How cancer arises from chronic inflammation, based on complexity theory
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Introduction: This paper discusses how cancer arises from chronic inflammation, based on complexity theory. We believe that this perspective may lead to new insights into cancer pathophysiology and treatment.

Methods: We reviewed the medical literature to identify cancer types strongly associated with chronic inflammation. We then classified the chronic inflammatory etiologies, determined general mechanisms through which they promote cancer and speculated on network changes involved in transforming cells from physiologic to cancer attractor states.

Results: Bacterial and viral infection, predominantly *Helicobacter pylori*, human papillomavirus and hepatitis B and C virus, are a common etiology of chronic inflammation associated cancer and cause 15% of cancer cases worldwide. Other etiologies are parasitic infestations by *Opisthorchis viverrini, Clonorchis sinensis* and *Schistosoma haematobium*; autoimmunity in Hashimoto thyroiditis, Sjögren syndrome and celiac disease; local trauma due to gastroesophageal reflux and hot beverages; excess weight; diabetes; Western diet (high fat, low fiber, low consumption of fruit and vegetables); aging and immune system dysfunction. General mechanisms through which these etiologies cause cancer are immune system activation that damages DNA by producing reactive oxygen and nitrogen species and nitrosamines; tumor immune evasion via immune suppression and immune senescence; antigen driven lymphoproliferation; continuous mitotic activity due to repair; synergy with other chronic stressors; creation of a tumor nurturing microenvironment; development of a “runaway” immune system; and microbiome changes that produce carcinogens or activate inflammation. Immune system dysfunction and germ line variations of inflammatory mediators can promote each step. From a network perspective, the usual physiologic state for many cellular processes consists of a delicate balance between stimulating and dampening forces, maintained by inherent network features and evolved control systems. Chronic inflammation may disturb this balance, leading to propagation of network instability throughout the cell, across adjacent tissues and ultimately systemically. This may create identifiable network hierarchies and intermediate states (hyperplasia, metaplasia or dysplasia), but some changes in network and molecular patterns may not alter histology. Ultimately, cells may move to a cancer attractor state.

Summary: Chronic inflammation causes cancer by initiating local changes to cellular networks and their microenvironment which facilitate their escape from physiologic states towards intermediate and cancer attractor states. This suggests that early detection and reduction of these inflammatory changes may reduce cancer mortality. Novel treatment options include more diverse treatment combinations, destabilizing existing cancer attractors and their microenvironment, stimulating physiologic pathways that steady networks, reducing other chronic stressors and optimizing rational medical care.

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Introduction

We previously discussed the importance of complexity theory in understanding cancer (**Pernick 2017a**, **Pernick 2018a**) and proposed that chronic cellular stress is the underlying cause of most adult cancer by disturbing the delicate balance that exists in cellular networks necessary for the major functions of the organism (**Pernick 2017b**). In this paper, we describe chronic inflammation as a chronic stressor and briefly discuss immune system dysfunction. Subsequent papers will focus on the other chronic stressors: exposure to carcinogens; reproductive hormones; Western diet (high fat, low fiber, low consumption of fruit and vegetables); aging; radiation; germ line changes and random chronic stress / bad luck.

Methods

We reviewed the medical literature, initially using PubMed and search terms “chronic inflammation” and cancer, as well as disorders associated with chronic inflammation, followed by subsequent citations to important references. Our focus was on malignancies with strong statistical associations with chronic inflammation, those whose mechanisms of action have been well described and malignancies with no known risk factors but with suggestive associations with chronic inflammation.

Complexity theory versus reductionism

Traditional biology relies on reductionist thinking, that 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 that themselves can be reduced to simpler parts (Mazzocchi 2008) and that disease is due to flawed parts or systems. In contrast, we believe that principles of complexity theory and self-organization create a more robust framework for understanding the origins and dynamics of biologic systems, including cancer.

In complex systems, the properties of the entire system are greater than the sum of the properties of each part (Kane 2015). They arise due to interactions between the parts, which leads to emergence of novel properties that cannot be predicted.

Cancer is an assault on the order typically maintained in cells and has “tapped into the heart of what makes a complex system difficult to predict, manage and control” (Johnson: Simple Complexity, page 177). Two overlapping theories explain how disorder arises in biologic systems: the “edge of chaos” and self-organized criticality. Disorder can be understood based on the concept of human biologic networks being delicately balanced 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. Positioning networks in this manner provides flexibility to coordinate sophisticated activities such as transcription, translation, mitosis and apoptosis; helps coordinate global functions such as response to environmental and physiologic threats (Kauffman, At Home in the Universe, page 86); and maximizes an organism’s evolutionary advantages, because rigid order would doom species that cannot respond to a changing and competitive environment (Kauffman and Johnsen 1991, Langton 1990).

Natural selection optimizes cellular networks to promote propagation of genetic material (Rifkin 2013). These cellular networks arise in the fertilized egg, influenced not just by its unique combination of DNA and translated proteins but also by the ovum microenvironment. The networks change autonomously, causing the organism to move through embryogenesis, fetal growth and development, childhood growth and development, sexual maturity and adulthood. These transitions are influenced by control mechanisms that keep the organism on path and are capable of responding to common threats to the health and reproductive capacity of the organism.

Self-organized criticality

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,” analogous to the “edge of chaos” (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 the 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 systemic response, leading to a major reconfiguration of the system (Bak, How Nature Works 1999).

Part of the tradeoff for maintaining a self-organized critical state is that catastrophic systemic failure is predictable. We suggest that the human body is composed of a myriad of interacting networks positioned at a critical state, and that cancer is an inevitable type of catastrophic failure that begins as a small number of network changes and eventually propagates through the body.

Attractors

Large numbers of mutually regulating genes create a type of network stability called an attractor, which makes cells relatively resistant to major changes (Kauffman, The Origins of Order 1993, page 467). Attractors have been analogized to a low energy state or valley on a topographic diagram that pulls in cells with similar network configurations (Waddington, The Strategy of the Genes 1957, Figure 1). We have proposed that cancer arises initially due to chronic stressors (Pernick 2017b), which act over years or decades to overcome the cell's stability and find or create "weak spots" in networks that cause them to move from their usual physiologic state towards neighboring attractors (Kauffman, At Home in the Universe, page 110). These local network changes may interact to create, within the context of other chronic stressors, a hierarchical structure, such as dysplasia or differentiation, with new biologic properties, such as inhibition of apoptosis, a prolonged cellular lifespan or constitutive expression of biomolecules that promote cell division. Intermediate states are often difficult to reverse, in contrast to hyperplasia or reactive changes, which more readily revert to prior states. Intermediate states interact with each other and with chronic stressors to create malignant cells that have their own version of stability termed "cancer attractors" that prevents them from reverting to normal physiologic states (Huang 2009).

Three important points should be noted about network changes. First, not all network changes result in histologic changes, even if genes are altered (Pernick 2018b). Changes in cellular function, not structure, are not necessarily identifiable under the microscope. This explains why how an aggressive malignancy such as well differentiated pancreatic adenocarcinoma can have altered molecular characteristics but histologically resembles chronic pancreatitis, a benign condition (Hruban 2007, Logsdon 2003). We speculate that molecular analysis of tissue adjacent to tumors without known intermediate states, such as glioblastoma, will reveal one or more intermediate states based on molecular patterns.

Second, a new intermediate state can be produced by different combinations of network changes. Thus, the classic histology of serrated polyposis of the colon may be due to mutations in different genes (He 2016). Similarly, tumors arising with different driver mutations (etiologies) may have similar histology and other properties because cells fall into the same attractors.

Third, the formation of new intermediate states in malignancy, such as atypical hyperplasia and dysplasia, occurs through bursts of activity, not through gradualism. Tumors characterized by multistep progression (Vogelstein 1993) may appear to arise linearly via increasingly unstable intermediate states but the process is actually not linear and the formation of the intermediate states themselves may be discontinuous. For example, breast cancer does not typically progress stepwise from hyperplasia to low grade DCIS to high grade DCIS to invasive carcinoma. Instead, multiple parallel, genetically distinct pathways may be present (Tang 2006).

Interdependence of biologic networks

To better understand cancer, we suggest physicians and scientists should embrace principles of complexity theory. Currently, they tend to think of biologic networks as accomplishing a single task and interacting with other networks in limited ways, comparable to machines, whose interactions are linear and predictable. However biologic networks have numerous and varied connections with each other, within and between various cellular components as well as cells as an entire unit, tissues and organs.

