addressing high-risk alcohol use is one strategy to reduce the burden of cancer. For example, in 2012, 5.5% of all new cancer occurrences and 5.8% of all cancer deaths worldwide were estimated to be attributable to alcohol.[1] In the U.S., it has been estimated that 3.5% of all cancer deaths are attributable to drinking alcohol.[2] Alcohol is causally associated with oropharyngeal and larynx cancer, esophageal cancer, hepatocellular carcinoma, breast cancer, and colon cancer.[3] Even modest use of alcohol may increase cancer risk but the greatest risks are observed with heavy, long-term use." LoConte 2017

Based on 2009 data, in the U.S., 3.5% of total cancer deaths are alcohol related, totaling 19,500 cancer deaths (NIH > NCI > Alcohol and Cancer Risk, accessed 12Nov17, Nelson 2013). The IARC has classified alcohol consumption as carcinogenic (IARC Monograph, Volume 44, 1988, IARC monographs 100E, 2012), citing "sufficient evidence" for cancers of the oral cavity, pharynx, larynx, esophagus and liver. A 2010 update added cancers of the colorectum and female breast (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 96, Alcohol Consumption and Ethyl Carbamate 2010, Table of Risks by Site). Similarly, the National Toxicology Program of the U.S. Department of Health and Human Services lists consumption of alcoholic beverages as a known human carcinogen (14th Report on Carcinogens 2016, file is 26 MB in zip form). The more alcohol a person drinks, particularly regularly over time, the higher the risk of developing an alcohol associated cancer. No level of alcohol consumption is considered safe with respect to cancer risk; any reduction in consumption will reduce cancer risk (Grundy 2016, World Cancer Report 2014, page 103).

The mechanisms of action between alcohol and cancer are: (a) metabolization to acetaldehyde, which damages DNA and proteins, (b) generating reactive oxygen species which can damage DNA, proteins and lipids, (c) impairing the ability to break down and

absorb vitamins A, B complex, C, D, E and carotenoids, (d) increasing blood levels of estrogen, and (e) alcoholic beverages may contain nitrosamines, asbestos fibers, phenols and hydrocarbons (NIH > NCI > Alcohol and Cancer Risk, accessed 10Nov17).

The risk of head and neck cancers decreases after cessation of drinking (World Cancer Report 2014, page 97) but the relationship at other sites may be more complex (for example, individuals may stop drinking due to cancer related symptom (LoConte 2017)

Head and neck cancer (oral cavity, pharynx, larynx) due to alcohol
Alcohol consumption is a major risk factor for head and neck cancer, particularly in the oral cavity (excluding the lips), pharynx and larynx (Baan 2007). The relative risk of cancers of the oral cavity and pharynx from alcohol consumption is 3.2 to 9.2 for more than 60 g/day (>4 drinks/day) when adjusted for tobacco smoking and other potential confounders (Goldstein 2010); another study showed a 2-3 times increased risk from those who consume 50+ grams of alcohol per day (3.5+ drinks per day) (Baan 2007).

The risk of these cancers is substantially higher among those who also use tobacco (Hashibe 2009, NIH > NCI > Alcohol, accessed 10Nov17, Maasland 2014). For French patients, the population attributable risks for oral cavity cancer was 0.3% for alcohol alone, 12.7% for tobacco alone and 69.9% for their joint consumption (Radoï 2015).

There is an increased incidence of cancer of the oral cavity and esophagus in ALDH2 deficient individuals who drink chronically although oral hygiene also is relevant (Tsai 2014). Alcohol is quickly absorbed through the stomach and duodenum into the blood. It is metabolized mainly in the liver via oxidation into acetaldehyde by ADH, CYP2E1 and catalase, then into acetate by ALDH. ALDH2 metabolizes acetaldehyde to nontoxic substances. Many people of East Asian descent carry an *ALDH2* variant that codes for a defective form of the enzyme leading to accumulation of acetaldehyde, which causes such unpleasant effects (including facial flushing and heart palpitations) that they do not consume large amounts of alcohol and so have a low risk of alcohol related cancers (NIH > NCI > Alcohol and Cancer Risk, accessed 10Nov17). However, those who become tolerant to these side effects and consume large amounts of alcohol have a higher risk of alcohol related head and neck cancers than individuals with the fully active enzyme who drink comparable amounts of alcohol. The risk of oral cancer for those with high risk genotypes of alcohol and aldehyde dehydrogenases also increases for light drinkers who also smoke (Varoni 2015). Other risk factors, described above, also interact with the carcinogen acetaldehyde to promote transformation of epithelial cells in the head and neck.

Esophageal squamous cell carcinoma due to alcohol
Alcohol is a major risk factor for esophageal squamous cell carcinoma, the most prevalent histological subtype of esophageal cancer worldwide. The relative risk for heavy daily drinkers (50g to 75g) ranges from 4.95 to 7.65 (Bagnardi 2015, Vioque 2008).

Proposed mechanisms of carcinogenicity are: (a) nutritional deficiencies and disturbance of systemic metabolism of retinoids, zinc, iron and methyl groups, (b) ethanol metabolism in oro-esophageal squamous epithelial cells generates reactive oxygen species and produces oxidative damage, and may also disturb fatty acid metabolism, (c) disturbance of signaling pathways in squamous epithelial cells by changing membrane fluidity and shape, which may impact multiple signaling pathways (Liu 2015), and (d) mutagenicity of acetaldehyde, the primary metabolite of ethanol, due to its ability to form DNA adducts (Peng 2016).

Polymorphisms of the alcohol dehydrogenase and aldehyde dehydrogenase gene families, the major enzymes that metabolize ethanol, alter enzymatic activity, cause individual variations in acetaldehyde exposure and affect alcohol carcinogenicity (Peng 2016) as do some polymorphisms of genes only indirectly involved with ethanol metabolism such as methylenetetrahydrofolate reductase (see Table).

See also section 2.5 (esophageal squamous cell carcinoma due to tobacco).

Liver cancer (hepatocellular carcinoma) due to alcohol
Consumption of alcoholic beverages is an independent risk factor for liver cancer (Grewal 2012). It causes 18% (current consumption) to 33% (former consumption) of cases of hepatocellular carcinoma in selected European countries (Schütze 2011), compared with 4.1% in Alberta (Grundy 2012, Table 5). After cessation, the risk of liver cancer decreases by 6-7% a year; after 23 years, the risk becomes identical to that of non-drinkers (Heckley 2011).

Mechanisms of action include: (a) metabolic generation of acetaldehyde and induction of CYP2E1, which generate reactive oxygen species (Wang 2015), (b) lipid peroxidation and DNA strand breaks, (c) indirect effects by causing cirrhosis (Testino 2014), (d) hypomethylation of DNA and (e) interplay of alcohol with the immune system, inflammation and neoangiogenesis (Sidharthan 2014).

Colorectal cancer due to alcohol
Alcohol consumption is associated with a modestly increased risk of cancer of the colorectum in men, and in many studies in women. Meta-analyses show increased risk from heavy alcohol use (50+ grams / 3.5 drinks of alcohol per day (NIH > NCI > Alcohol and Cancer Risk, accessed 11Nov17), moderate and heavy drinking (Fedirko 2011) and any alcohol use more than occasional, with a significant dose response relationship (Wang 2015). In Alberta, alcohol is estimated to cause 3.9% of colorectal cancer cases (Grundy 2016, Table 5).

Proposed mechanisms of action include: (a) high levels of acetaldehyde degrades folate, a nutrient that may reduce the risk for colorectal cancer (Homann 2000), (b) chronic alcohol consumption is a methyl group antagonist, producing genomic DNA hypomethylation, an early step in colonic carcinogenesis (Choi 1999, Nishihara 2014), (c) immune suppression, (d) delay of DNA repair, (e) activation of liver procarcinogens by induction of cytochrome P450 enzymes and (f) changes in bile acid composition (Kune 1992, Wang 2015).

