How Pancreatic Cancer Arises, Based on Complexity Theory

Nat Pernick, M.D.

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Introduction

This is the third paper in a series discussing the top 20 causes of US cancer death and how they arise based on complexity theory (see **How Lung Cancer Arises-Pernick 2021**, **How Colon Cancer Arises-Pernick 2020a**). We first discuss the population attributable fraction of pancreatic cancer risk factors and their mechanism of action, then integrate these mechanisms into our theory about how cancer arises in general (**Pernick 2017**) and in the pancreas, and finally suggest curative treatment approaches for pancreatic cancer. This essay focuses on pancreatic adenocarcinoma, the most common (>90%) histologic subtype.

Pancreatic cancer epidemiology

Pancreatic cancer is the third leading cause of US cancer death after lung and colorectal cancer with a projected 48,220 deaths in 2021 (men 25,270, women 22,950, **Cancer Facts & Figures 2021**). It is projected to become the second leading cause of US cancer death by 2030 (**Rahib 2014**) as pancreatic cancer deaths increase due to excess weight and type 2 diabetes (**Gordon-Dseagu 2018**) and as colorectal cancer deaths continue to decrease (**Cancer Facts & Figures 2021**). Americans have a 1.6% lifetime risk of pancreatic cancer based on 2015-17 data (**SEER**, accessed 12Feb21).

Pancreas cancer has a 5 year relative survival rate of only 10% (**Cancer Facts & Figures 2021**), with minimal improvements since the mid-1970s, unlike other cancers (**Siegel 2018**). Most patients (52%) are diagnosed with metastatic disease and have a 5 year relative survival of only 2.9% (**SEER**, accessed 12Feb21). For the 11% of patients with locally confined disease, the 5 year survival is still only 39% (**Cancer Facts & Figures 2021**).

Attributable risk factors for pancreatic cancer

Table 1 lists the risk factors for pancreatic cancer, discussed below in declining order of population attributable fraction (**World Health Organization - Metrics: Population Attributable Fraction (PAF)**, accessed 12Feb21), assessed using conservative figures.

Table 1 - Population attributable fraction of pancreatic cancer risk factors

Random chronic stress / bad luck - 25-35%
Non O blood group - 17%
Excess weight - 15%
Cigarette smoking (tobacco) - 15%
Type 2 diabetes - 9%
Excessive alcohol use - 5%
Diet - 5%
Family history / germline - 2%
Chronic pancreatitis - 1%

Controversial: aspirin, *Helicobacter pylori* infection, smokeless tobacco

Protective: allergies (atopy) - 3-7%

References in text

Random chronic stress / bad luck

We propose that the most common risk factor for pancreatic cancer is random chronic stress / bad luck, accounting for 25-35% of US cases. This figure is calculated as 100% minus the population attributable fraction of known risk factors but we provide a range because we use conservative figures for attributable risk. In contrast, Tomasetti estimated that 77% of pancreatic cancer driver mutations were due to nonenvironmental and nonhereditary factors (**Tomasetti 2017**).

Random chronic stress / bad luck refers to rare, seemingly random cellular "accidents" that cause network dysfunction that may propagate to surrounding cellular networks and promote malignancy. These accidents are due to: (a) DNA replication errors in noncancerous stem cells (Tomasetti 2015, Tomasetti 2017), estimated at 1 per 100,000 nucleotides but reduced to less than 1 per 100 million after cellular error correction (Pray 2008); (b) errors in how DNA is organized or modified by epigenetic events (Wikipedia-Cancer epigenetics, accessed 12Feb21); (c) errors in the distribution of cell components during cell division, such as transcription factors (López-Lázaro 2018a); (d) failure to restore physical interactions between tissue components after cell division, such as contact inhibition (López-Lázaro 2018b); and (e) immune system dysfunction that, for a particular patient, is ineffective at eliminating premalignant or malignant cells. In addition, cancer risk factors not yet discovered, too infrequent to achieve statistical significance or not clinically evident in a patient, such as chronic pancreatitis without symptoms (Fujii 2019) or microscopic changes (Cobo 2018) may be included in the category of random chronic stress / bad luck.

We estimate that there is a baseline rate of pancreatic cancer cases due to random chronic stress of 2 cases per 100,000 people per year (age standardized), compared with the current age standardized rate of pancreatic cancer of 7.7 in Europe and 7.6 in North America (Rawla 2019). This estimate is based on the lowest incidence observed worldwide in 2020 of 2.3 per 100,000 in Africa (rates are lower in some countries such as Malawi 0.63, Botswana 0.66 or Guinea 0.98 [Cancer Today, IARC, accessed 12Feb21]). In the US population of 330 million, this baseline rate would account for 6,600 unadjusted and 13,360 age adjusted cases, which comprises 23% of the projected 57,600 cases, compatible with our projected population attributable fraction of 25-35% for random chronic stress. Of note, this estimated baseline rate for pancreatic cancer due to random chronic stress is identical to that proposed for lung cancer (Pernick 2021). Due to these baseline rates, new cancer cancers will continue to arise and a "world without cancer" is not foreseeable (American Cancer Society, accessed 2Feb21).