This nonlinear behavior of biologic networks is essential to enable physiologic transitions between different patterns of behavior, such as embryogenesis and the response to trauma (acute and chronic inflammation). These transitions are typically associated with changes to control mechanisms in networks throughout the body that keep the process on track and prevent inappropriate activation.

We believe these transitions are recapitulated during carcinogenesis, but in a disordered way. Small initial changes to a limited number of networks, induced by chronic stressors as described below, overcome inherent and evolved controls and lead to an acceleration of changes that may emulate physiologic transitions, leading to biologic features resembling embryogenesis, marked cell growth and a chronic inflammatory state. These changes may also disrupt the coordinated timing of network cycles, similar to how climate change causes botanical pollinator mismatch (Morton 2017).

Chronic cellular stress causes most adult cancer
We previously proposed that chronic cellular stress is the underlying cause of most adult cancer, typically by creating a field effect that acts on cells throughout an organ or organ system (Pernick 2017b).

Initially, this chronic stress disturbs the delicate balance that exists in biologic networks of susceptible stem or progenitor cells, and the instabilities propagate to surrounding networks within and adjacent to the cell. Over time, the instabilities are amplified and ultimately may produce network trajectories associated with increased and relatively uncontrolled cell division which may (hyperplasia, metaplasia, dysplasia, thyroiditis, gastric atrophy) or may not be distinctive histologically. These new network states may be difficult to reverse.

Typically, sustained exposure to multiple chronic stressors is necessary to overcome the stability of physiologic attractors. The chronic stressors alter the microenvironment, enabling additional changes and emergence of cellular phenotypes that would not be possible with the initial microenvironment. This process, although difficult to document in human cellular networks, is readily demonstrated in plants by species changes during forest succession (University of Wisconsin-Madison, accessed 16May20).

We previously identified nine chronic stressors (chronic inflammation, exposure to carcinogens; reproductive hormones; Western diet [high fat, low fiber, low consumption of fruit and vegetables]; aging; radiation; immune system dysfunction; germ line changes and random chronic stress / bad luck) as causing cause most adult cancer (Pernick 2017b). 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 2017a). Third, evolution has added intricate control systems to existing genes and pathways that are not easily disrupted (Molecular Biology of the Cell (4th Ed), How Genomes Evolve, accessed 16May20, Glassford 2015). However, natural selection cannot reduce the negative impact of chronic stressors that are historically recent (less than 1 million years, Uyeda 2011) or that do not affect the reproductive capacity of the organism. In addition, there may be no easy evolutionary solution to widespread changes induced by tobacco smoke or other chronic stressors without a major redesign of the affected biological systems.

Stressors continuing over years or decades may overcome this inherent resistance to change. Chronic stressors acting on weak spots in a network may cause subtle structural changes similar to those seen in a sandpile after adding a grain of sand. In this new microenvironment, a simple network change may trigger an avalanche of changes or provide a niche for other changes that may further increase network instability and ultimately produce premalignant hierarchical structures.

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

Section 1.0 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). Currently, cancer is considered to arise from sites of infection and inflammation but only in the context of a permissive microenvironment that contains growth factors (cytokines, chemokines), activated stroma and DNA damaging agents (Coussens 2002, Comen 2018). 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 chronic inflammation persists over years. Tumors have been described as wounds that do not heal (Dvorak 1986, PDF, Dvorak 2015). In typical wounds, tissue injury causes inflammation and cell proliferation, but when the trauma ceases and the repair is complete, the inflammation and cell proliferation also subside and the microenvironment returns to its initial, more stable condition. In inflammation associated carcinogenesis, the associated microenvironment persists.

Chronic stressors, including chronic inflammation, may initiate cancer through subtle alterations in cellular networks at all levels. Initially, they may simply activate physiologic functions, such as the immune system response to a foreign or self antigen, leading to a new and less stable microenvironment that reverts to normal once the stimulus recedes. However, the continued presence of the stimulus over years or decades, assisted by additional chronic stressors, may be amplified due to changes in interacting pathways, even if the interaction is remote and infrequent. Ultimately, these altered networks may propagate into other areas of the cell and set off other malignant changes involving neighboring cells and local tissues and eventually cause systemic changes (Mbeunkui 2009, Morgillo 2018).

Inflammatory networks are inherently more unstable than other physiologic networks because of their ability to rapidly initiate sophisticated repair processes in response to varied stimuli. Continuous stimulation of these networks produces pro-carcinogenic reactive oxygen and nitrogen species, growth factors, pro angiogenesis factors and attenuation of local cell mediated immunity (Kanda 2017, Figure 3, Rasch 2014, Nath 2010). Any of these factors can be the grain of sand that causes an avalanche of additional network changes. The microenvironment created by the chronic inflammation nurtures mutated cells, helps them escape immune surveillance (Dalgleish 2006) and ultimately promotes invasion by activating cells to mimic physiologic “invasion” of wounded epithelium through the extracellular matrix (Bleaken 2016, Coussens 2002). Germ line variations in inflammatory mediators may facilitate inflammation associated cancer that might not arise otherwise (Amador 2016, Zhang 2015).

Section 1.1 Specific types of chronic inflammation associated with malignancy
We describe below how chronic inflammation associated with microorganisms (bacterial and viruses), parasites, autoantigens, trauma, excess weight, diabetes and other diseases contributes to specific types of malignancy, either directly or indirectly. We briefly discuss associations with diet, aging and immune system dysfunction.

Table 1 - Types of cancer discussed:
Bladder squamous cell carcinoma - section 1.6
Breast cancer - introduction, sections 1.8, 1.9, 2.1
Cervix - section 1.9
Cholangiocarcinoma - section 1.6
Colorectum - sections 1.8, 1.9, 2.1
Cutaneous squamous cell carcinoma - section 1.7
Esophageal adenocarcinoma - sections 1.7, 1.8
Esophageal squamous cell carcinoma - section 1.7
Gallbladder cancer - section 1.5
Gastric carcinoma - section 1.5
Glioblastoma - introduction, section 2.2
Hepatocellular carcinoma - section 1.8
Kaposi sarcoma - section 1.2
Kidney cancer - section 1.8
Lung cancer - sections 1.9, 2.1
Lymphoma - breast implant associated anaplastic large cell lymphoma - section 1.3
Lymphoma - Burkitt - section 2.2
Lymphoma - diffuse large B cell - sections 1.3, 1.4
Lymphoma - enteropathy associated T cell - section 1.4
Lymphoma - hepatic - sections 1.3, 1.4
Lymphoma - Hodgkin - section 2.2
Lymphoma - MALT - sections 1.3, 1.4

Lymphoma - primary cutaneous- section 1.3
Pancreatic adenocarcinoma - introduction, sections 1.8, 1.9, 2.1
Prostate cancer - section 2.1
Uterus - section 1.8

Section 1.2 Infections
Infections are a major contributor to cancer. In 2012, 15.4% (2.2 million) of the 14 million new cancer cases worldwide were attributed to ten infectious agents, including *Helicobacter pylori* (770,000 cases), human papillomavirus (640,000 cases), hepatitis B virus (420,000 cases), hepatitis C virus (170,000 cases), Epstein-Barr virus (120,000 cases), Kaposi sarcoma herpesvirus / HHV8 (44,000 cases), *Schistosoma haematobium* (7,000 cases), HTLV1 (3,000 cases) and *Clonorchis sinensis* and *Opisthorchis viverrini* (1,300 cases) (**Plummer 2016**). The International Agency for Research on Cancer (IARC), the specialized cancer agency of the World Health Organization (WHO), has classified all of these infectious agents as Group 1 (definite) carcinogens in humans, as well as HIV1 (**IARC Monograph on the Evaluation of Carcinogenic Risks to Humans 2017**). In sub-Saharan Africa, Kaposi sarcoma is the second largest contributor to new cancer cases. Totals were not given for HIV1 because (a) it increases risk only in combination with other carcinogenic infectious agents and totals are allocated to the coinfection; and (b) the number of HIV related cancer cases could not be obtained in most countries.