Breast cancer due to alcohol
Moderate alcohol consumption is linked to a 30-50% increased risk in breast cancer (McDonald 2013). Heavy consumption (45 grams or 3 drinks per day) has the highest risk although very light, low and moderate consumption also increases the risk (Choi

2017, Allen 2009, NIH > NCI > Alcohol and Cancer Risk, accessed 11Nov17). There is an additional risk associated with heavy episodic drinking (White 2017). These findings apply to African American women as well as women of European descent (Williams 2017). In one study, the increased risk was limited to ER+ invasive lobular or ductal carcinoma (Baglia 2017). In Alberta, alcohol is estimated to contribute to 3% of breast cancer cases (Grundy 2016, Table 5).

The precise mechanism of alcohol in promoting breast cancer is unclear. Possible mechanisms include: (a) promoting increased estrogen levels (Oyesanmi 2010), (b) inducing oxidative damage, (c) affecting folate and one carbon metabolism pathways (Dumitrescu 2005, Singletary 2001, McDonald 2013), and (d) producing acetaldehyde, an ethanol metabolite typically produced by the liver. It is also regulated and expressed in breast where it may create genomic instability by (i) binding proteins and DNA, (ii) interfering with the anti-oxidative defense system, (iii) interfering with DNA synthesis and repair and (iv) affecting epigenetic histones and DNA methylation.

Section 3.0 Reproductive hormones

In this section, we describe how constitutive expression of estrogen, testosterone and their metabolites promote carcinoma of the breast, endometrium and prostate by stimulating cellular proliferation through receptor mediated pathways, which increases cellularity instability. As these risk factors are almost universal, cofactors are particularly important and include years of hormone exposure, increasing age, germ line variations in cancer susceptibility genes and the extent of other chronic stressors. It is unclear why this association does not exist with other hormones that are regularly produced (excluding insulin, see section 3.4); we hypothesize that the stem cells affected by the sex hormones are more prone to instability compared to other hormones, or are less likely to destroy proliferating cells.

Section 3.1 Breast carcinoma due to chronic estrogenic stimulation

In American women, breast cancer is the second leading cause of cancer death after lung cancer. In 2017, there will be an estimated 41,070 breast cancer deaths (40,610 women, 460 men). During 1989 to 2014, the female breast cancer death rate declined by 38% due to improvements in early detection and treatment (Cancer Facts and Figures 2017).

Many breast cancer risk factors are associated with lifetime exposure of breast tissue to hormones, including a long menstrual history, recent use of oral contraceptives, never having children, having a first child after age 30, high natural levels of sex hormones and postmenopausal hormone use (combined estrogen and progestin). Other factors that influence hormonal levels include weight gain after age 18, being overweight or obese (for postmenopausal breast cancer), physical inactivity and alcohol consumption. Factors associated with a decreased risk include breastfeeding for at least one year, regular moderate or vigorous physical activity and maintaining a healthy body weight (Cancer Facts and Figures 2017).

Endogenous estrogens are associated with breast cancer in postmenopausal women (Key 2002, Tamimi 2007) but this relationship has not been firmly established in premenopausal women, possibly due to the large variations in hormone levels during the menstrual cycle, the small number of studies and the small number of cases of premenopausal breast cancer.

The proposed mechanisms of breast carcinogenesis due to estrogen are: (a) stimulation of cellular proliferation through receptor mediated signaling pathways, (b) direct genotoxic effects by increasing mutation rates through cytochrome P450 mediated metabolic activation, (c) induction of aneuploidy (Russo 2006), (d) formation of DNA adducts (Gaikwad 2013) and (e) carcinogenicity of 17 beta-estradiol (E2), the predominant circulating ovarian estrogenic steroid (Russo 2002).

Germ line mutations in 7 breast cancer susceptibility genes or gene sets with high penetrance (relative risk >5) are associated with increased breast cancer risk: *BRCA1* and *BRCA2* (DNA damage repair), *CDH1* (E-cadherin), *PTEN* (tumor suppressor phosphatase and tensin homolog), *SKT11* (serine threonine kinase), *TP53 (*tumor suppressor) and DNA mismatch repair genes (*MLH1*, *MSH2/6*, and *PMS2)*. Germ line mutations in *BRCA1* and *TP53* are predominantly associated with invasive ductal carcinoma while *BRCA2* germ line mutations are associated with both ductal and lobular cancers. Fifty percent of women with *CDH1* mutations develop invasive lobular carcinoma but not invasive ductal carcinoma (Dossus 2015). Cumulatively, these genes are drivers of carcinogenesis in only 5-10% of breast cancer cases (Matthews 2016).

One could logically explain, after the fact, why mutations in these genes may promote malignancy based on their functions: DNA damage repair - *BRCA1*, *BRCA2 and DNA* mismatch repair genes; promotion of apoptosis - *TP53* and *STK11*; regulation of cell proliferation and survival - *PTEN*; mediation of cell-cell adhesion - *CDH1* (Berx 2001). Our analysis based on complexity theory suggests that what is most important is the chronic disturbance of the delicate balance of networks that maintains physiologic stability throughout the diverse repertoire of cell activities and these genes just happen to be in sensitive positions in the web of network activity.

Genetic polymorphisms in estrogen metabolism enzymes may also modify breast cancer risk (Samavat 2015). In addition genome wide association studies have identified 80 low and moderate penetrance variants, which explain 50% of the heritability of breast cancer (Skol 2016), supporting our hypothesis that the disturbances in network activity may be more important than the specific part of the networks that is disturbed.

Epidemiological evidence suggests that postmenopausal breast cancer risk might be reduced by lowering lifetime exposure to estrogens through changes in lifestyle and reproductive behavior; as a practical matter, this means reducing body mass to below 25 kg/m^2, minimizing alcohol consumption and engaging in regular physical exercise. Long term hormone replacement therapy should be avoided unless there are strong clinical indications. Extended breastfeeding produces a small decrease in breast cancer risk, in addition to benefits for the child (Travis 2003).

Selective estrogen receptor modulators, including tamoxifen and raloxifene, reduce breast cancer in women at high risk (Thorat 2017). Aromatase inhibitors, which block the production of estrogens from androgens, also prevent breast cancer (Chumsri 2015, Costa 2017).

Section 3.2 Endometrial carcinoma due to estrogens

High levels of estrogen are a strong risk factor for endometrial carcinoma, which will kill an estimated 10,920 U.S. women in 2017. From 2005 to 2014, the death rate for endometrial cancer increased 1% per year among white women and 2% per year among black women (Cancer Facts and Figures 2017).

Risk factors for endometrial carcinoma include clinical factors that increase circulating estrogen, including obesity (androgens are aromatized to estradiol in adipose tissue), abdominal fatness, postmenopausal estrogen, late menopause, never having children and a history of polycystic ovary syndrome (Li 2014). Sedentary behavior is also a risk factor, mediated through associated obesity (Schmid 2014) and possibly higher estrogen levels (Oh 2017). Tamoxifen increases risk slightly because it has estrogen-like effects on the uterus. Medical conditions that increase risk include Lynch syndrome and diabetes. Factors that decrease unopposed estrogen are associated with reduced risk and include pregnancy, use of oral contraceptives and intrauterine devices (Cancer Facts and Figures 2017).

Continuous estrogenic exposure promotes proliferation of endometrium, leading to hyperplasia (Plaza-Parrochia 2017), a relatively unstable hierarchy, which may combine with other sources of chronic stress to bring about malignancy. The precise mechanism is unknown (Banno 2014). Endometrial carcinoma has been divided into type I and more aggressive type II tumors but they share common risk factors and may have similar etiologic mechanisms (Setiawan 2013).

There is a markedly increased risk of endometrial cancer in patients with a family history (Johnatty 2017) and with germ line mutations in mismatch repair genes, including Lynch syndrome (Banno 2014).

Metformin combined with oral contraceptives may reverse atypical endometrial hyperplasia in women with polycystic ovary syndrome and insulin resistance, as well as reverting early endometrial carcinoma to normal endometria, perhaps by stimulating insulin activity (Shao 2014).