How does a random event lead to cancer?

Self-organized criticality, which describes catastrophic events such as earthquakes and stock market crashes, helps us understand how a single random event in a cell can propagate to malignancy. Our cellular networks are poised at a critical state in which small disturbances typically cause no network changes, occasionally cause small network changes and rarely set off a cascade of changes in the initial network and those it interacts with (Bak, How Nature Works 1999). By analogy, individual grains of sand dropped on a sandpile usually have no apparent impact, occasionally cause small avalanches and rarely cause the entire sandpile to collapse. Dropping a single grain of sand with no apparent impact causes small structural changes in the sandpile that ultimately may enable an additional grain to set off an avalanche. It is important to focus on the sandpile itself as the functional unit, not the grain of sand (Bak, How Nature Works 1999). Similarly, cellular networks are the functional unit when studying malignancy, not the individual mutations. Of note, gene regulatory networks in pancreatic cancer demonstrate fractal characteristics (Grizzi 2019, Vasilescu 2012), a property of self-organized criticality (Ghorbani 2018, Metze 2013, Almassalha 2018).

Self-organized criticality is nature's way of making enormous transformations over a short time scale based on individual factors often thought too trivial to consider. In punctuated equilibrium of species, one sees prolonged periods of apparent stasis (i.e. no new species), followed by bursts of new species (Eldredge & Gould 1972). During the "quiet" periods, minor changes are accumulating. Similarly, human cellular networks have long periods with accumulation of minor changes with no apparent clinical or microscopic changes, followed by bursts of activity leading to obvious premalignant or malignant changes (Cross 2016). Self-organized criticality contrasts with the theory of gradualism, in which major changes occur due to the steady accumulation of small changes that produce visible differences. Gradualism is logical and predictable and was promoted by Darwin (Gould 1983) but it does not accurately describe evolution or malignant progression (Sun 2018).

Clinical differences between pancreatic cancer due to chronic random stress and traditional risk factors

Patients with pancreatic adenocarcinoma due to random chronic stress may have superior survival compared to those with traditional risk factors. First, this is true for lung cancer, which has such striking differences between the epidemiological, clinical and molecular characteristics of lung cancer in cigarette

smokers (80-90% of cases) compared to never smokers that some authors have concluded that they are distinct clinical entities (Yano 2008, Smolle 2019). Second, for pancreatic cancer, cigarette smoking is associated with higher death rates and poorer survival (Ben 2019, Yuan 2017). However, unlike lung cancer, pancreatic cancer has other risk factors (described below) causing a high percentage of cases, and we are not aware of any studies comparing clinical and molecular characteristics of pancreatic cancer patients with and without these risk factors.

There are at least two reasons that patients with pancreatic cancer due to random chronic stress may have superior survival. First, these tumors may be less aggressive due to fewer molecular alterations that disrupt networks. For example, cigarette smokers have decades of exposure to 7,000 substances in tobacco smoke, including at least 60 carcinogens (The Health Consequences of Smoking - 50 Years of Progress: A Report of the Surgeon General 2014, page 154, PDF page 183), which causes a heavy burden of network alterations and DNA change affecting multiple biologic pathways. Analysis of a case of poorly differentiated lung adenocarcinoma showed more than 50,000 single nucleotide variants (Lee 2010), and a small cell lung cancer cell line had over 20,000 somatic mutations (Pleasance 2010). This level of mutations likely overwhelms the capacity of the DNA repair pathway, both due to its magnitude and because mutations may damage the repair pathways themselves and may be associated with particularly aggressive disease. A similar impact may occur in the pancreas.

Second, initial changes due to random chronic stress most likely occur in only one cell. In contrast, cancer risk factors, such as cigarette smoking, have a field effect, promoting network changes that may promote malignancy in a broad range of cells exposed to the risk factor (Steiling 2008, Lochhead 2015).

Non O blood group

People with blood group O may have a lower risk of pancreatic cancer than those with blood groups A or B (Amundadottir 2009, Zhu 2020). Overall, 17.0-19.5% of pancreatic cancer cases in 2 prospective cohort studies (Wolpin 2009) and 12 prospective cohorts (Wolpin 2010) were attributable to blood groups A, B or AB, with an increased risk as each non O allele was added and a large increased risk for blood group BB. Similar results were found in other studies, although an attributable risk was not calculated (Sun 2015, Li 2018, Antwi 2018).

ABO blood group antigens are glycoproteins expressed on the surface of circulating red blood cells and epithelial cells of the gastrointestinal tract. The A and B alleles encode glycosyltransferases that attach N-acetylgalactosamine and D-galactose, respectively, to the H antigen backbone. In contrast, the O allele encodes a nonfunctional glycosyltransferase so the H antigen is unchanged.