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 infection with a microorganism compared to no infection (**World Health Organization - Metrics: Population Attributable Fraction**, accessed 16May20, **Alberg 2013**). The attributable fraction for cancers due to infection varies from more than 50% in some countries in sub-Saharan Africa to less than 5% in the United States, Canada, Australia, New Zealand and some countries in Western and Northern Europe (**Plummer 2016**, **Oh 2014**, **Schottenfeld 2015**, **Gredner 2018**).

We describe microorganisms that promote carcinogenesis primarily through chronic inflammation. Those which promote carcinogenesis primarily through oncogenic proteins, including bacterial toxins, will be described in a subsequent paper.

Section 1.3 Antigen driven lymphoproliferation - infections
We describe five chronic bacterial infections and one viral infection that directly cause MALT lymphoma or other low grade non-Hodgkin B cell lymphoma through a process called antigen driven lymphoproliferation. This mechanism accounts 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 occurring in susceptible cells within the correct microenvironment. For example, 1.7 billion people worldwide are infected with *Mycobacterium tuberculosis* (**Centers for Disease Control and Prevention > Global Health > Tuberculosis**, accessed 16May20) but even when untreated it does not induce 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. To date, we cannot predict the precise combination of infectious agents, susceptible cells and microenvironment that can produce malignancy.

Gastric MALT lymphoma due to chronic *Helicobacter pylori* infection
Gastric MALT lymphoma due to chronic *Helicobacter pylori* gastritis demonstrates the classic features of antigenic driven lymphoproliferation: (a) the persistence of bacteria or viruses that cannot be killed by the immune system causes chronic immune stimulation, which creates instability in networks affecting B lymphocytes, leading to clonality and occasionally overt malignancy; it may also lead to instability in interacting networks that propagate over time throughout the cell, tissue and organism; (b) the immune stimulation is directed at countering the microorganisms and is not a generalized proliferation; (c) there is no apparent intermediate state based on histology; and (d) these network changes are typically reversible; removal or antagonism of the bacterial or viral stimuli by antibiotics or anti-virals may cause

reversion towards the original nonmalignant state (Suarez 2006), although interacting networks may not completely revert.

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 causes 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* (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 a new attractor state characterized by chronic lymphoid proliferation. Infiltrating macrophages induced by *H. pylor*i and *H. pylori* specific T cells produce high levels of cytokines and chemokines (Russo 2016, Munari 2011, Kuo 2010), as well as reactive oxygen and nitrogen species (Kanda 2017), which act on these inherently unstable lymphocytes to produce additional network alterations and increase the risk of transformation of clones that are dependent on antigenic stimulation (Suarez 2006).

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

Antibiotics directed against *Helicobacter pylori* (“eradication therapy”) lead to long term regression in 75-85% of cases of low grade gastric MALT lymphoma (Nakamura 2012, Sugizaki 2018). The antibiotics cause reversion of the cancer attractor state towards the physiologic state 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, Gong 2016, Kuo 2017), which is attributed to: (a) their association with antibiotic sensitive *Helicobacter heilmannii* (Morgner 2000, Joo 2007, Bento-Miranda 2014), (b) false negative *H. pylori* testing (Gisbert 2006) due to low numbers of *H. pylori* present (Park 2010); (c) intestinal microbiota other than *H. pylori* which may contribute to MALT lymphoma; or (d) the antiproliferative effect of macrolide antibiotics included in eradication therapy, such as clarithromycin (Ohe 2013, Van Nuffel 2015, Ferreri 2015). Eradication therapy may also be useful for other *H. pylori* associated lymphoma, such as *H. pylori* positive gastric diffuse large B cell lymphoma (Kuo 2012, Kuo 2013, Paydas 2015).

Why might antibiotics be ineffective? We suggest that the cancer attractor state initially created by *H. pylori* is unstable. Over time, or due to other chronic stressors, this may lead to additional network changes that are *H. pylori* independent. *Helicobacter pylori* infection may also induce 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* (Coeuret 2014) or *H. pylori* (Dutta 2010) causes 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 or Mediterranean lymphoma, 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, Carron 2018, Bianchi 2018).

Chronic *C. jejuni* infection can elicit a strong IgA mucosal response which leads to sustained stimulation of the mucosal immune system, expansion of IgA secreting clones and ultimate selection of a clone that secretes α heavy chains and eludes antibody-antigen Fc dependent down regulation (Lecuit 2004). IPSID is considered a variant of MALT lymphoma that arises in small intestinal mucosa associated

lymphoid tissue, representing a new attractor state characterized 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, (PathologyOutlines.com > Bone marrow neoplastic > Heavy chain disease, accessed 16May20). It is also associated with impaired cellular and humoral immunity (Bianchi 2018). Cytogenetic studies demonstrate clonal rearrangements involving predominantly the heavy and light chain genes, including t(9;14), affecting the *PAX5* gene (Al-Saleem 2005).

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 with tetracycline, possibly with the addition of metronidazole (Pervez 2011), with 30-70% complete remission. Cases refractory to antibiotics may have permanent genetic changes demonstrated by the translocation, or have other network changes associated with bacterial independent growth. In these cases, or in advanced disease such as diffuse large B cell lymphoma, CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone) is indicated (Economidou 2006).

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 1-2% of non-Hodgkin lymphoma cases and 80% are MALT subtype. It shows a mature B cell phenotype derived from post germinal center B cells. *C. psittaci* are obligate intracellular bacteria 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 of the respiratory tract (Perrone 2016).

The association between *Chlamydia psittaci* infection and ocular adnexal lymphoma demonstrates more geographic variability than *Helicobacter pylori* infection, which suggests differences in *Chlamydia psittaci* prevalence or genetics, rates of EBV coinfection, host genetics or other host factors (Mosleh 2011a, Moslehi 2011b, Perrone 2016). 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 by country, Ferreri 2012) but another international study showed lower rates in Germany (47%), the US East Coast (35%), the Netherlands (29%), Italy (13%), the UK (12%) and Southern China (11%) (Chanudet 2006). Studies focusing on single locations showed prevalence rates varying from 80% in Italy (Ferreri 2004), 79% in Korea (Yoo 2007) and 54% in Austria (Aigelsreiter 2008) to 0% in Kenya (Carugi 2010), Florida (Rosado 2006) and China (Cai 2012).

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 instability, possibly with chromosomal abnormalities, and ultimately transform to MALT lymphoma (Stefanovic 2009, Suarez 2006). However, the geographic variability of the association reinforces the overriding theme that chronic stressors cause malignancy only in the correct context of other chronic stressors and the appropriate micro- or macroenvironment, which appears to be necessary to create a new attractor.

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). Non responsive cases may be due to clones with translocations or other characteristics that are no longer bacterial dependent.

Primary cutaneous lymphoma due to chronic *Borrelia burgdorferi* infection
Primary cutaneous lymphoma is associated with *Borrelia burgdorferi* infection but there is strong geographic variability, similar to ocular adnexal MALT lymphoma due to chronic *Chlamydia psittaci* infection. The association is strong in areas endemic for Lyme disease, such as the Scottish Highlands (Goodlad 2000), Austria (Cerroni 1997) and Yugoslavia (Jelić 1999) and in a nonendemic area of France (de la Fouchardiere 2003), but no association was found in the US (Takino 2008, Wood 2001), Asia (Li 2003), Central Italy (Goteri 2007) and Northern Italy (Ponzoni 2011). The association may not

be detectable in nonendemic areas with few cases. It is also possible that specific features of the bacteria and hosts or the dynamics of the bacterial-host relationship differ in endemic vs. non-endemic areas.

B. burgdorferi is thought to provoke chronic antigen stimulation similar to *H. pylori*, *C. jenuni* and *C. psittaci,* which may lead to primary cutaneous lymphoma. Infection may cause chronic inflammation of the skin with a dense lymphocytic infiltrate followed by atrophy, which may be considered an intermediate state.

Antibiotics are effective in many but not all lymphoma cases, 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).

Breast implant associated anaplastic large cell lymphoma due to bacterial contamination
Breast implant associated anaplastic large cell lymphoma, first described in 1997 (Keech 1997), is a rare T cell lymphoma exclusively associated with textured breast implants (Rastogi 2018). It was first recognized by the US Food and Drug Administration (accessed 16May20) in 2011, and is a newly recognized provisional entity in the 2017 revision of the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues (Swerdlow 2017). Its incidence has been estimated at 0.1 to 0.3 per 100,000 women with a breast prostheses but may be higher (Laurent 2016, Mempin 2018). Patients typically present with a delayed seroma and less commonly with a capsular mass or systemic disease at a mean 8 to 10 years after implantation. The tumor morphology and immunophenotype are similar to ALK negative anaplastic large cell lymphoma (Quesada 2018).