Section 3.3 Prostate adenocarcinoma due to androgens / estrogens

Prostate cancer is the third leading cause of cancer death in men (after lung and colon), with an estimated 26,730 deaths in 2017. The prostate cancer death rate has been decreasing 3% per year since the early 1990's (Cancer Facts and Figures 2017, page 51). Prostate cancer has the highest prevalence of any non-skin cancer, with a similar incidence worldwide regardless of diet, occupation, lifestyle or other factors (Bostwick 2004). Essentially all men with circulating androgens develop microscopic prostate cancer if they live long enough (80% by age 80 years). Up to 72% of U.S. men will die with prostate cancer but only 3% die due to prostate cancer (Bostwick 2004).

Prostate cancer shares a number of features with its precursor, prostatic intraepithelial neoplasia (PIN) - an increase in prevalence with age, androgenic dependence for growth and development and response to androgen deprivation treatment.

Testosterone plays a significant role in the development and progression of prostate cancer by stimulating prostate cell growth, similar to the proposed development and progression of breast cancer (Bostwick 2004). It stimulates cell division and over a lifetime the large number of cell divisions may lead to spontaneous mutations in prostate cells which may activate proto-oncogenes and inactivate tumor suppressor genes. Androgens significantly alter prostate cancer growth rates and altered androgen metabolism may disturb the delicate balance between epithelial proliferation and apoptosis (Kyprianou 1996) or promote progression of prostate cancer from preclinical to clinically significant forms. Elevated concentrations of testosterone and its metabolite, dihydrotestosterone, over many decades, may increase prostate cancer risk but results have been inconsistent (Cancer Facts and Figures 2017).

Surprisingly, levels of circulating estrogens correlate with the incidence of prostate cancer. Thus, African American and Dutch-European men, with high rates of prostate cancer, have higher levels of circulating estrogens than Caucasian American and Japanese men, who have lower rates. In addition as men age there is a significant increase in the ratio of circulating estrogen to androgen levels, often referred to as andropause (Ho 2011). Smoking is not a risk factor but is associated with a higher death rate from prostate cancer, due to advanced stage and less well differentiated tumors (The Health Consequences of Smoking - 50 Years of Progress, A Report of the Surgeon General 2014, page 8, PDF page 37).

Chronic inflammation has been inconsistently associated with prostate cancer (Sfanos 2012, St Hill 2015). For example, it has been associated with *Trichomonas vaginalis* infection (Sutcliffe 2006, Cheng 2010, Stark 2009), which may be mediated by *T. vaginalis* macrophage migration inhibitory factor, a proinflammatory cytokine (Twu 2014). However, other reports deny this association (Sutcliffe 2009, Fowke 2016). Associations have been reported for sexually transmitted infections in Asians (Chung 2013), gonorrhea in African Americans (Lian 2015), HPV (Yang 2015) and BK virus (Delbue 2014). However, many reports show no association with sexually transmissible infections (Huang 2008, Hrbacek 2013, Yow 2014).

Prostate cancer and PIN are usually multifocal and are heterogeneous in their morphology and genotype. Virtually the entire genome participates in prostatic carcinogenesis, with no apparent unique pathways as seen in other cancers (Bostwick 2004, Lamont 2011). Although the widespread presence of prostate cancer in elderly men suggests a linear process, in fact, the process takes decades, occurs through variable mechanisms and pathways, is due to temporal and spatial heterogeneity and produces tumors with disparate molecular and morphologic features (Shoag 2016).

Germ line polymorphisms appear to be particularly important in prostate cancer. American men, and African American men in particular, have the highest incidence of prostate cancer in the world, with an almost two fold difference in prostate cancer incidence

in the U.S. between Hawaii (lowest rate) and Metropolitan Detroit (highest rate, Bostwick 2004). Prostate cancer appears to have a stronger familial aggregation than colon or breast cancer (Bostwick 2004); strong familial predisposition may be responsible for 5-10% of prostate cancer. These germ line differences may be mediated by sex hormone binding globulin and 5-α-reductase (Bostwick 2004). In addition variants in NFκB related genes may modulate prostate cancer risk (Cui 2015, Han 2015). Inherited conditions associated with increased risk include Lynch syndrome and mutations in BRCA1 and BRCA2 (Cancer Facts and Figures 2017).

Aspirin use is associated with a lower prevalence of prostate cancer in some (Liu 2014, Vidal 2015) but not all studies (Huang 2016, Wright 2016), apparently due to its inhibition of cyclooxygenase 2.

Section 3.4 Cancer due to other hormones

Constitutive expression of other hormones, such as thyroxine, parathormone, calcitonin, cortisol, insulin and glucagon, are not major factors associated with carcinoma.

There appears to be no consistent association of hyperthyroidism with cancer although disparate reports show various associations. For example, a Finnish study found an increased risk of gastric and respiratory tract cancers (Ryödi 2015). A study of female American radiation technologists found an association with breast cancer mortality after age 60 (Journy 2017), and a Danish study found that hyperthyroidism was associated with a slightly increased breast cancer risk (Søgaard 2016). A Taiwanese study found an increased risk of thyroid cancer associated with hyperthyroidism (Yeh 2013 but see Pazaitou-Panayiotou 2012).

There are no described associations of parathormone, cortisol or glucagon with cancer.

Calcitonin nasal spray for women with osteoporosis has been associated with liver cancer in higher dose users (Sun 2014), prostate cancer (Warrington 2017) or cancer in general (Hsiao 2017). However, the results have not been consistent and other studies have doubted the association (Wells 2016). Another study indicated that calcitonin treatment should be discontinued primarily due to lack of efficacy (Overman 2013).

The association of insulin levels with malignancy was discussed above in sections 1.8 (excess weight) and 1.9 (diabetes) and will be discussed in section 4.1 (diet).

Section 4.0 Western diet (high fat, low fiber, low vegetable consumption)

In this section, we describe how diet is associated with various cancers, mediated primarily by consumption of fat, vegetables, fruit and fiber, as well as a “proinflammatory” diet overall. Diet also interacts with excess weight (see section 1.8) and diabetes (see section 1.9). The Western diet has been described as one with high fat and cholesterol, high protein, high sugar, excess salt intake, frequent consumption of processed and “fast foods” and low consumption of fiber, vegetables and fruit (Myles 2014).

Diet influences inflammatory responses, including markers of systemic inflammation, as well as the risk of premalignant and malignant conditions. Researchers at the University of South Carolina Cancer Prevention and Control Program developed the dietary inflammatory index (DII), which predicts levels of inflammatory markers and related health outcomes (Shivappa 2014a). The DII is based on reviewing and scoring the scientific literature on diet and inflammation and obtaining nutritional surveillance data sets from around the world. A higher DII score indicates a proinflammatory dietary milieu. The DII is associated with multiple serum inflammatory markers, including C reactive protein (Shivappa 2014b), IL6, homocysteine and metabolic syndrome. It is also associated with cancer of the prostate, colorectum, pancreas and other GI sites (Shivappa 2016a), total mortality, cardiovascular disease and COPD, mediated through systemic inflammation and insulin resistance (Shivappa 2016d).

The foods with the highest inflammatory index are butter, beer, coffee, fried food, liquor, high sugar beverages and french fries (see Table 2); those with the lowest inflammatory index are vegetables other than potatoes, low fat dairy, fish, fruit (not juice) and nuts. The DII studies differ from prior studies in which isolated foods were tested to determine if they cause DNA changes related to carcinogenesis or if excessive intake or exposure causes tumor promotion (Sugimura 2000). A proinflammatory diet not only has components which move receptive network pathways towards malignancy (fat, high temperature cooking, alcohol) but has fewer foods which are protective against malignancy (vegetables, fruits, fiber).

Spices and foodstuffs, such as curcumin, resveratrol, epigallocatechin gallate, genistein, lycopene and anthocyanins have anti-inflammatory effects, which may modulate the chronic inflammatory mileu (Samadi 2015).