Although important today for transfusions and transplantation (Dean 2005), the primary function of ABO antigens is to mediate protein maturation and turnover, cell adhesion and trafficking, and receptor binding and activation (Rizzato 2013). They also appear to affect the systemic inflammatory state, a known chronic stressor for malignancy (Pernick 2020a, Pernick 2020b). Genome wide association studies have suggested that the ABO locus may affect inflammatory adhesion via ICAM1 (Paré 2008), E-selectin (Paterson 2009) and P-selectin (Barbalic 2010). These surface molecules are also recognized by the immune response and may facilitate immunosurveillance for malignant cells (Wolpin 2009). ABO blood group antigens may interact with CagA strains of *H. pylori* to modify the risk of pancreatic cancer. A possible mechanism is differential bacterial binding to these blood group antigens (Rizzato 2013, Risch 2013), which affects gastric and pancreatic secretions, which is synergistic with the Western diet and tobacco use in promoting pancreatic cancer (Risch 2011).

Excess weight

Pancreatic cancer is associated with excess weight, which includes overweight, defined as a body mass index (BMI) of 25 or more, and obesity, defined as a BMI of 30 or more (Centers for Disease Control and Prevention, accessed 12Feb21). The incidence of pancreatic cancer increases 10-14% for each 5 kg/m^2 increase in BMI; obese individuals have a 20% greater risk of pancreatic cancer compared with normal weight controls (Malli 2017). These results have been confirmed by Mendelian randomization, which aims to improve causal inference in observational studies by assessing risk associations of the genetically determined component of environmental exposures and intermediate phenotypes (Carreras-Torres 2017, Tsilidis 2017).

Excess weight has a stronger association with pancreatic cancer when it occurs at younger ages. For example, Israeli men and women with excess weight as teenagers (based on BMI ≥ 85th percentile for age and gender, recorded during physical exams at age 17 years when entering the military) were at an increased risk for subsequent early onset pancreatic cancer, with a population attributable fraction (PAF) of 10.9% (Zohar 2019; see also Chao 2018, De Rubeis 2019). In a pooled analysis of 14 cohort studies, pancreatic cancer risk was 54% higher for those who were overweight in early adulthood and obese at baseline (Genkinger 2012).

A US study of potentially modifiable risk factors for pancreatic cancer indicated the PAF for excess body weight was 16.3% for men and 17.5% for women (Islami 2018), compared with a PAF for North America in another study of 14% for men and 11% for women (not adjusted for hormone replacement therapy and smoking) (Arnold 2015). For Table 1, we used an intermediate figure of 15%. Table 2 shows the variability in PAF due to excess weight by region, gender and research study:

Table 2
Population attributable fraction of pancreatic cancer due to excess weight (BMI ≥ 25)

Region	Men	Women	Total	Source
Worldwide	8%	8%		Arnold 2015 (not adjusted for HRT and smoking)
Worldwide			3-16%	Maisonneuve 2015
North America:				
North America	14%	11%		Arnold 2015 (not adjusted for HRT and smoking)
United States	16.3%	17.5%	16.9%	Islami 2018
Canada (Alberta)	5.2%	7.7%	6.6%	Brenner 2017
Canada	10.6%	9.7%	10.2%	Zakaria 2017
Europe:				
Europe		7.8%		Renehan 2010
Europe	10-12%	10-11%		Arnold 2015 (not adjusted for HRT and smoking)
Germany			13.0%	Behrens 2018
Germany	16.0%	12.9%		Wienecke 2018 (BMI > 21)
United Kingdom	12.8%	11.5%	12.2%	Parkin 2011
Australasia:				
Korea	2.9%	3.9%		Park 2014 (BMI ≥ 23)
Other:				
Indonesia	9.1%	9.9%		Riantoro 2019
Nigeria	4.3%	5.6%	5.0%	Odutola 2019

HRT: hormone replacement therapy

Excess weight promotes pancreatic cancer via chronic inflammation, immune system dysfunction and hormonal alterations. First, excess weight is associated with chronic inflammation, typically low grade, subclinical and affecting white adipose tissue, due to chronic activation of the innate immune system (Bastard 2006, Brocco 2020, Cascetta 2018). This is also mediated through its association with adipocyte hypoxia (Lee 2014), which promotes inflammation and fibrosis in the normal pancreas and creates a microenvironment supportive of tumor growth (Divella 2016, Quail 2019). Whether aspirin, due to its anti-inflammatory properties, reduces the risk of pancreatic cancer is controversial (yes; Streicher 2014, Risch 2017, Sun 2019; no: Amin 2016, Khalaf 2018); the risk reduction may be limited to patients with existing pancreatic cancer risk factors (Choi 2019).

Second, excess weight is associated with an unhealthy diet (high fat, Western diet), described below, which is proinflammatory. It may activate oncogenic *KRAS*, present in many healthy individuals, and

elevate COX2, which sustains the activity (Philip 2013, Eibl 2019). This leads to enhanced aerobic glycolysis (Wang 2019) and may otherwise enhance growth responses critical to malignant progression (Eibl 2017).

Third, excess weight causes immune system dysfunction beyond chronic activation of the innate immune system discussed above. For example, severely obese patients have lower NK cell cytotoxic activity compared with normal individuals, which may be reversed by weight loss (De Pergola 2013, Elisia 2020).

Finally, excess weight is associated with constitutive hormone production, including hyperinsulinism, insulin resistance and abnormalities of the IGF1 system, which promote cell cycle progression and inhibition of tumor cell apoptosis (Avgerinos 2018, Trajkovic-Arsic 2013), as described below. Excess weight is also associated with diabetes, as discussed below.