The etiology is unknown but may be due to chronic bacterial antigen stimulation of T cells in genetically predisposed women, comparable to *Helicobacter pylori* associated gastric MALT lymphoma (Nava 2018). This theory is supported by patterns of cytokine and transcription factor expression (Kadin 2016) and a higher bacterial load composed of different bacteria in implant capsules (*Ralstonia* species) compared to patients with normal capsular contracture (Hu 2015). The presence of a foreign body may also lead to a microenvironment rich in cytokines that stimulate IL6, a driver of some cases of lymphoma and carcinoma, and other cytokines that promote immune suppression (Mempin 2018).

Another theory is that the silicone in the implant capsule is the chronic inflammatory stimulus. It degrades over time and presents antigens to the host, which is more common in textured implants (Britez 2012). The presence of T cells producing IL17 and IL13 is suggestive of an autoimmune process (Quesada 2018). In either case, it appears that textured breast implants disturb the local microenvironment, whether due to bacteria or foreign antigens, which creates increased network instability conducive for this lymphoma to arise.

Explantation with a complete capsulectomy removing all disease, without chemotherapy, is usually considered curative treatment (Quesada 2018). The effectiveness of this treatment suggests that the microenvironmental changes were confined and eliminated by surgery and did not propagate in a significant way to networks beyond the surgical margins.

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 diffuse large B cell lymphoma (Bronowicki 2003, Kikuma 2012) and marginal zone lymphoma (Arcaini 2012, Nieters 2006, De Re 2012). This association appears strongest in highly endemic areas such as Italy, Japan and the Southern US (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 with high HCV prevalence compared with <1% in low prevalence areas (Dal Maso 2006), in which small numbers of HCV positive subjects may make it difficult to detect an association (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 (Quinn 2001, but see Ng 2014) , (b) the histology of these cells is often typical of germinal center and post germinal center B cells (Kedia 2014), (c) HCV infection is only associated with lymphoma subtypes that originate from germinal center or post germinal center B cells but not other lymphoma subtypes such as mantle cell, Burkitt and T cell lymphoma (de Sanjose 2008), (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, Bunchorntavakul 2018), with massive clonal expansion of marginal zone B cells that recognize the HCV E2 protein of HCV and may ultimately override immune system control (Visentini 2013, Dustin 2014). In addition, HCV may broadly upregulate B cell receptor signaling in primary B cells (Dai 2016) and may promote lymphomagenesis via microenvironmental changes (Carbone 2013). Finally, HCV may cause a “hit and run” effect of triggering the process and causing secondary effects, but not being detectable (Forghieri 2012, Machida 2004).

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) and possibly HCV associated diffuse large B cell lymphoma (Pellicelli 2018, Tsutsumi 2017). The high response rate suggests that these lymphomas have strong HCV dependency; antiviral treatment either reverts networks towards their physiologic states or towards states that lack malignant features. Treatment failure may be due to independence from the antigen driven mechanism, possibly due to chromosomal translocations, other genetic aberrations (Zignego 2012) or acquisition of new attractor states.

Section 1.4 Antigen driven lymphoproliferation - autoantigens
Antigen driven lymphoproliferation may also occur due to autoantigens, with a similar pathophysiology as cases due to microorganisms. Autoimmunity is a well described risk factor for lymphoma (Baecklund 2014, Kleinstern 2018, Wang 2015). Similar to the lymphomas described above, the B or T cell proliferations appear to be directed against the autoantigens; i.e., there is not 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. The autoimmune associated lymphoproliferation may be considered an intermediate network state, similar to those described above for antigen driven lymphoproliferation due to infections.

However, in contrast to antigen driven lymphoproliferation due to infections, treatment is directed at the tumor itself via surgery or chemoradiation. With the exception of celiac disease, treatment is not directed at suppressing autoantigens because the side effects of this therapy, namely an increase in other malignancies, infections and steroid related side effects, outweigh the possible benefits of preventing an indolent lymphoma. “Tuning” the immune system to ignore autoantigens is currently not possible, although chimeric antigen receptor T cell therapy (c-ART) is under investigation (Ellebrecht 2016).

MALT lymphoma of thyroid gland due to autoimmune (Hashimoto) thyroiditis
Autoimmune (Hashimoto) thyroiditis, also called chronic lymphocytic thyroiditis, is the most common cause of hypothyroidism in iodine sufficient regions (Chaker 2017). It is also a major risk factor for primary thyroid lymphoma, including MALT lymphoma, with a relative risk of 67 to 80 times compared to 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. It has an incidence of 30 to 60 cases per 100,000 population per year and a prevalence in women of at least 2% (Endotext [Internet]. Hashimoto's Thyroiditis, accessed 16May20). 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 (Caturegli 2014).

Primary MALT lymphoma of the thyroid gland is rare. It represents 10-40% of all cases of primary thyroid lymphoma, but this accounts for only 1-5% of thyroid malignancies (Vardell 2019, Chai 2015). Patients are usually women who often have Hashimoto thyroiditis (Stein 2013). The predominance of this and other autoimmune disease in women may be due to their stronger adaptive immune system responses, partially modulated by sex hormones (Purnamawati 2018, Fairweather 2008, Elenkova 2017), as well as by obesity or higher levels of leptin (Popławska-Kita 2014). When present, Hashimoto thyroiditis may

have clonal bands with a polyclonal smear pattern. This is not considered malignant (Saxena 2004), although the sequence similarity between clonal bands in Hashimoto thyroiditis and subsequent thyroid lymphoma suggests that it is a precursor lesion (Moshynska 2008). This progression is not well understood (Schreuder 2017) but may involve the NFκB pathway (Troppan 2015), an important regulator of numerous inflammatory genes, with both pro- and anti inflammatory roles (Lawrence 2009). We speculate that chronic autoantigenic stimulation pushes lymphocytes towards network states with increasing instability and a higher likelihood of affecting interacting networks, similar to gastric *Helicobacter pylori*. Hashimoto thyroiditis may represent an intermediate state, with a propensity to transform to overt malignancy in the presence of other chronic stressors.

In the thyroid gland, MALT lymphoma is considered low grade with an excellent prognosis after treatment with surgery or chemoradiation therapy (Chai 2015, Cha 2013, Oh 2012). As a result, Hashimoto thyroiditis itself is not treated to reduce the risk of primary or recurrent lymphoma, although complications may be treated with steroids (Yu 2014, Cyranska-Chyre 2019).

MALT lymphoma of salivary gland due to lymphoepithelial sialadenitis of Sjögren syndrome
Patients with lymphoepithelial sialadenitis of Sjögren syndrome have 44 times the 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 9 times more common in women than men, with a peak onset during menopause (Mavragan 2014). It is characterized by hypergammaglobulinemia, serum autoantibodies and marked B cell hyperactivity. Progression to B cell lymphoma, which occurs in 5% (Alunno 2018), can be predicted based on the presence of salivary gland enlargement, lymphadenopathy, Raynaud phenomenon, anti-Ro/SSA or anti-La/SSB autoantibodies, rheumatoid factor positivity, monoclonal gammopathy and C4 hypocomplementemia (Fragkioudaki 2016).

Sjögren syndrome is characterized histologically by a benign lymphoid infiltrate with lymphocytic epitheliotropism in salivary glands. Lymphoepithelial sialadenitis (LESA) is common, characterized by 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 ducts even in the absence of lymphoma (Jaffe 2002). In up to 50% of cases, some foci of intraepithelial B cell infiltration are clonal, as demonstrated by PCR for immunoglobulin heavy chain gene rearrangement. Despite clonality, the infiltrates usually have a benign clinical course, analogous to lymphocytic gastritis associated with *Helicobacter pylori* and *Hashimoto thyroiditis,* 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), although LESA and the presence of clonality appear to represent an intermediate state in the transformation to lymphoma.