Section 4.1 Diet and specific cancers

Breast cancer due to dietary factors

Higher DII scores are associated with breast cancer risk among women in the U.S. (particularly if obese and postmenopausal, Shivappa 2017a but see Tabung 2016), China (Huang 2017) and Sweden (particularly if postmenopausal, Shivappa 2015a).

An adolescent and early adulthood diet characterized by sugar sweetened and diet soft drinks, refined grains, red and processed meat and margarine, and low intake of green leafy vegetables, cruciferous vegetables and coffee may increase the incidence of premenopausal breast cancer (Harris 2017, Farvid 2015). A high fiber diet during adolescence is associated with a lower breast cancer risk (Farvid 2016, Chen 2016). The breast is particularly vulnerable to carcinogenic influences during adolescence due to rapid proliferation of mammary cells and lack of terminal differentiation. Bioactive components in fruits and vegetables, including carotenoids, vitamin C, flavonoids, fiber, magnesium and potassium may act through multiple mechanisms to reduce risk of breast cancer (Farvid 2016).

It has been suggested that breast cancer prevention efforts will have the greatest effect when initiated at an early age and continued over a lifetime. Between menarche and the first full term pregnancy, breast tissue proliferates rapidly and risk accumulates rapidly (Colditz 2014).

The Mediterranean diet (high consumption of whole grains, vegetables, fruits, legumes, extra virgin olive oil and fresh fish; regular but moderate red wine consumption; low intake of saturated animal fats) may regulate estrogen metabolism in postmenopausal women in a manner that reduces potentially harmful genotoxic compounds and subsequent breast cancer (Carruba 2016). Although this diet as a whole is protective, consuming alcoholic drinks increases the risk of premenopausal breast cancer (World Cancer Research Fund: Diet, nutrition, physical activity and breast cancer 2017).

Colorectal cancer due to dietary factors
Consumption of a proinflammatory diet is associated with an increased risk of colorectal carcinoma in U.S. women (Tabung 2015, Shivappa 2014a), U.S. retirees (Wirth 2015), in a U.S. multiethnic cohort (Harmon 2017) and in Korean men and women (Cho 2016).

Proinflammatory diets can increase insulin resistance by increasing systemic inflammation, which could increase levels of insulin, triglycerides and nonesterified fatty acids, which can then promote excessive proliferation of colonic epithelial cells and potentially expose them to reactive oxygen species. Diets high in red and processed meats are high in N-nitroso compounds, which damage DNA. Diets high in fruit and vegetables contain antioxidants and micronutrients with antitumor capabilities, as well as fiber which decreases transit time in the digestive tract (Wirth 2015). In addition, as discussed in section 1.5, diet affects the symbiotic interactions between gut microorganisms and the digestive tract and may lead to dysbiosis and the presence of *E. coli* or related bacteria with pro-carcinogenic properties (Gagnière 2016).

Esophageal cancer due to dietary factors
A higher dietary inflammatory index is associated with a higher risk of esophageal squamous cell carcinoma in Italy (Shivappa 2015b) and Iran (Shivappa 2015c), even after controlling for alcohol and smoking. Hot beverages (mate) and hot foods (boiled meat) also appear to be important determinants in the risk of esophageal squamous cell carcinoma, allowing the penetration of carcinogens in tobacco and alcohol into the esophageal mucosa (Brazil / Uruguay) while fresh vegetables and fruit have a protective effect (De Stefani 2014).

Diets with a high glycemic index and glycemic load may increase the risk of esophageal squamous cell carcinoma and suggest a possible role for excess circulating insulin and related insulin-like growth factor 1 in esophageal cancer development (Eslamian 2013).

Various germ line mutations increase the risk of esophageal squamous cell carcinoma in Asians, including: (a) ADH1B*47Arg, especially when coupled with alcohol drinking or the ALDH2*504Lys allele (Zhang 2010), (b) ECRG1 Arg/Gln and Gln/Gln genotypes (Rasool 2011) and (c) both heterozygous and homozygous mutations in Fanconi anemia predisposing genes in Iranian patients (Akbari 2011).

Lung cancer due to dietary factors
Doll and Peto estimated that 20% of lung cancer is avoidable due to dietary change although they indicated that the evidential basis for estimating cancer due to diet is “a chronic source of frustration and excitement to epidemiologists” (Doll and Peto 1981, Willett 1995, Blot 2015). A high dietary inflammatory index is associated with lung cancer risk for current smokers (Hodge 2016). Fruit consumption and to a lesser extent vegetable consumption reduce lung cancer risk (Alberg 2013, Lam 2010). Similar findings were reported for the “Tex-Mex" and "fruits and vegetables” diet but may be mainly applicable to current or former smokers (Tu 2016). For nonsmokers, dietary beta carotene, raw fruit, vegetables and vitamin E supplements reduce the risk of lung cancer (Mayne 1994).

These studies reflect the importance of high intakes of whole grains, vegetables and fruit, which contribute phytochemicals that may reduce cancer risk (World Cancer Research Fund: Second Expert Report: Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective 2007). This may be mediated through multiple effects of these pro-inflammatory substances, including reactive oxygen and nitrogen species which damage DNA, changes in gene expression, genetic instability, insulin resistance and blunted immune response (Hodge 2016).

The overwhelming contribution of cigarette smoking as a cause of lung cancer makes it difficult to assess diet’s role in its etiology. In addition cigarette smoking is closely associated with unhealthy lifestyles, including diet, exercise and alcohol. Optimizing or improving any of these variables may improve some of the others.

Prostate cancer due to dietary factors
Diet is also associated with prostate cancer via a proinflammatory diet (Shivappa 2015e, Graffouillère 2016, Shivappa 2015f). Specific foods identified as risk factors include red meat and white fish cooked at high temperatures (Joshi 2012), select deep fried foods (Stott-Miller 2013) and a high fat diet (Di Sebastiano 2014). African-American men have a higher intake of dietary fat and this may contribute to their higher risk (Bostwick 2004). Japanese men have traditionally consumed a relatively low fat diet; as its fat content has increased toward Western levels, the incidence of prostate cancer has increased (Haas 1997). The isoflavones and green tea intake in a typical Japanese diet may decrease the risk of prostate cancer (Sawada 2017).

Other cancers due to dietary factors
A more proinflammatory diet has been associated with an increased risk of epithelial ovarian cancer (Peres 2017, Shivappa 2016b), pancreatic cancer (Shivappa 2015d, Ilic 2016, Antwi 2016) and stomach cancer (Shivappa 2016c, Stojanovic 2017).

Section 5.0 Aging

In this section, we describe the importance of aging in malignancy. The incidence of most malignancies increases exponentially with age during adulthood; more than 75% of invasive cancers occur at age 55 years or older (Benz 2008). Advancing age is the most important risk factor for cancer overall and for many individual cancer types. The median age of a cancer diagnosis overall is 66 years; it is 61 years for breast cancer, 68 years for colorectal cancer, 70 years for lung cancer and 66 years for prostate cancer (NIH > NCI > Age, accessed 12Nov17).

Aging is associated with stem cells with increased transformation potential. It is also associated with an elevated inflammatory environment, perhaps because age related cellular senescence causes the secretion of proinflammatory cytokines, chemokines and growth factors.

Aging related molecular changes trigger malignant transformation. Although somatic mutations are usually considered the tumor initiating events, aging is also accompanied by the accumulation of specific epigenetic modifications which may contribute to aberrant chromatin conformation and stability, particularly DNA methylation changes that resemble addition or removal of methyl groups to cytosines in a CpG dinucleotide context. Aging is associated with highly reproducible DNA methylation changes in normal tissue ("aging related sites"), which lower the threshold for malignant transformation (Xu 2014, Slieker 2016).