Cigarette smoking (tobacco)
Cigarette smokers have a 75% increased risk of pancreatic cancer compared with never smokers and the risk remains elevated for at least 10 years after cessation (Iodice 2008). The population attributable fraction (PAF) of pancreatic cancer deaths due to tobacco smoking is 11-32%, based on a summary of 117 pooled and meta-analytical studies (Maisonneuve 2015, see also GBD 2017 Pancreatic Cancer Collaborators 2019). Cigar and pipe smoking (Malhotra 2017, Christensen 2018) also increase the risk, although no PAF has been calculated. Whether smokeless tobacco increases the risk is controversial (yes: Araghi 2017, Alguacil 2004, no: Hassan 2007, Bertuccio 2011, Burkey 2014; minimal at most: Zheng Sponsiello-Wang 2008). Secondhand smoke (Zhou 2014) does not appear to increase the risk.

In the US, cigarette smoking caused 12.1% of the estimated 37,289 US deaths due to pancreatic cancer in 2011 (Siegel 2015-Table), although this PAF is much lower than the PAF determined for Alberta, Canada in 2012 (19.3%, Grundy 2017) and for UK cancer cancers in 2010 (28.7%, Parkin 2011). As a result, we used an intermediate estimate of 15% for the PAF in Table 1. Totals in other countries are shown in Table 3.

Table 3 - Population attributable fraction of pancreatic cancer due to tobacco by country

Country	Attributable fraction	Reference
US	2011, 12.1% of deaths	Siegel 2015
Australia	2019, 21.7% of future pancreatic cancer burden	Arriaga 2019
Canada	2012, Alberta, 19.3% of cases	Grundy 2017, Poirier 2016
Germany	2018, 29.7% of cases in men 18.5% of cases in women	Mons 2018
Italy	1991-2008, 13.6% of cases	Rosato 2015
Korea	2009, 27.4% of cases in men, 0.8% of cases in women	Park 2014, Table 3
UAE region	2018, 8.2-20.3% of cases	Al-Zalabani 2020
United Kingdom	2010, 28.7% of cases	Parkin 2011

Tobacco use promotes pancreatic carcinogenesis by altering DNA. It induces DNA adducts leading to mutations, not in the known pancreatic cancer driver genes *KRAS*, *TP53*, *CDKN2A/p16* or *SMAD4* but in less commonly mutated genes that do not produce a characteristic profile (Blackford 2009). Smoking related carcinogens N-nitrosamine NNK and its major metabolite NNAL also induce inflammation and fibrosis, which inhibit cell death, stimulate cell proliferation and create a microenvironment that supports tumor growth (Edderkaoui 2013; How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease, A Report of the Surgeon General 2010). Tobacco use also accentuates the effects of excess weight, diabetes and chronic pancreatitis (Weissman 2020).

Type 2 diabetes mellitus

Individuals with type 2 diabetes have 1.5 to 2.0 times the risk for pancreatic cancer compared with those without (Huxley 2005, Li 2018, Saarela 2019, Linkeviciute-Ulinskiene 2019), including African Americans and Latinos (Setiawan 2019). However, pancreatic cancer also causes type 2 diabetes (Tan 2017, Huang 2020, Wang 2003, Li 2012, Yuan 2020).

Rosato attributed 9.7% of cases of pancreatic cancer in Northern Italy to diabetes (Rosato 2015), comparable to the attribution of 9.4% of cases in India (Midha 2016) and the attribution of 8.8% of pancreatic cancer deaths to high fasting plasma glucose in a worldwide study (GBD 2017 Pancreatic Cancer Collaborators 2019). In a meta-analysis of Asian and Australasian studies, in which the population has a lower prevalence of diabetes, the PAF ranged from 3.1% to 7.3% for pancreatic cancer deaths due to diabetes (Lam 2011). For US cases, we used the figure of 9% in Table 1.

Diabetes may promote pancreatic cancer through several mechanisms. First, as discussed below, hyperinsulinemia seen in type 2 diabetes may promote proliferation and survival of acinar and ductal cells adjacent to islets (Andersen 2017), mediated through IGF1, which stimulates cellular proliferation in the pancreas (Lam 2011). This may be due, in part, to promotion of the Warburg effect (Warburg 1927), in which cancer cells rely on glycolysis, which is antagonized by metformin (Velazquez-Torres 2020). Second, glucose and glycation end products promote reactive oxygen species, which causes DNA damage and cell proliferation (Yuan 2020, Abudawood 2020).

Excessive alcohol use

Numerous studies have associated excessive alcohol use with pancreatic cancer, particularly among heavy drinkers (3 or more drinks of liquor per day, Gapstur 2011) and in men (Naudin 2018).

Only a few studies have calculated the population attributable fraction of cases due to alcohol. In Northern Italy, Rosato attributed 13.0% of cases to heavy alcohol drinking (Rosato 2015). In Ireland, Lafoy attributed 6.6% of cases in men and 3.0% in women to alcohol use (Laffoy 2013). Maisonneuve reviewed 117 meta-analytical or pooled data reports and calculated a PAF of < 9% (Maisonneuve 2015). In Table 1, we conservatively used 5% as the PAF for US cases.