MALT lymphoma in the salivary glands typically arises due to autoimmunity associated inflammation, which causes a proliferation of B cells directed against the autoantigen. The increased proliferation may lead to stimulation of NFκB pathways and reactive oxygen species that damage DNA (Schreuder 2017). This occasionally leads to clonal overgrowth, secondary genetic changes and MALT lymphoma (Jaffe 2002). In contrast to gastric MALT, salivary gland cases usually have no translocations involving the *MALT1* gene (Mulligan 2011, Ye 2003), perhaps because the lymphocyte network in salivary glands in this microenvironment exhibits greater stability.

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 which plays a key role in controlling NFκB activation (Nocturne 2013). Germ line abnormalities of *TNFAIP3* may affect the inherent stability of the immune response, leading to decreased control of the NFκB pathway, which promotes survival of B cells and oncogenic mutations (Nocturne 2015).

LESA is treated symptomatically or with surgery as a last resort. LESA itself is not treated to reduce the risk of any associated lymphoma because the lymphoma is usually low grade and indolent (median overall survival is 18.3 years, Jackson 2015), and the side effects of therapy likely outweigh any possible benefit. Currently, Sjögren associated lymphoma is treated effectively 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 which occurs in 14% of patients with celiac disease, an autoimmune disease triggered by gluten ingestion. EATL incidence has increased significantly in the US, reflecting either increasing seroprevalence of celiac disease or better recognition of rare T cell lymphoma subtypes. EATL incidence may continue to rise given the large number of undiagnosed individuals with celiac disease (Sharaiha 2012). EATL type II, now known as monomorphic epitheliotropic intestinal T cell lymphoma, is rarer, has no known association with celiac disease, and has a different histology and immunophenotype (Swerdlow 2016).

Celiac disease has a 1% prevalence in Western populations and may be clinically silent (Brito 2014). It is usually diagnosed by demonstrating gluten enteropathy in a small bowel biopsy or by tissue transglutaminase antibodies in serum (Webb 2015). Patients typically have HLA-DQ2 and DQ8 haplotypes (Bao 2012) and increased immunological responsiveness to prolamins (plant storage proteins) such as dietary wheat gliadin and similar proteins in barley, rye and possibly oats. A dysregulated microbiome may also contribute to celiac disease (Kim 2015).

Antigen driven lymphoproliferation directly drives lymphomagenesis in celiac disease patients. Initially, 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 (Kim 2015). These cytotoxic T cells, stimulated by both IL15 and gluten specific CD4+ T cells, may become clonal and malignant (Kooy-Winkelaar 2017). Initial histologic changes of celiac disease (PathologyOutlines.com > Small Bowel > Celiac Sprue, accessed 16May20) may represent an intermediate, premalignant state.

Celiac disease is treated by a strict gluten free diet for life, which is usually effective in preventing the subsequent enteropathy associated T cell lymphoma (Holmes 1989, Rashtak 2012) although rare cases are refractory (Woodward 2016). Some refractory cases may be due to T cells which arise from a small subset of unusual innate-like T cells present in normal intestine (Malamut 2019), due to different antigens or creation of a different attractor because of variations in the microbiome.

Enteropathy associated T cell lymphoma is an aggressive lymphoma with a 5 year survival of 8-60% (Nijeboer 2015) and median overall survival of only 10 months (Delabie 2011). Typically, local debulking is followed by anthracycline based chemotherapy, possibly followed by high dose chemotherapy and autologous stem cell transplantation (Nijeboer 2015). Although *Helicobacter pylori* eradication has been successful in treating aggressive diffuse large B cell lymphoma of the stomach (Paydas 2015), dietary manipulation as treatment of EATL has not been described, to our knowledge.

Hepatic lymphoma due to autoimmune disease
Persistent inflammatory processes associated with Hepatitis B or C infection or autoimmune disease (primary biliary cholangitis, Sjögren syndrome, autoimmune hepatitis and rheumatoid arthritis) may play independent roles in the lymphomagenesis of hepatic B cells (Kikuma 2012), although primary hepatic lymphoma is rare (0.06% of non-Hodgkin lymphoma). 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 lymphoma 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), a possible intermediate state, leading to MALT lymphoma (Prabhu 1998), diffuse large B cell lymphoma (Kanellopoulou 2011) and lymphoplasmacytic lymphoma (Koumati 2011). It appears that numerous factors cause local network instability, which, when coupled with a permissive microenvironment, can propagate into adjacent networks and cause lymphoma.

Typical treatment is CHOP chemotherapy or radiotherapy (Ugurluer 2016), and is not directed at the antigen driven lymphoproliferation. In a recent study, median overall survival was 13.5 years (Ugurluer 2016).

Section 1.5 Bacterial driven carcinoma

Chronic bacterial infection promotes epithelial cell malignancy through chronic inflammation, although bacterial mutagenic toxic proteins are also important (Cummins 2013, Table 1, Armstrong 2018). 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 epithelial stem or progenitor cells. Elimination of the bacteria reduces this stress. However, unlike lymphocytes which undergo apoptosis when no longer triggered by antigen, the stem or progenitor cells persist and may accumulate additional mutations.

Gastric carcinoma due to chronic *Helicobacter pylori* infection
Chronic gastric infection by *Helicobacter pylori* is a major cause of gastric carcinoma, the world's third largest cause of cancer death after lung and colorectal cancer (World Health Organization, accessed 16May20), but only the 17th largest cause of US cancer death (Cancer Facts & Figures 2020). *Helicobacter pylori*, first identified by Marshall and Warren (Marshall 1984), is classified by the IARC as a Group 1 carcinogen in relation to gastric carcinoma (IARC 1994). Only patients with *H. pylori* infection appear to develop gastric carcinoma (Uemura 2001).

H. pylori induces prominent chronic inflammation that is considered necessary but not sufficient 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 alpha (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 (chronic gastritis, gastric atrophy, intestinal metaplasia and dysplasia) that may lead to cancer (Castaño-Rodríguez 2014, Kidane 2018). In addition, the *H. pylori* CagA protein has a direct oncogenic effect on gastric epithelium.

Cofactors that increase the risk of gastric carcinoma are a proinflammatory diet (Shivapp 2016, Lee 2017), tobacco, alcohol and excess weight. In addition, 10-15% of diffuse histology cases are familial (Zanghieri 1990), often due to mutations in *CDH1* (E cadherin) (Hansford 2015, van der Post 2015) or other genes (Huang 2015, Gaston 2014, Masciari 2011, Ansari 2018).

Overall, it appears that multiple network changes initiated by bacteria and the host immune response are needed to move gastric epithelial cell networks from their physiologic attractor states towards histologic changes that act as intermediate states and then to cancer attractor states. This process is consistent with Farber's theory of initiation and promotion (Farber 1984), which progression due to multiple chronic stressors.

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 carcinoma (Chey 2007, Howden 2014). This reduces recurrence in early gastric carcinoma treated with endoscopic resection according to some (Fukase 2008, Rokkas 2017) but not all studies (Kim 2016, Tahara 2016). Treatment failure may be due to a field effect creating widespread pre-neoplastic lesions (atrophic gastritis, intestinal metaplasia and dysplasia, Rokkas 2007, Ohba 2016) and network changes reducing their dependence on bacterial stimulation.

Gallbladder cancer due to chronic *Salmonella typhi* infection
Gallbladder carcinoma is projected to cause 4,090 US deaths in 2020 (Cancer Facts & Figures 2020), with the highest rates in Native Americans in New Mexico (Nemunaitis 2018). It is associated with chronic carriage of *Salmonella typhi,* the cause of typhoid fever; these patients have 4 to 14 times the risk of gallbladder carcinoma compared to non carriers (Gonzalez-Escobedo 2013, Nagaraja 2014, Koshiol 2016).

The incidence of gallbladder carcinoma is highest in women in Southeast Asia and South America, including Delhi, India (21.5 per 100,000 women), South Karachi, Pakistan (13.8) and Quito, Ecuador (12.9), due to high levels of *S. typhi carriage*; low rates (<3 for women, 1.5 for men) are found in most of Northern Europe, the US, Canada (Randi 2006, Nath 2010) and Shanghai, China, due to low prevalence of chronic *S. typhi* carriers (Safaeian 2011). PCR may be the most sensitive diagnostic tool for *S. typhi*

infection (Tewari 2010) because bacterial culture isolation rates are very poor in the gallbladder (Nath 2010).