The rate of aging is controlled in part by nutrient sensing pathways (insulin or IGF1 signaling, mTOR, AMPK and sirtuins) that have been evolutionary conserved from worms to humans (Yokoyama 2015). These pathways are also commonly involved in carcinogenesis and cancer metabolism. Metformin, resveratrol, Rhodiola and other agents that target these pathways often have both anti-aging and anti-cancer efficacy. These agents not only reprogram energy metabolism of malignant cells but also target normal post mitotic cells by suppressing their conversion into senescent cells, which confer systematic metabolism benefits.

Section 5.1 Specific malignancies

Aging and breast cancer

Breast cancer incidence and mortality rates increase with age; nearly half of all new breast cancer diagnoses occur in women age 65 and older. By 2030, when 20% of the U.S. population will be 65 years or older, there may be exponential growth of older women with breast cancer (Barginear 2014).

In the breast, aging is associated with an expansion of CD49fhi mammary stem cells, which show a decline in function, increased transformation potential and association with an elevated inflammatory environment and old mammary glands (Dong 2016). "Inflammaging", which designates human aging characterized by chronic low grade inflammation, may be mediated in the breast through NFκB pathways highly influenced by specific micro RNAs (Cătană 2015).

Aging and colorectal cancer

Aging is one of the main risk factors for colorectal cancer, based on DNA methylation alterations of age related, epigenetic clock genes during development. Aging also influences the main colorectal cancer associated signal transduction pathways, such as WNT and PI3K/Akt (Galamb 2016).

Aging and lung cancer

Lung cancer is also considered an aging related disease because its incidence increases with age and less than 2% of lung cancer cases occur in patients younger than 45 (Zagryazhskaya 2014). MicroRNAs exhibit changes during aging, which are associated with lung cancer initiation, progression and resistance to anticancer therapy (Zagryazhskaya 2014).

Aging and prostate cancer

The extraordinary linkage of prostate cancer with age suggests that it results from accumulation of genetic damage, perhaps due to oxidative stress or other endogenous or exogenous factors. Although eukaryotic cells are equipped with multiple antioxidant defense mechanisms, they may be inadequate with advanced age (Bostwick 2004). In principle, inhibition of aging through caloric restriction or otherwise (Cadoni 2017, Moskalev 2015) should delay cancer (Blagosklonny 2008) but clinical data are limited.

Section 6.0 Radiation

In this section, we describe how ultraviolet radiation and radon contribute to malignancy based on extent of exposure, which is typically preventable. As with carcinogen exposure, damage may be permanent and the increased risk does not disappear when exposure ceases.

Section 6.1 Skin cancer (basal cell carcinoma, squamous cell carcinoma and melanoma) due to ultraviolet radiation

Cutaneous basal cell carcinoma and squamous cell carcinoma are usually found in sun exposed sites, especially the head and neck. Their risk is related to the amount of ultraviolet radiation received and inversely proportional to the degree of skin pigmentation. Ultraviolet B radiation (wavelength, 290 to 320 nm) from sunlight is principally responsible, with ultraviolet A radiation (320 to 400 nm) adding to the risk (Alam 2001). Although the ratio of basal cell to squamous cell carcinoma is 4:1 for the head and neck, squamous cell carcinoma has a ten fold higher risk of metastasis and mortality (Narayanan 2010).

Other risk factors for squamous cell carcinoma include occupational sun exposure (Diepgen 2014), chronic inflammation, Xeroderma pigmentosum, fair skin, history of repeated sunburn, hazel or blue eyes, blonde or red hair and albinism (Medscape: Cutaneous Squamous Cell Carcinoma, accessed 12Nov17).

Melanoma represents 3% of U.S. skin cancers but accounts for 75% of skin cancer deaths. Ultraviolet radiation exposure from the sun or artificial tanning beds is its most important environmental risk factor (Kanavy 2011). In men, severe sunburn, particularly on the trunk, is associated with melanoma, more than squamous cell carcinoma or basal cell carcinoma (Wu 2016).

Ultraviolet radiation causes DNA damage by creating pyrimidine dimers which lead to mutations in the *TP53* gene. Subsequent ultraviolet radiation causes keratinocytes to undergo clonal expansion, acquiring further genetic defects, ultimately leading to invasive cancer (**Medscape: Cutaneous Squamous Cell Carcinoma**, accessed 12Nov17, **University of Minnesota: Exposure to Environmental Hazards**, accessed 12Nov17).

Immunosuppression is a risk factor for the development of skin cancer, including organ transplants, phototherapy and HIV infection. In organ transplant recipients, the risk of cutaneous squamous cell carcinoma development is increased 64 to 250 times (**Hardin 2010**); these tumors are also more aggressive, with a higher rate of local recurrence, metastasis and death (**Medscape: Cutaneous Squamous Cell Carcinoma**, accessed 12Nov17).

We believe that the pathophysiology of skin cancer reflects current views about DNA damage and repair described above. Radiation leads to DNA damage, particularly to stem cells, that may or may not be repaired, based on the magnitude of DNA damage (sunburn vs. mild exposure), the chronicity of the exposure and the capability of the repair process, which is influenced by immune status and germ line variations. Radiation exposure early in life is a substantial risk factor (**Armstrong 2001**), either because the stem cells are more sensitive to damage at this age or because there is a longer period for malignancy to occur.

NSAIDs may mildly reduce the development of cutaneous SCC (**Muranushi 2015**).

Section 6.2 Radon and lung cancer

Lung cancer due to radon

In 1988, the International Agency for Cancer Research declared radon to be carcinogenic for humans and classified it as a proven human carcinogen (**IARC Monograph 43,1988**). An estimated 3-14% of lung cancer cases are attributable to radon, depending on the average radon concentration and the calculation methods. The lung cancer risk increases proportionally with increasing radon exposure. Most (86%) radon induced lung cancer cases occur among current and former smokers (**Lantz 2013**) due to strong synergy between radon exposure and smoking (**WHO Handbook on Indoor Radon: A Public Health Perspective**, accessed 12Nov17).

Radon is radioactive; when its atoms decay, the radon progeny are electrically charged and attach to tiny dust particles which are easily inhaled and adhere to the pleura. The deposited atoms decay by emitting alpha radiation which disrupts DNA and promotes carcinogenesis (**Health Effects of Exposure to Radon: BEIR VI (1999), Chapter 2**). Due to the limited range of alpha radiation, other organs are typically not affected. As with skin cancer, reductionism may adequately describe the initial interaction between radiation and DNA damage but complexity theory is helpful in understanding subsequent interactions between a damaged cell and DNA repair over years or decades, subsequent damage, malignant change and immune response.

Section 7.0 Immune system dysfunction

In this section, we initially describe how the immune system typically prevents clinical malignancy. We speculate that a “runaway” immune system is associated with malignancies with unknown risk factors, and discuss immunosuppression associated malignancy. This association of immune system dysfunction with malignancy confirms that cancer should not focus just about tumor cells but must consider their relationship with their environment:

“Cancer is no more of a disease of cells than a traffic jam is a disease of cars. A lifetime of study of the internal combustion engine would not help anyone to understand our traffic problems. The causes of congestion can be many. A traffic jam is due to failure of the normal relationship between driven cars and their environment and can occur whether they themselves are running normally or not.” **(**Smithers 1962**,** Camacho 2012**)**.

Although our focus is on the initial causes of carcinogenesis, we acknowledge that immune system dysfunction also arises during carcinogenesis. Cells acquire malignant characteristics as they also evade the immune system through “camouflage and sabotage” (**Poschke 2011**), resulting in tumor escape from immune surveillance (**Ward 2014**). The dynamics of this coevolutionary process may be similar to untreated HIV infection and CD4+ T cells, in which “escape mutants” of HIV arise faster than the immune system can respond (**Nowak 1995a**, **Goulder 1997**).

Section 7.1 Normal physiology

The immune system has several generalized antitumor functions. First, it kills viruses, bacteria and parasites that can induce tumors, directly or indirectly (see sections 1.2 to 1.6 and 2.2 to 2.4). Second, by eliminating pathogens and promoting prompt resolution of inflammation, it prevents establishment of a proinflammatory microenvironment that would facilitate tumorigenesis. Third, it eliminates tumor cells in certain tissues by recognizing ligands for activating receptors on innate immune cells and tumor antigens that are co-expressed in nascent transformed cells (**Marcus 2014**).