Heavy alcohol consumption produces acetaldehyde, a carcinogenic metabolite that increases production of reactive oxygen species and DNA adducts (Naudin 2018) and initiates inflammatory and fibrotic cascades (Gupta 2010). Animal and human studies of tobacco and alcohol related pancreatic carcinogenesis suggest multimodal, overlapping mechanistic pathways (Duell 2012b), although the synergistic effects between alcohol and tobacco are uncertain (Rahman 2015, Yadav 2013, Korc 2017). Heavy alcohol use may potentiate the effect of other chronic stressors, such as a poor diet (Duell 2012b) and inflammation due to alcohol related chronic pancreatitis (Gupta 2010).

Diet

The relationship between diet and risk of pancreatic cancer is controversial. Many studies show an increased risk with high consumption of animal products, refined sugars and cereal and with low consumption of vegetables and fruit (Bosetti 2013). Similarly, a higher dietary inflammatory index, due to a high fat diet with highly processed foods and low consumption of vegetables and fruit, is associated with a higher risk of pancreatic cancer (Shivappa 2015d, Antwi 2016, Antwi 2018, Zheng 2017, Jayedi 2018). Pancreatic cancer risk is reduced by a high quality diet (abundant vegetables, fruits and whole grains; low fat, minimal processed food, Arem 2013, Lucas 2016 but see Zhang 2020). However, other studies show no association between diet and pancreatic cancer risk (Schulpen 2019, Zheng 2019, Zheng 2018, Molina-Montes 2017). Diet may be a cofactor with cigarette smoking and diabetes in

increasing risk beyond that of any of these factors alone (Antwi 2016); whether diet is synergistic with alcohol in increasing risk is difficult to determine because each dietary assessment program evaluates alcohol consumption differently.

There is limited data on attributable risk of pancreatic cancer due to diet. Rosato attributed 11.9% of cases in Northern Italy to low adherence to a Mediterranean diet (Rosato 2015). Maisonneuve found that increasing red or processed meat caused 2-9% of cases and increasing fruit or folate intake reduced risk by < 12% (Maisonneuve 2015). For Table 1, we used an estimate of 5%.

A proinflammatory (high fat, Western) diet may increase production of proinflammatory cytokines, leading to release of proteolytic enzymes and reactive oxygen species, which may damage DNA (Shivappa 2015d, Farrow 2002). Chronic inflammation may also promote release of platelet derived growth factor and transforming growth factor alpha, leading to increased pancreatic cell proliferation. Red meat cooked at high temperatures or for prolonged times may increase risk through the production of heterocyclic amines and polycyclic aromatic hydrocarbons (Sugimura 2000). Finally, the proinflammatory diet is associated with excess weight and diabetes, known risk factors discussed elsewhere.

Family history or germline alterations

The National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) recommend that all patients with pancreatic cancer undergo risk assessment for associated hereditary syndromes (Daly 2020, Stoffel 2019) because 7% have familial components and 3% have hereditary components (Llach 2020).

Patients with familial pancreatic cancer have 2 or more first degree relatives with pancreatic cancer but no known associated hereditary syndrome (Stoffel 2019). The relative risk is 1.68 for any relative affected but it increases to 4.6, 6.4 and 32.0 for one, two and three affected first degree relatives (Genkinger 2020). Although 7% of patients have familial components, this is much higher than the calculated attributable fraction due to family history in the only 2 studies we identified: 0.6% in Northern Italy (Rosato 2015) and 1.3% in a meta-analysis (Permuth-Wey 2009). For Table 1, we used an attributable fraction of 2%.

Ethnicity may also be relevant. After adjustment for risk factors, Native Hawaiians, Japanese Americans and African Americans had a higher risk of pancreatic cancer compared with European Americans (Huang 2019).

Germline alterations that affect cell division, DNA repair and apoptosis are frequently associated with pancreatic cancer (PathologyOutlines.com-Molecular aspects of pancreatic cancer, accessed 12Feb21). For example, mutations in 5 DNA repair related genes (*ATM*, *BRCA1*, *BRCA2*, *MLH1*, *TP53*) and *CDKN2A*, which induces cell cycle arrest, were associated with pancreatic cancer in 5.5% of pancreatic cancer patients referred to a Mayo Clinic facility, including 7.9% of patients with a family history (first or second degree relative) and 5.2% without (Hu 2018). In British Columbia, Canada, germline pathogenic variations were detected in 14.1% of patients with pancreatic cancer referred for testing (Cremin 2020).

As discussed below, DNA damage, either germline or tumor related, appears to be necessary to “rewire” networks so they ultimately overcome inherent and evolved controls and produce a malignant phenotype (Trigos 2019). In the presence of other chronic stressors and in the correct cellular environment, this rewiring may promote damage to multicellular processes and inhibit their physiologic suppression of unicellular activities, such as cell division (Trigos 2018).