Bile is considered sterile (Csendes 1975, Ikeda 1990, Suna 2014), but 3-5% of typhoid fever 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 (Di Domenico 2017). Chronic infections can persist for decades; although highly contagious through fecal spread, patients are typically asymptomatic (Gonzalez-Escobedo 2013). Recommended followup 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 causes molecular disturbances in the cell cycle of gallbladder mucosa (Nath 2010). In addition, increased cell turnover and oxidative stress promote cell cycle deregulation, apoptosis, replicative senescence and *TP53* alterations (Espinoza 2016). The bacteria also metabolize primary bile acids to produce potentially carcinogenic toxins and metabolites, including bacterial β glucuronidase, which produces cytolethal distending toxin, the first bacterial genotoxin described, as well as mutagenic intermediates and other primary and secondary bile acid metabolites (Nath 2010). This unresolved chronic inflammation may lead to metaplasia, dysplasia and ultimately carcinoma (Espinoza 2016).

Other bacterial species associated with gallbladder cancer are *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 are chronic cholelithiasis, chronic infection and obesity (Nath 2010).

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

Gallbladder cancer has a dismal 5 year survival rate of less than 5% (Goetze 2015). Prevention based on treating typhoid fever is recommended (Di Domenico 2017).

Section 1.6 Parasite driven carcinoma
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 a specific combination of chronic stressors in the proper microenvironment is needed to push physiologic networks into 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 daily consumption of raw freshwater and salt fermented fish beginning in childhood, particularly in Thailand, results in repeated exposure to liver flukes and nitrosamine contaminated food (Pairojku 1991, Alsaleh 2018).

Opisthorchis viverrini and *Clonorchis sinensis* damage bile duct epithelia via several mechanisms. First, after ingestion of the parasite metacercariae in contaminated fish, the larvae develop and migrate to bile ducts, where adult worms feed on biliary epithelia and contents in the bile, causing mechanical damage (Ogorodova 2015). Second, the presence of the parasites 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 may directly induce proliferation of biliary progenitor cells and inhibit DNA repair and apoptosis (Lee 1997, Sripa 2012). Fourth, the liver fluke may induce contributory changes in the biliary tract microbiome, which intensify the degree of inflammation and proliferation of biliary epithelium

(Prueksapanich 2018, Xu 2018). Primary sclerosing cholangitis (Rizvi 2015) and dysplasia may be intermediate states (Kerr 2014).

Nitrosamines may be necessary for the development of cholangiocarcinoma (Pairojku 1991, Sripa 2016) - Syrian golden hamsters only develop cholangiocarcinoma with dimethylnitrosamine plus fluke infestation; either alone is insufficient (Lee 1993). Other established risk factors are alcohol (Miwa 2014), tobacco (Steele 2018) and biliary tract stone disease (Cai 2011, Chang 2013). Germ line polymorphisms in IL6 may be important (Prayong 2014, Surapaitoon 2017).

Treatment of liver fluke infestation by praziquantel is very successful but only with early diagnosis and correct species identification (Huang 2012). Community wide prevention programs are also helpful (Sripa 2015). Surprisingly, repeated praziquantel treatment for liver flukes is associated with cholangiocarcinoma (Luvira 2018), perhaps because repeated treatments are confounded with reinfection rates (Kamsa-Ard 2015).

Bladder squamous cell carcinoma due to *Schistosoma haematobium*
Schistosomiasis due to infestation by *Schistosoma haematobium* is strongly associated with bladder squamous cell carcinoma (Ishida 2018). First identified in 1851 by Theodor Bilharz, *S. haematobium* is a blood fluke residing in venules and capillaries of the bladder and other pelvic organs. 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 classified *S. haematobium* as a Group 1 carcinogen (IARC 1994).

The mechanism of carcinogenesis in *S. haematobium* is similar to liver flukes: the parasite causes chronic inflammation, leading to epithelial metaplasia, an intermediate state in this setting. The presence of nitrosamines (exogenous in liver flukes, endogenous with schistosomiasis) acts as a cofactor (Ishida 2018). Adult *S. haematobium* worms commonly invade the venous plexus around the urinary bladder. The adult worms release eggs, leading to chronic granulomatous inflammation in the bladder mucosa and submucosa, followed by urothelial squamous metaplasia. Chronic granulomatous inflammation also causes bladder fibrosis, urine stasis and bacterial 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, Abdel Mohsen 1999).

Schistosomiasis is not implicated in the etiology or pathogenesis of any other malignant disease (Khaled 2013). Despite endemics in 52 countries causing 290 million people to receive preventative treatment in 2018 (World Health Organization, Schistosomiasis Fact Sheet, accessed 16May20), fewer than 25 cases of schistosomiasis have been reported to be associated with prostatic adenocarcinoma (Figueiredo 2015, Mazigo 2010), confirming our hypothesis that a specific combination of chronic stressors in the proper microenvironment is needed to push physiologic networks into malignant pathways.

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

Nonmuscle invasive bladder cancer (stages Ta, Tis and T1) is treated with transurethral resection of the bladder tumor and intravesical chemotherapy with mitomycin C, possibly followed by intravesical bCG or other chemotherapy (Bladder Cancer Treatment (PDQ®), accessed 16May20). 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. The overall 5 year relative survival for 2008-2014 is 77%, varying from 96% for in situ disease to 5% for distant disease (American Cancer Society > Survival Rates for Bladder Cancer, accessed 16May20).

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, hot beverages or hot food) and skin (due to osteomyelitis, various dermatoses, deep burns, fistulas, scars, sinus tracts and ulcers).

Esophageal adenocarcinoma due to gastroesophageal reflux
Gastroesophageal reflux disease (GERD) 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, including reduced pressure and increased reflux episodes associated with transient relaxation of the lower esophageal sphincter and formation of a hiatal hernia (Ness-Jensen 2016). GERD causes esophageal squamous epithelium to transform to increasingly unstable hierarchical structures of columnar epithelium (Barrett metaplasia), epithelial dysplasia and adenocarcinoma (Goldblum 2003). In the US, the overall incidence of esophageal cancer has been stable for many years (American Cancer Society - Key Statistics for Esophageal Cancer, accessed 16May20) but as with lung cancer, the rate of adenocarcinoma has been increasing as the rate of squamous cell carcinoma has been decreasing.

Esophageal adenocarcinoma is a classic example of inflammation associated cancer (O'Sullivan 2014), although the mechanism involves trauma and repair, not infection or autoimmunity. 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 may lead to Barrett metaplasia (replacement of squamous epithelium by columnar epithelium), a process facilitated by reflux related nitric oxide production and Sonic Hedgehog secretion by squamous cells (Souza 2016).

Other risk factors for esophageal adenocarcinoma are cigarette smoking (Cook 2010), obesity (Long 2014, Zakaria 2017) and the Western diet (high fat, low fiber, low consumption of fruit and vegetables, Neto 2016, Lu 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 below).

The risk of Barrett esophagus and esophageal adenocarcinoma is influenced by many germ line genetic variants of small effect (Ek 2013, Dong 2018), including *VSIG10L* (Fecteau 2016) and *MGST1* (Buas 2017).

Treatment is based on surgery and chemoradiation (Esophageal Cancer Treatment (Adult) (PDQ®), accessed 16May20), but the overall 5 year survival is only 20% (American Cancer Society, accessed 16May20), with no survival differences between esophageal adenocarcinoma and squamous cell carcinoma (Tustumi 2016). Currently, treatment does not target the inflammatory microenvironment that triggered the malignant transformation.

Prevention is particularly important and focuses on early detection and treatment of premalignant lesions (Bornschein 2019). Lifestyle modifications include increasing physical activity, eating more 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 due to hot beverages and food
Esophageal squamous cell carcinoma is also associated with chronic inflammation but via different mechanisms. Its highest incidence occurs in the “Asian esophageal cancer belt” from Iran east to China and north to Russia (Melhado 2010). Ingesting hot beverages (mate) and hot foods (boiled meat) may increase the risk due to thermal damage; swallowing hard food without sufficient chewing may irritate the esophageal epithelium (Tai 2017, Chen 2015, Okaru 2018). Chronic thermal irritation may also stimulate the formation of reactive nitrogen species and nitrosamines or may impair the barrier function of the epithelium, making it more vulnerable to intraluminal carcinogens in tobacco and alcohol (Tang 2013), while fresh vegetables and fruit have a protective effect (De Stefani 2014, Zhao 2018). The degree of chronic inflammation correlates with esophageal precursor lesions. Persistent chronic inflammation may also 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 other causes (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 that 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, Sinha 2017). 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
According to the IARC and World Cancer Research Fund, up to 20% of worldwide cancer cases are due to obesity (De Pergola 2013, Calle 2003), with the strongest association for adenocarcinoma of the esophagus, colorectum and breast (postmenopausal) and carcinoma of the endometrium and kidney.