The first line of defense against microbes or cancer cells in mammals is the innate immune system, also called the cellular immune system. It is composed of natural killer cells, macrophages, dendritic cells, neutrophils, eosinophils, basophils and mast cells, and is activated by a molecular sensor system which use Toll-like receptors. These receptors recognize: (a) molecular patterns conserved among microbes (**2011 Nobel Prize in Physiology or Medicine, Scientific Background**, accessed 26Nov17) and (b) damage associated molecular patterns released from injured tissue, which initiate immune responses during tissue inflammation (**Liu 2012**). The cellular immune system must distinguish foreign and self molecules (such as major histocompatibility antigens, MHC). Natural killer cells, macrophages, dendritic cells, neutrophils and mast cells kill non MHC expressing cancer cells by releasing perforin, granzyme and other proteins that cause apoptosis in target cells.

The second line of defense is the active (humoral, B and T cell) immune system. The molecules of the innate system, including Toll-like receptors, induce maturation of dendritic cells, which patrol peripheral tissues to take up antigen and which have an exceptional ability to activate T cells and direct them to specific effector functions, including tumor cell killing (**2011 Nobel Prize in Physiology**

or Medicine, Scientific Background, accessed 26Nov17). Natural killer cells and cytotoxic T lymphocytes (CTL) identify malignant cells through germ line receptors and by presentation of antigen through the T cell receptor. However, these systems may fail to prevent cancer development due to changes in tumor identifying ligand expression or secretion, resistance to cytotoxicity or compromised cytotoxic cell activity through immune tolerance mechanisms (Taylor 2015).

Section 7.2 Runaway immune system / nonspecific immune system dysfunction

We consider the immune system to be particularly well described by self-ordered criticality, with a delicate balance between activating and dampening forces. We speculate that this balance occasionally undergoes major disruption by seemingly trivial events, leading to a "runaway" immune system associated with the malignancies described below (glioblastoma, classical Hodgkin lymphoma, nodular lymphocyte predominant Hodgkin lymphoma and nonendemic Burkitt lymphoma) that are considered to have "unknown risk factors", because the trivial events are either random or individually have low frequency. This situation is analogous to the grain of sand that causes an avalanche on a sandpile. Even just before the avalanche occurs, there is no evidence that a major problem is about to occur. Known examples of a runaway immune system include: (a) antigen driven lymphoproliferation, discussed in sections 1.3 and 1.4, (b) viral driven lymphoma, discussed in section 2.3 and (c) hemophagocytic lymphohistiocytosis, a nonmalignant condition (see Hemophagocytic lymphohistiocytosis, accessed 12Nov17, Grzybowski 2017). I

We describe four well known malignancies that appear to be due to runaway immune dysfunction. Due to their apparently trivial causes, it is difficult to devise prevention, detection or treatment options based on reductionist thinking. More useful is focusing on patterns of behavior, as described with complexity theory, that emerge from the disparate causes and mechanisms of these diseases. For example, as described below, there are common inflammatory patterns that can be detected and targeted. It may also be possible to detect patterns of germ line variations promoting these diseases, and to develop strategies to reduce their impact.

Glioblastoma due to microglial activation

Primary glioblastoma multiforme is a highly malignant brain tumor with an average posttreatment survival of less than 2 years (Medscape: Glioblastoma Multiforme, 12Nov17). Overall incidence is similar among countries although slightly more common in the U.S., Scandinavia and Israel than in Asia, which may reflect differences in genetics, diagnosis and reporting practices. Most tumors are sporadic, with no risk factor identified (Thakkar 2014), and no known precursor lesion.

There is limited evidence that aberrant activation of microglia creates a proinflammatory and immunosuppressive environment, which creates the proper milieu for glioblastoma to arise (Yang 2010). Microglia comprise 5-20% of the total glial cell population and are as numerous as neurons. In a healthy environment, resting microglia display low expression levels of inflammatory molecules but when activated they abandon their ramified surveillance morphology, become ameboid, acquire phagocytic functions and migrate to the injured site to release inflammatory molecules (Perrotta 2015), similar to Reed-Sternberg cells (Charles 2011). Once the CNS microenvironment becomes activated, local cells are converted to a reactive phenotype and secrete various factors which further influence tumor biology, including cytokines and chemokines. These changes decrease the stringency of the blood-brain barrier, allowing entry of soluble factors and peripheral immune cells including macrophages, natural killer cells and lymphocytes (Yang 2010). In support of this theory, glioblastoma typically displays a coordinated overexpression of proinflammatory genes (Tafani 2011).

The familial form of glioblastoma occurs in 1% of cases although it has a different genetic background. Other genetic diseases associated with glioblastoma multiforme include tuberous sclerosis, Turcot syndrome, multiple endocrine neoplasia type IIA and neurofibromatosis type I (Urbańska 2014).

Regular use of nonsteroidal anti-inflammatory drugs is associated with a reduced incidence of glioblastoma (Qiu 2017).

Classical Hodgkin lymphoma due to B cell activation and immune system failure

Hodgkin lymphoma is the most common U.S. cancer in young adults. The American Cancer Society projects 8,260 new cases and 1,070 deaths from Hodgkin lymphoma in 2017 (American Cancer Society, What Are the Key Statistics About Hodgkin Lymphoma?, accessed 12Nov17). It has a bimodal age distribution that differs geographically and ethnically; in developing countries, the early peak occurs before adolescence compared with the mid to late 20s in industrialized countries (Kennedy-Nasser 2011). The early peak is predominantly the nodular sclerosis subtype compared with the mixed cellularity subtype in the later age peak (Salati 2014).

Hodgkin lymphoma may actually represent three distinct diseases: (a) classical Hodgkin lymphoma - mixed cellularity and lymphocyte depleted subtypes as part of a biologic continuum, (b) classical Hodgkin lymphoma - nodular sclerosis subtype, whose epidemiology, clinical presentation and histology is distinct from mixed cellularity and lymphocyte depleted but may be related to primary mediastinal B cell lymphoma and mediastinal grey zone lymphoma (Mani 2009), and (c) nodular lymphocyte predominant Hodgkin lymphoma.

Classical Hodgkin lymphoma, which comprises 95% of cases, has large mononucleated Hodgkin and giant multinucleated Reed-Sternberg cells, collectively referred to as Hodgkin and Reed-Sternberg cells (HRS). These malignant cells are clonally related and nearly always derive from B cells and only rarely from T cells (Küpper 1994, Kennedy-Nasser 2011). In contrast, nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) has LP cells (formerly called L&H cells) as well as a different biology and prognosis (Kennedy-Nasser 2011).

Hodgkin disease is unusual in that its malignant cells account for less than 1% of the total tumor cell population, similar to glioblastoma. Most tumor associated cells are reactive inflammatory cells including lymphocytes, histiocytes, eosinophils, neutrophils, plasma cells and fibroblasts, which develop due to HRS cytokine release. T cells are usually the largest population of cells in the tumor, encompassing Th cells, T(regs), and cytotoxic T lymphocytes (CTL). Th cells and T(regs) presumably provide essential survival signals for the HRS cells; the T(regs) also play an important role in rescuing HRS cells from attack by CTLs and NK cells (Wein 2016).

Hodgkin lymphoma appears to be due to a “runaway” immune system, coupling the inherent instability of activated B lymphocytes with defects in apoptosis and other immune system control mechanisms, either congenital or acquired. The pattern of somatic mutations in rearranged immunoglobulin V genes suggests that they are derived from preapoptotic germinal center B cells (Cossman 1999). Although its pathogenesis is still largely unresolved, aberrant activation of several signaling pathways is key to HRS cell survival. Apoptosis of HRS cells is inhibited by several mechanisms: (a) constitutive activation of NFκB, either autonomously, by rosetting T cells, by EBV or by inactivation of IκB or its other inhibitors, (b) inactivation of the CD95/Fas death receptor pathway (Mani 2009), (c) inhibition of executors of apoptosis by expressing X linked inhibitor of apoptosis (XIAP) and (d) altered regulation of BCL2 family proteins.