Chronic pancreatitis

Chronic pancreatitis markedly increases the risk of pancreatic cancer, with a standardized incidence ratio of 14.4 and cumulative risks of 1.8% at 10 years and 4.0% at 20 years (Lowenfels 1993); these risks persist after adjusting for tobacco and alcohol use (Ling 2014). However, the population attributable fraction of chronic pancreatitis is only 1.3% (Duell 2012a). Autoimmune pancreatitis, considered a pancreatic manifestation of IgG4-related disease, is associated with cancer in general (Okamoto 2019, Tahara 2018) but not in the pancreas (Ikeura 2016).

Chronic pancreatitis may cause malignancy through several mechanisms: (a) by creating reactive oxygen species and reactive nitrogen intermediates, which induce epigenetic alterations, DNA mutations and abortive repair (Ling 2014, Chiba 2012); (b) through macrophage secreted inflammatory cytokines, which cause pancreatic acinar cells to undergo ductal metaplasia, which induces differentiation to a duct-like phenotype and contributes to pancreatic intraepithelial neoplasia and pancreatic adenocarcinoma (Guerra 2007, Seimiya 2018, Liou 2013); (c) by promoting epithelial to mesenchymal transition and blood stream dissemination of histologically preinvasive pancreatic epithelial cells (Rhim 2012) in which metastatic cells are dormant but can be later reactivated by chronic inflammation (Park 2020). This process also occurs in breast cancer (Hüsemann 2008) and colorectal cancer (Hu 2019). In the pancreas, the mechanisms of early dissemination are unknown but may involve hijacking existing pancreatic migratory processes, such as stem cell migration to repair damage caused by acute pancreatitis (Gong 2014) or embryonic epithelial cell migration (Mussar 2014).

Alcohol and tobacco use, the major causes of chronic pancreatitis, are independently associated with pancreatic cancer, as described above. However, for gallstones (Schernhammer 2002, Zhang 2014, Huang 2020) and hyperlipidemia (Wang 2015), which also cause chronic pancreatitis, there is no consistent association.

***Helicobacter pylori* infection**

Helicobacter pylori infection is a controversial risk factor for pancreatic cancer. Although there is no evidence of direct pancreatic colonization, an increased risk of pancreatic cancer has been reported for patients with CagA negative *H. pylori* seropositivity and non O blood type in Connecticut (Risch 2010) and China (Risch 2014), as well as in two meta-analyses (Xiao 2013, Trikudanathan 2011), and its population attributable fraction was estimated at 4-25% in Western countries (Maisonneuve 2015). However, other studies found no association (Yu 2013, Wang 2014, Chen 2016, Liu 2017, Huang 2017, Hirabayashi 2019).

H. pylori colonization may enhance the pancreatic carcinogenic effect of N-nitrosamines conveyed by smoking or dietary sources (Risch 2003). This effect is modulated by host inflammatory responses to the organism (Rabelo-Gonçalves 2015).

Allergies

Allergies, in particular those related to atopy, seem to be associated with a decreased risk of pancreatic cancer in many studies (Gandini 2005, Olson 2013, Cotterchio 2014, Wang 2020), with a protective population preventable fraction of 3-7% (Maisonneuve 2015), although a prospective study reported no association except among those age 70+ (Huang 2018). The risk reduction does not appear to be due to allergy medications (Cotterchio 2014).

Although the mechanism of this protective effect is unknown, the increased immune activation associated with allergic hypersensitivity may increase immune surveillance against tumors (Gandini 2005). A Swedish study showed an inverse association between pre-diagnostic serum levels of IgG (but not IgA or IgM) and risk of pancreatic cancer (Sollie 2020). A previous study found no relationship between IgE levels and risk (Olson 2014), although IgE antibodies are cytotoxic to pancreatic cancer cells (Fu 2008). Preliminary findings suggest certain atopy related gene variants may reduce pancreas cancer risk (Cotterchio 2015).

Aging

The risk of pancreatic cancer increases with age; the average age at diagnosis is 70 years, almost all patients are older than 45 and two-thirds are at least 65 years (American Cancer Society, accessed 14Feb21). No population attributable fraction has been reported for aging.

There are many possible mechanisms underlying this association. First, somatic mutations increase markedly with age. Mutation frequency at age 80 in epithelial tissues is 10 times higher than in germline tissues, sufficient to account for tumorigenesis even without mutagens (Simpson 1998). This may be due to accumulation of random errors, leading to “error catastrophe” of somatic genes involved in DNA replication and repair (Milholland 2017) or to epigenetic modifications that contribute to aberrant chromatin conformation and stability as well as somatic mutation (Wagner 2015). Second, chronic stressors cause network changes and mutations associated with malignancy that accumulate later in life

(Martincorena 2015). Third, aging is associated with immune system dysfunction and chronic inflammation, known chronic stressors that cause malignancy (Zhang 2016, Bottazzi 2018, Keenan 2019).

Discussion

Cancer is an assault on the physiologic order maintained by living systems. To cure pancreatic cancer, we need to understand how life arises, how order is typically maintained within its networks and how it is lost during carcinogenesis so we can effectively target the disrupted networks.