In the US in 2012, being overweight (BMI of 25 or more) or obese (BMI of 30 or more) 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 16May20); attributable fractions varied in men from 6% for rectal cancer to 33% for esophageal adenocarcinoma and in women from 4% for rectal cancer to 34% for endometrial cancer and esophageal adenocarcinoma (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, Ramos-Nino 2013) and cardiovascular disease, as well as various types of cancer (Divella 2016). Obesity is associated with diet (see below), 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 free fatty acids, 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 to be discussed in detail in a subsequent paper.

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 (Metrakos 2018, Page 2009).

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 (Ip 2013). 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 modulation, leading to malignant transformation.

Lifestyle modifications, including weight loss, physical activity and a Mediterranean diet have been recommended to reduce NAFLD (Romero-Gómez 2017). 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).

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. Men and women with excess weight as adolescents are also at an increased risk for subsequent pancreatic cancer (Zohar 2019). This risk may be mediated through insulin resistance and an altered adipokine milieu, or through obesity associated chronic low grade inflammation with production of inflammatory mediators (Rebours 2015).

Other risk factors for pancreatic adenocarcinoma are chronic pancreatitis and diet (see below), tobacco, family history (McWilliams 2016) and alcohol consumption (Korc 2017).

The traditional view that pancreatic cancer undergoes stepwise development through pancreatic intraepithelial neoplasia (PanIN) has been challenged because (a) pancreatic adenocarcinoma often metastasizes rapidly and early with complicated genetic abnormalities, consistent with punctuated equilibrium (isolated episodes of rapid speciation between long periods of little or no change) as the principal evolutionary trajectory (Notta 2016); (b) pancreatic cancer may originate by colonizing the ductal system and accumulates spatial and genetic divergence over time (Makohon-Moore 2018).

In network terms, it appears that chronic inflammation in the pancreas, aided by various risk factors, triggers a cascade of increasing instability in pancreatic ductal cells. This either leads to PanIN, intermediate states marked by molecular patterns that are not identifiable histologically, or proceeds directly to malignant states.

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). Whether aspirin reduces the risk of pancreatic cancer is controversial (yes; Streicher 2014, Risch 2017; no: Amin 2016, Khalaf 2018).

Section 1.9 Other
Other types of inflammation associated with cancer are diabetes (independent of its association with obesity), chronic pancreatitis, pneumonia and chronic lung disease.

Cancer due to diabetes
Patients with diabetes have a 20% increased risk of cancer (primarily breast, cervical, colon and pancreatic cancer), due in part to associated obesity, insulin resistance (which features hyperinsulinemia and increased insulin-like growth factor, Ashamalla 2018), chronic inflammation and abnormalities in sex hormone metabolism or adipokines (Scappaticcio 2017). The plethora of molecules operating within distinct signaling pathways suggests cross talk between the multiple pathways at the interface of the diabetes-cancer link (Tudzarova 2015). Low grade chronic inflammation, insulin resistance and glucose intolerance may create a microenvironment which promotes cancer development (Gristina 2015). Metformin, an anti-diabetic drug, reduces the incidence of cancer in diabetic patients (Fukumura 2016), and illustrates how disrupting the inflammatory milieu that sustains malignant transformation may prevent malignancy.

Pancreatic adenocarcinoma due to chronic pancreatitis
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 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, chronic pancreatitis is estimated to cause only 1.3% of cases of pancreatic adenocarcinoma (Duell 2012). In autoimmune pancreatitis, the incidence of subsequent pancreatic cancer ranges from 0 to 4.8% (Ikeura 2016). These low rates support our general theory that chronic inflammation require additional stressors, in the correct microenvironment, to cause malignancy.

Chronic pancreatitis may cause malignancy through: (a) inflammation related reactive oxygen species and reactive nitrogen intermediates, enhanced by growth factors and cytokines which may induce DNA damage and abortive repair (Ling 2014), (b) macrophage secreted inflammatory cytokines which induces pancreatic acinar cell differentiation to a duct-like phenotype (ductal metaplasia) and contribute to pancreatic intraepithelial neoplasia and pancreatic adenocarcinoma (Guerra 2007, Strobel 2007, Seimiya 2018), mediated by NFκB and matrix metalloproteinases (Liou 2013), (c) creation of a tumor microenvironment in which the immune response is actively suppressed (Evans 2012), (d) promoting 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).

Lung carcinoma due to chronic inflammation
The overwhelming contribution of smoking to lung carcinogenesis makes it difficult to determine additional risk factors but a 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, Zhang 2017; smokers only: Wang 2012; never smokers: Brenner 2011). Additional risk factors related to chronic inflammation are recurrent pneumonia in AIDS patients (Shebl 2010, Hessol 2015, Marcus 2017 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). NSAIDs may protect against lung cancer risk (smokers - Harris 2002, women - Van Dyke 2008, men - Erickson 2018 but see Jiang 2015-no effect).

Section 2.0 Independent etiologies associated with chronic inflammation
Diet, aging and immune system dysfunction are associated with chronic inflammation but also have independent mechanisms of action. They are summarized below, with detailed discussions to follow in a future paper.

Section 2.1 Diet
The typical Western diet of high consumption of fat, cholesterol, sugar and salt, processed foods and "fast foods" and low consumption of vegetables, fruit and fiber, is strongly associated with cancer (Myles 2014); an estimated 5.2% of US cancer cases are associated with a suboptimal diet (Zhang 2019). Diet also interacts with excess weight (section 1.8) and diabetes (section 1.9).

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 almost 2,000 articles in the scientific literature on diet and inflammation and obtaining nutritional surveillance data sets from around the world. Qualifying articles were scored based on whether each dietary parameter increased, decreased or had no effect on inflammatory biomarkers IL-1β, IL4, IL6, IL10, TNF-α and C reactive protein (Shivappa 2014c). A higher DII score indicates a proinflammatory dietary milieu. The DII is associated with low grade inflammation using a composite score of plasma and cellular biomarkers (Shivappa 2018a, Shivappa 2015g). It is also associated with cancer of the breast, colorectum, esophagus, lung, pancreas and prostate, as well as mortality from all causes, cardiovascular disease and COPD (Shivappa 2016d).

Foods with the highest inflammatory index are beer, sugary beverages, butter, coffee, french fries, other fried food, liquor and nitrate processed meat (Shivappa 2014a, bottom of Table 2), which move network pathways towards malignancy. Those with the lowest inflammatory index are vegetables other than potatoes, low fat dairy, fish, fruit (not juice), nuts and whole grains, which protect against malignancy. 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).

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

Section 2.2 Aging
Aging is a major risk factor for cancer (Finkel 2007), perhaps because it is associated with an inflammatory tissue microenvironment and immune senescence **(**Chang 2007, Marongiu 2017, Ostan 2015). However, it is also associated with a progressive loss of physiologic complexity, which causes a functional decline by diminishing the range of adaptive responses to environmental challenges (Chatterjee 2017, Manor 2013, Lipsitz 1992). In addition, aging is associated with a greater time for network dysfunction and DNA replication errors to occur and accumulate.

Section 2.3 Immune system dysfunction
Immune system dysfunction may promote malignancy, based on several types of evidence. First, transplant related immunosuppression antagonizes the usual immune system controls of neoplasia, leading to posttransplant lymphoproliferative disorder, cutaneous squamous cell carcinoma (Chockalingam 2015) and other malignancies.

Second, patients with autoimmune or other nonmalignant diseases treated with immunosuppressive agents are at higher risk for subsequent malignancy, for similar reasons (Penn 1973, Geller 2018). Treatment of malignancies with immunosuppressants may also lead to second primary malignancies (Kumar 2019).