Epstein-Barr virus infection causes B cell activation in classical Hodgkin lymphoma, typically affecting the mixed cellularity and lymphocyte depleted subtypes (Jarrett 2002). EBV involvement varies by geography: Kenya - 92%, Greece - 90%, China - 65%, Turkey 62%, Peru and Mexico - 50-95%, Egypt - 50%, Italy 48%, Israel - 30% (Bedouins - 67%) (Salati 2014). It also varies by ethnicity, being present in 93% of Asian and 86% of Hispanic children with Hodgkin lymphoma, compared with 46% of Caucasian and 17% of African American children.

Patients with high EBV titers are at increased risk of Hodgkin lymphoma; those with a history of infectious mononucleosis have a twofold to fivefold increased risk (Flavell 2000). In Hodgkin lymphoma and peripheral T cell lymphoma, EBV typically has a type II latency pattern, with expression of EBNA1, LMP1 and LMP2 (Roschewski 2012). LMP1 may activate both canonical and noncanonical NFκB signaling pathways through its mimicry of CD40, which may promote the pathogenesis of Reed-Sternberg cells.

Delayed infection has been hypothesized as a risk factor for Hodgkin lymphoma (Chang 2004, Gutensohn 1981) as well as childhood acute lymphoblastic leukemia (Ma 2002), adult lymphocytic leukemia (Vineis 2003) and non Hodgkin lymphoma (Vineis 2000). Having older siblings and attending nursery school and day care may facilitate early childhood exposure to common bacterial and viral infections, which may promote maturation of Th1 immunity, which defends against intracellular bacterial and viral infections but is typically relatively weak at birth (Chang 2004, Simon 2015). For Hodgkin lymphoma, early EBV exposure reduces the risk of adolescent mononucleosis, an established risk factor.

Immunosuppression is an established risk factor for Hodgkin lymphoma and may be due to congenital disorders such as autoimmune lymphoproliferative syndrome (Bleesing 2017, van den Berg 2002), HIV/AIDS with moderate immunosuppression (Biggar 2006), allogeneic bone marrow transplantation (Rowlings 1999) or methotrexate for autoimmune disorders (Kamel 1993, Mariette 2002).

Genetic susceptibility underlies Hodgkin lymphoma based on studies of identical twins (Mack 1995) and HLA polymorphisms associated with infectious mononucleosis (Houldcroft 2015).

Nodular lymphocyte predominant Hodgkin lymphoma due to B cell activation
Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is rare and distinct from classical Hodgkin lymphoma (Lazarovici 2015). Almost all cases are EBV negative (Englund 2016); its etiology is unknown. Patients often present with early stage disease without B symptoms, and clinical behavior mimics indolent non Hodgkin lymphoma (Goel 2014). Less than 10% of cases transform into diffuse large B cell lymphoma (Kenderian 2016).

The malignant LP cell in NLPHL is presumably derived from selected germinal center B cells, based on frequent BCL6 gene rearrangements (Mani 2009). However, unlike HRS cells that carry crippling immunoglobulin gene rearrangements, LP cells often show ongoing somatic hypermutation. Activation induced cytidine deaminase (AID), an enzyme indispensable for class switch recombination and somatic hypermutation of immunoglobulin genes, is expressed consistently in LP cells but only infrequently in HRS cells of classical Hodgkin lymphoma.

Nodular lymphocyte predominant Hodgkin lymphoma is characterized by a low percentage of LP cells in a background of lymphocytes (Englund 2016). Unlike HRS cells, the LP cells have a B cell phenotype (CD19+, CD20+, CD45+, CD79a+, BOB.1+, OCT2+) and are negative for CD15 and CD30 (Smith, PathologyOutlines.com - Nodular lymphocyte predominant Hodgkin lymphoma, accessed 12Nov17). Nodular lymphocyte predominant Hodgkin lymphoma and T cell / histiocyte rich large B cell lymphoma may represent opposite ends of a spectrum of a common disease that affects middle aged men, has a low tumor content of malignant cells, has a distinct gene expression profile (Hartmann 2013) and has familial components (Saarinen 2013, Merli 2013, Rüdiger 2002). Typically NLPHL is indolent but T cell / histiocyte rich large B cell lymphoma presents with advanced stage disease and behaves aggressively.

Burkitt lymphoma (sporadic) due to B cell activation
Three clinical subtypes of Burkitt lymphoma are recognized: endemic (discussed in section 2.3), immunodeficiency associated (related to HIV infection [Guech-Ongé 2010] or solid organ transplantation [Mbulaiteye 2013]) and sporadic. All have *c-MYC* rearrangements that contribute to lymphomagenesis.

The sporadic form has no specific geographic distribution. It tends to arise in lymphoid tissues of the terminal ileum and upper respiratory tract (e.g. Waldeyer’s ring), and is associated with EBV in 30% of cases (Pagano 2009). No risk factors have been identified although a recent study found associations in younger patients with eczema (Mbulaiteye 2014).

Next generation sequencing studies have identified mutations in the *TCF3* transcription factor or its negative regulator *ID3* in 70% of sporadic and immunodeficiency related cases and 40% of endemic cases (Swerdlow 2016).

The precise mechanism of sporadic Burkitt lymphoma is unknown. We speculate that it is due to various combinations of EBV infection, other chronic stressors, conditions of relative immune dysfunction, germ line variations and “bad luck” that ultimately push B cell related networks towards states similar to those created in endemic or immunodeficiency associated Burkitt lymphoma.

Brief duration, high intensity chemotherapy, including aggressive CNS prophylaxis, leads to very high rates of complete remission and overall survival in adults (Pagano 2009).

Section 7.3 Cancer due to HIV infection

HIV infection promotes malignancy through immunodeficiency as well as directly. HIV related immunodeficiency is associated with all cancers except prostate cancer (Silverberg 2011) and lung cancer (Marcus 2017), which suggests that immune response is not an important component of these malignancies. HIV appears to directly promote lymphomagenesis (Dolcetti 2016) because even after highly effective combined antiretroviral therapy treatment (cART), HIV patients have higher rates of non Hodgkin and Hodgkin lymphoma, as well as Kaposi sarcoma and anal cancer (Lee 2016). This may be mediated by its p17 protein, which binds to the CXCR2 chemokine receptor and activates the ERK1/2 signaling pathway (Caccuri 2017); mutations to p17 may activate the PTEN pathway and promote B cell clonogenic activity (Giagulli 2017). Although cART may normalize CD4 counts and eliminate HIV from peripheral blood, the virus may persist because: (a) viral replication can still occur in lymphoid tissues, (b) HIV+ macrophages and T cells may persist in adipose tissue (Totonchy 2016) and (c) although chronic B cell stimulation is partially reversed, markers of exhaustion are not completely reversed compared to HIV negative individuals (Goncalves 2016).

Section 7.4 Cancer due to other immunodeficiency

Transplant related immunosuppression causes post transplant lymphoproliferative disorder and cutaneous squamous cell carcinoma (Chockalingam 2015). Post transplant lymphoproliferative disorder was first recognized in 1969 in kidney transplant recipients (McKhann 1969, Penn 1969) as due to EBV infection and a deficient, EBV specific, cellular immune response secondary to immunosuppression. Although EBV infects 95% of the adult population, it is typically held in check by CD8+ and CD4+ T cells. However, use of anti-thymocyte globulin and anti CD3 monoclonal antibodies to prevent graft versus host disease removes these T cells from the graft and host, allowing EBV activation of B cells (Roschewski 2012). Management of EBV associated lymphoma involves restoration of the host immune response to EBV by reduction of the iatrogenic immunosuppression (Grulich 2015), multi-agent chemotherapy with rituximab (DeStefano 2017, Nieto-Rios 2016) or Epstein-Barr virus specific cytotoxic T cell therapy as first line therapy; unselected donor lymphocyte infusions or chemotherapy are options for second line therapy (Styczynsk 2016). The increased cancer risk is largely reversed when the immunodeficiency is decreased.