How cancer arises

First, life is a complex system (Pernick 2017a), meaning the properties of the entire system are greater than the sum of the properties of each part (Kane 2015). Emergent properties arise from self-organization of networks of biomolecules, organelles, cells, tissues and organs. This view differs from traditional reductionist thinking that considers life to be merely a collection of building blocks with an aggregation of their individual properties (Mazzocchi 2008). Studying networks is important because disease typically reflects perturbations in intracellular and intercellular networks that link tissue and organ systems, not just abnormalities in a driver mutation (Barabási 2011, Chagoyen 2019). The impact of a specific genetic abnormality is not restricted to the activity of its gene product, but can spread along the links of the network to affect gene products that otherwise carry no defects. Thus, curative treatment must disable entire networks, not just particular genes.

Second, we propose that coordination of network activity is a basic physiologic mechanism disrupted by malignancy. Isolated network activity can be useful or destructive, depending on its context, but for sophisticated processes to be successful, such as inflammation and embryogenesis, groups of networks must work together in a specific, prescribed manner. The inflammatory response consists of a coordinated program to facilitate tissue repair and kill foreign microorganisms. Physiologic triggers of inflammation simultaneously initiate the process of its resolution (Serhan 2005). As the trauma is repaired or the threat from foreign organisms subsides, the resolution process causes networks to revert towards their initial states to prevent bystander damage to tissue (Sugimoto 2016). During carcinogenesis, malignant risk factors trigger the inflammatory process with no simultaneous initiation of the resolution process (Fishbein 2020). This leads to persistent inflammation, which promotes genomic instability, which further drives the malignant process (Shimizu 2012), an issue that must be halted by curative treatment.

Embryogenesis also has many features of malignancy coordinated towards a useful end. This includes rapid cell division (Kermi 2017), which leads to the transition of gene expression from maternal control and meiosis to embryonic control and mitosis (Clift 2013); embryonic morphogenesis (Shahbazi 2020, Iino 2020), influenced by asymmetric patterns of morphogens or self-organizing patterns of chemical activators and inhibitors (Turing 1952, Schweisguth 2019); cell differentiation (Li 2014) and migration of cells of different lineages over short and long distances throughout the body (Reig 2014, Kurosaka 2008). In this microenvironment, these coordinated programs halt during the fetal stage. However, risk factors associated with malignancy may activate these same networks through a non coordinated process that, unlike fertilization, has no programmed pathway towards cessation, another issue that must be addressed by curative treatment.

Third, multicellular organisms evolved from unicellular organisms by adding new genes and more intricate controls to existing networks for metabolism and replication (Trigos 2018, Trigos 2019). This enables greater communication and coordination between cells through cell signaling and cell-cell adhesion and makes possible differentiation, apoptosis and senescence (Trigos 2018). The new control mechanisms keep cellular and systemic processes on track and shift the survival focus from individual cells towards the organism as a whole (Davies 2011). The operation of multicellular and unicellular programs appears to be somewhat mutually exclusive. When multicellular controls are sufficiently damaged, an existing genetic toolkit of pre-programmed, malignant behavior that evolved in the earliest unicellular species is activated, although some multicellular features are retained (Jézéquel 2018). This has been described as the atavism hypothesis of cancer (Davies 2011, Trigos 2017, Bussey 2017), although it has not yet been studied extensively for pancreatic cancer. The shift from multicellular to unicellular type activities causes histologic changes of pancreatic ductal or acinar hyperplasia or metaplasia, which are typically reversible, as well as benign or malignant neoplasms, which are not.

Fourth, cell phenotypes and their ordered physiology are maintained due to attractors, which are stable equilibrium states corresponding to gene expression profiles in normal cells, based on expression of thousands of mutually regulating genes. Attractors stabilize cellular networks against common perturbations (Kauffman 1969, Noble 2015) and have been analogized to a low energy state or valley on a topographic diagram that pulls in cells with similar network configurations (Waddington 1957, image #1, image #2). Essentially, the environment of biological substances forces them to have similar behavior even though they behave very differently when isolated. Sustained exposure to cancer risk factors over years to decades may overcome the stability of physiologic attractors and activate local and systemic networks through non physiologic mechanisms that cannot easily be reversed. The activated networks may move cells from physiologic attractors to premalignant attractors and ultimately to cancer attractors, which are gene expression profiles that may pre-exist in healthy genomes but are normally not accessible, analogous to dangerous cliffs that are avoided by well planned highways (Huang 2009, Deschênes-Simard 2016, image). These new attractor states are associated with sustained cellular proliferation that may (intraductal papillary mucinous neoplasms, pancreatic intraepithelial neoplasia) or may not (well differentiated pancreatic adenocarcinoma) be easily identifiable histologically. Curative treatment must dislodge networks from cancer attractors and move them towards less harmful states.

Fifth, we previously proposed that most adult cancer is caused by 9 chronic cellular stressors, namely inflammation (due to infection, infestation, autoimmune disorders, trauma, obesity, diabetes and other causes, Pernick 2020b), exposure to carcinogens; reproductive hormones; Western diet (high fat, low fiber, low consumption of fruit and vegetables); aging; radiation; immune system dysfunction; germline changes and random chronic stress / bad luck (Pernick 2017b).