Third, HIV related immunodeficiency is associated with all cancers except prostate cancer (Silverberg 2011, Dutta 2017). This may be due to inadequate suppression of infectious causes of cancer such as HPV, HCV and other viruses or due to reduced immune surveillance for malignant cells (Ribatti 2017).

Fourth, primary immunodeficiency has a prevalence of 30 - 50 per 100,000 population (Kobrynski 2014), and consists of at 430 single gene inborn errors of metabolism (Bousfiha 2020). In these patients, malignancy is the second most prevalent cause of death in children and adults after infection (Mortaz 2016).

Fifth, immune system dysfunction may arise during carcinogenesis. Cells evade the immune system through “camouflage and sabotage” as they acquire malignant characteristics (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).

Sixth, a fully functioning immune system kills viruses, bacteria and parasites that can induce tumors, directly or indirectly, as described above. By eliminating pathogens and promoting prompt resolution of inflammation, it also prevents establishment of a proinflammatory microenvironment that facilitates tumorigenesis. Immune system dysfunction attenuates these anti-tumor properties.

Finally, a “runaway” immune system may play a prominent role in malignancies with no known risk factors, such as classical Hodgkin lymphoma, nodular lymphocyte predominant Hodgkin lymphoma, sporadic Burkitt lymphoma and glioblastoma (Yang 2010, da Fonseca 2013). The immune system typically maintains a delicate balance between activating and dampening forces which may be disturbed by trivial events, as described by self organized criticality, as well as by chronic stressors. Over time, these disturbances in local networks may propagate throughout the immune system and create cancer attractors involving immune system networks that either have malignant properties themselves or nurture other cells that become malignant.

Section 3.0 Treatment recommendations
Current cancer treatment is based on reductionist principles, namely killing malignant cells where they are known or suspected to exist. However, we believe that focusing on cellular networks is important because (a) these networks created the malignant properties of cells and altering them may promote tumor destruction; (b) they may cause additional cancers due to the field effect generated by most chronic stressors; and (c) they are important in understanding and overcoming treatment resistance.

Complexity theory suggests that curative treatment for cancer must combine multiple strategies that target existing tumor networks at different points, prevent future tumors from arising and optimize the overall health of the patient.

1. Curative treatment for adult tumors related to chronic inflammation must adequately address tumor heterogeneity and the diverse origins of these tumors. Only a small percentage of cancer cases have distinct etiologies that can be directly targeted or reversed, such as lymphomas caused by infection related antigen driven lymphoproliferation and tumors due to immune system suppression. Antibiotics, antiviral agents or restoration of the immune system have high cure rates in these cases.

For other adult tumors related to chronic inflammation, based on experience with curative therapy for childhood leukemia, Hodgkin lymphoma and testicular cancer, we must combine effective treatments based on different mechanisms of action with techniques that minimize side effects (**Mukherjee: The Emperor of All Maladies 2010**). However, adult tumors exhibit more molecular heterogeneity than childhood tumors (**de Sousa 2018**, **Punt 2017**, **López 2017**, **Taherian 2017**), molecular features that evolve over time (**Baretti 2018**), and more field effects, suggesting that more treatment diversity is needed for cure. In addition, since multiple triggers ("hits") typically created the altered networks that caused the adult cancer, we suggest that multiple disruptions to the network may be required to move it to a less dangerous state. As discussed below, it may be necessary to target not only the tumor cells but their microenvironment, etiologic factors (chronic stressors), immune system factors and independent pathways that promote network stability. However, trial and error will be required to determine what treatment combinations are tolerable and whether specific treatment combinations will be synergistic or antagonistic.

2. Targeting the microenvironment that nurtures tumor cells may have therapeutic value. This may disrupt the fertile "soil" (microenvironment) necessary for cancer "seeds" to grow (**Tsai 2014**, **Fidler 2003**) by interfering with crosstalk between cancer cells, host cells and the extracellular matrix (**Sounni 2013**), as exemplified by Hodgkin Reed-Sternberg cells (**Mani 2009**). Microenvironment targets include angiogenesis (**Gkretsi 2015**), inflammatory cells and mediators, cancer associated fibroblasts and the extracellular matrix. Normalizing the microenvironment may also enhance drug delivery and effectiveness (**Polydorou 2017**) or make existing tumors or intermediate states more susceptible to immune system attack.

3. Moving cancer networks into less lethal states may be useful. Novel approaches are required to push networks towards a less lethal state. If chronic cellular stress moves cellular networks from physiologic attractor states to intermediate states and cancer attractors, how can network balance be reestablished? Often the chronic stressors cannot be eliminated or networks do not revert to normal after their removal. The goal is to create a network state that limits morbidity and mortality, which likely will differ from the premalignant network state.

A theoretical framework to move malignant networks to a less hazardous state has been described (**Huang 2013**, **Kim 2017**, **Zhou 2016**). However, the dynamic nongenetic heterogeneity of tumor cells makes them moving targets and drives replenishment of the tumor with surviving, nonresponsive cells (**Huang 2013**, **Chowell 2018**).

Constant perturbation of networks with drugs that destabilize the existing state may move them towards a more differentiated or less hazardous state **(Cho 2016**), and possible targets have been identified (**Kim 2017**). Alternatively, an initial treatment may calm the disordered networks to make them more sensitive to subsequent therapy. For example, regional hyperthermia combined with radiotherapy (**Seifert 2016**, **Sharif-Khatibi 2007**) may be particularly effective for cancer stem cells (**Oei 2017**).

It may also be helpful to investigate biomolecules or pathways with a physiologic role in influencing malignant-type behavior associated with chronic inflammation, such as (a) agents that promote maturation, differentiation or lineage reprogramming, including retinoids for acute promyelocytic leukemia (**Nowak 2009**), metformin for insulin pathway related malignancies, myeloid differentiation promoting cytokines and other differentiation or lineage reprogramming agents (**McClellan 2015**); (b) factors halting the wound healing process (**Shah 2018**, **Kareva 2016**); and (c) countering chronic inflammatory processes associated with tobacco, excess weight, diet and inflammatory bowel disease.

4. Novel treatments may take advantage of sophisticated network associations in physiologic cells which is lost in advanced and aggressive cancers. This includes “lethal challenges” that require sophisticated functioning for cells to survive, such as high dose methotrexate with leucovorin rescue (**Howard 2016**), immune checkpoint inhibitors that target the large mutational burden of aggressive tumors (**Rizvi 2015**) and treatments directed towards other aspects of chaotic or unstable states such as cell-extracellular matrix detachment (**Crawford 2017**).

5. Reducing chronic inflammation should be part of any treatment plan because it causes network changes that may ultimately lead to cancer. Chronic inflammation interacts with other chronic stressors in unpredictable ways to alter network pathways. As the magnitude of each stressor is reduced, the interactions are markedly reduced. As a result, the networks may revert towards a more stable state and fewer new tumors are likely to arise. We suggest that physicians consider chronic inflammation and its etiologies to be risk factors for cancer that are evaluated and treated similar to risk factors for coronary heart disease; this may not only affect the acute disease but possible recurrences (**Riegel 2017**).

Many behavioral changes can reverse chronic inflammation, including smoking cessation, reducing exposure to secondhand smoke and eating a healthier diet (see **European Code Against Cancer**). This is important because current knowledge is inadequate to reverse downstream network changes, but earlier changes can often be effectively targeted.

Patients may have germ line changes which reduce the efficiency of inflammation in killing tumor cells. Although fixing these genetic errors may not be feasible now, it may be possible to develop chemoprevention strategies for high risk patients using non-steroidal anti-inflammatory drugs, polyamine inhibitors and the antihelminth drug mebendazole (**Williamson 2016**, **Gerner 2018**).

6. Screening is important, both for premalignant and malignant lesions, since it is difficult to reverse advanced network changes. Screening should be based on known individual germ line variations, coexisting diseases and other risk factors. Effectiveness should be studied in similar terms as cancer treatment regimens.

7. Promoting rational medical care is important at the individual and societal level. Complexity theory recognizes that countering a systemic disease such as a cancer requires optimizing all factors affecting it, even if not directly part of the malignant process. Thus, improving overall health for individuals makes it easier to detect signs and symptoms associated with malignancy and improves performance status, which increases the range of possible treatments. Improving health at the societal level will uncover new behavioral causes and treatments for cancer, and possibly other risk factors.

** End **