Primary immunodeficiency occurs in 1 per 10,000 births. In these patients, malignancy is the second most prevalent cause of death in children and adults, after infection. The primary immunodeficiencies most often associated with cancer include common variable immunodeficiency, Wiskott-Aldrich syndrome, ataxia-telangiectasia and severe combined immunodeficiency (Mortaz 2016). This increased incidence of cancer is attributed to defective elimination of altered or transformed cells or other defective immunity towards cancer cells.

Section 8.0 Cancer due to germ line changes

In this section, we consider germ line changes associated with a high probability of malignancy, with the goal of ultimately devising a counter strategy. We exclude sporadic cancers, even with a significant polygenic germ line component (Lu 2014) but consider them in section 9.0 as a component of random chronic stress.

A 2008 comprehensive review identified 54 hereditary cancer syndromes. Most are autosomal dominant, including retinoblastoma (*Rb* gene), Li-Fraumeni syndrome (*TP53* gene), neurofibromatosis (*NF1, NF2*), von Hippel-Lindau disease (*VHL*), familial adenomatous polyposis (*APC)* and hereditary breast and ovarian cancer (*BRCA1*, *BRCA2*) (Lindor 2008, PDF).

Germ line changes often affect gene products whose function has obvious relevance to uncontrolled cell growth, such as DNA repair (*BRCA1*) or apoptosis (*TP53*, *BCL2*). However, genes products such as the VHL protein, which plays a key role in cellular oxygen sensing (Gossage 2015), seem totally unrelated to malignancy. If we remember the role of complexity in establishing cellular networks, the possible importance of seemingly obscure proteins makes more sense, much as pulling on a spider web affects distant and apparently unrelated threads.

We recommend that primary care physicians: (a) take a thoughtful family history, (b) learn the clinical features that suggest a cancer syndrome, (c) refer all children with cancer to a clinical geneticist or a pediatrician skilled in clinical dysmorphology examination (germ line mutations in cancer predisposing genes were recently identified in 8.5% of children and adolescents with cancer by DNA sequencing of 565 genes but family history did not predict the presence of an underlying predisposition syndrome in most patients [Zhang 2015]) and (d) restrict genetic testing to those with a reasonable prior probability of having the disorder for which the testing is performed (Lindor 2008).

Section 9.0 “Random” chronic stress / bad luck

In this section, we postulate that there are baseline rates of malignancy in many organs, assuming common germ line patterns, environmental conditions and immune system responses. These rates are generally expected to be constant over time and through different cultures, unless there are changes in exposures. In support of this thesis, Vogelstein and Tomasetti indicated that variation in cancer risk among tissue type could often be attributed to "bad luck” or random mutations arising during DNA replication in normal, noncancerous stem cells (Tomasetti 2015, Tomasetti 2017).

Comparable to the “runaway” immune system discussed above regarding some lymphomas, tumors with no significant risk factors may be due to a myriad of isolated chronic stressors that impact weak points in networks. Uncommon stressors may have a similar impact to a known risk factor but due to their rarity, may not be detectable in epidemiological studies. Alternatively, these stressors may individually have a minimal impact, similar to the drop of sand on a sandpile discussed above but each stressor may subtly change the internal configuration of the network so that a particular combination of stressors in the appropriate microenvironment

may cause a marked network disruption promoting malignancy, similar to an avalanche caused by repeated drops of a grain of sand. Looking backwards, it may be difficult to understand how the preceding stressors worked together to produce this result.

These unexplained chronic stressors may be the leading “risk factor” for cancers of unknown etiology in patients with no obvious risk factors, including some lung cancer in nonsmokers (excluding cases associated with radon, second hand smoke or familial), pancreatic adenocarcinoma of the usual type (excluding cases associated with chronic pancreatitis, alcohol, tobacco or familial), glioblastoma, some Hodgkin lymphoma, sporadic Burkitt lymphoma and others. We speculate that the pathophysiology of no risk factor cases often involve similar network changes and molecular alterations as those with risk factors but due to random factors or low risk causes that cannot be predicted.

Random chronic stress or bad luck may be a paradigm for cancer in general. Life consists of a delicate balance of network activity, which provides enough flexibility for organisms to move between different major forms (fertilized egg, embryo, fetus, prepubertal, pubertal) and to respond to infections, trauma or deficiency conditions. This balance may be optimized for humans in general but not necessarily for each individual, who has multiple genetic polymorphisms that may provide an advantage or disadvantage under varying conditions. In addition selection is limited to promoting the reproductive dissemination of genetic material; living longer provides a minimal selective advantage, particularly since historically, most people did not live very long (the average lifespan in early modern England was only 33-40 years, compared to a world average of 48 years in 1950 [**Wikipedia - Life Expentancy**, accessed 12Nov17]). Thus, there may be no control mechanisms to specifically prevent cancer in those who have passed the typical active reproductive age.

Part of the delicate balance relates to control of cell growth and differentiation, which are paramount to movement between different major forms and to respond to environmental challenges. Chronic stressors may damage control mechanisms that guide networks along desired paths in unpredictable ways. For example, chronic stressors that increase the growth rate may also affect differentiation, because cells with rapid growth rates lack the gap phases necessary to transcribe some long genes associated with differentiation.

Personalized cancer recommendations

For long term health related to cancer, in addition to treating any known malignancy, we recommend strategies to reduce chronic stressors in general. This includes: (a) maintain optimal health to minimize potential chronic stressors, (b) reduce known chronic stressors or risk factors, (c) screen for premalignant / malignant disorders based on personalized variations, known diseases and conditions and (d) counter known germ line changes that likely will challenge health. Promoting rational medical care, limited as it may sometimes be, is also important at the individual and societal level. Although rarely the proper medical approach may be as intricate and hidden as a “crown of feathers” (**Singer 1981**), in most cases, rational treatment is known and is not controversial.

These prevention and treatment related thoughts for cancer are analogous to those for coronary heart disease. Both have multiple causes and risk factors; treatment focuses not just on the current pathophysiologic problem but on reducing future problems. Coronary artery disease treatment may not only require bypass grafts or stent placement for the acute problem but long term treatment focused on reducing obesity, tobacco use, diabetes and hypertension. Although anti-cancer therapy must similarly initially focus on the present tumor(s), through surgery, chemoradiation and immunotherapy, it must also reduce recurrence, metastases and new tumors by countering the chronic stresses to the extent possible. This philosophy is exemplified by treatments for gastric MALT lymphoma (antibiotics for *H. pylori t*o reduce bacterial antigen induced lymphoproliferation), intestinal T cell lymphoma (gluten-free diet to reduce autoantigen induced lymphoproliferation) and breast carcinoma (antiestrogens or aromatase inhibitors to reduce the impact of constitutive estrogen expression).

Effective lifestyle interventions, such as dietary modification and physical activity, can be thought of as mechanisms through which etiologic fields can be attenuated throughout the body, preventing cancer occurrence and progression and decreasing the cancer burden in our society (**Lochhead 2015**).

It may be possible to move malignant pathways to a nonmalignant state in markedly different ways, such as through retinoic acid for acute promyelocytic leukemia (**McCulloch 2017**), as well as by reducing chronic stressors. Some tumors are in a stable state due to cancer attractors, which makes alteration more difficult. In addition the dynamic nongenetic heterogeneity of cancer cell populations makes them moving targets and drives the replenishment of the cancer attractor with surviving, nonresponsive cells from neighboring abnormal attractors (**Huang 2013**). Finally, targeting the microenvironment that nurtures the tumor cells may be useful (**Sounni 2013**, **Tsai 2014**, **Gkretsi 2015**, **Polydorou 2017**).

* End *