We now propose that these nine chronic stressors can be consolidated into 5 cancer “super promoters”: chronic inflammation, DNA alterations (somatic or germline) / network rewiring, random chronic stress / bad luck, immune system dysfunction (individual or societal) and hormonal effects. The chronic inflammation category includes components of diet, aging and carcinogen exposure (Fishbein 2020). The DNA alterations / network rewiring category includes carcinogen exposure, radiation, germline changes and a component of aging. The mechanisms of action of each super promoter are now described:

How chronic inflammation acts as a super promoter for pancreatic cancer
Activation of the inflammatory process accompanies many malignancies (Coussens 2002). For pancreatic cancer, as discussed above, inflammation is activated by excess weight, smoking related carcinogens, heavy alcohol consumption, a proinflammatory diet and aging, acting both individually and synergistically (Weissman 2020, Antwi 2016).

Inflammation promotes pancreatic carcinogenesis through numerous mechanisms. First, inflammation appears to play a central role promoting carcinogenesis due to its inherent instability, which readily propagates through its diverse connections with other networks. Although complexity theory suggests that any network alteration can propagate, this is more likely in networks that themselves are unstable and well connected. Many of the key network issues discussed below are activated by or associated with inflammation.

Second, as described above, inflammation that is non coordinated is constitutively active, with no programmed process of resolution, leading to nongenetic network perturbations (Huang 2009) that may wear down pro stability factors in inflammatory and adjacent networks, particularly when accompanied by other super promoters.

Third, chronic inflammation creates a microenvironment supportive of pancreatic tumor growth in multiple ways (Divella 2016, Quail 2019): (a) adipose tissue hypoxia in obesity may create an altered adipokine profile with elevated levels of proinflammatory factors, leading to a peritumoral environment promoting tumor growth and progression; (b) chronic pancreatitis causes pancreatic acinar cells to undergo ductal metaplasia, which induces differentiation to a duct-like phenotype and contributes to pancreatic intraepithelial neoplasia and pancreatic adenocarcinoma (Guerra 2007, Seimiya 2018, Liou 2013); (c) chronic inflammation creates a microenvironment that promotes an embryonic phenotype with epithelial to mesenchymal transition (EMT), attainment of stem cell properties (Grippo 2012, Rodriguez-Aznar

2019) and motility associated with pancreatic branching (Shih 2015, Lin 2017), but with no physiologic program to differentiate into more stable states.

Fourth, chronic inflammation increases the impact of oncogenic *KRAS* (Philip 2013, Eibl 2019) and other DNA alterations. Obesity and a high fat diet, by promoting inflammatory pathways, interact with oncogenic *KRAS* to increase aerobic glycolysis, which then associates with other pathogenic processes to promote pancreatic cancer. The importance of this inflammatory pathway is demonstrated by the reversal of this process after ablation of COX2, a proinflammatory enzyme (Wang 2019).

Fifth, we propose that sustained, non physiologic activation of the inflammatory system disrupts multicellular controls and tilts the balance between multicellular and unicellular programming towards activation of pro malignant unicellular gene expression, as discussed above.

Sixth, inflammatory pathways may promote DNA alterations. For example, a proinflammatory (high fat, Western) diet may increase production of proinflammatory cytokines, leading to release of proteolytic enzymes and reactive oxygen species, which may damage DNA (Shivappa 2015d).

How DNA alterations / network rewiring act as a super promoter for pancreatic cancer
Major pancreatic cancer risk factors associated with DNA alterations include: (a) tobacco, whose carcinogen NNK stimulates proliferation and inhibits apoptosis of normal pancreatic ductal cells (Edderkaoui 2013); (b) heavy alcohol consumption, which produces acetaldehyde, a carcinogenic metabolite that produces reactive oxygen species and DNA adducts (Seitz 2007); (c) chronic inflammation, which may produce reactive oxygen species that damage DNA (Shadhu 2019); (d) aging related DNA changes discussed above and (e) germline changes discussed above.

DNA alterations or network rewiring are required for cellular networks to overcome inherent and evolved controls that prevent malignancy (Trigos 2019). This ultimately damages multicellular processes sufficiently to inhibit their physiologic suppression of unicellular activities associated with carcinogenesis (Trigos 2018).

KRAS mutations are necessary but not sufficient for pancreatic carcinogenesis. Although oncogenic *KRAS* is found in almost 100% of pancreatic adenocarcinoma tumors (Waters 2018), it is also frequently found in the non malignant pancreas. For example, *KRAS* mutations were found in the duodenal pancreatic juice of 73% of pancreatic patient patients but also in 19% of controls and 50% of asymptomatic individuals at high risk of pancreatic cancer (Eshleman 2014; see also Lu 2002, Zhou 2004, Yan 2005, Wang 2018). Despite the frequent presence of *KRAS* mutations, the lifetime risk of US pancreatic cancer is low (1 in 64, American Cancer Society, accessed 14Feb21). In addition, *KRAS* (wild or oncogenic) is not constitutively active (Waters 2018) but can be activated by upstream stimulants (Huang 2014, Wang 2019), including inflammation, which create a feed forward loop to maintain the stimulus indefinitely (Logsdon 2016).

Activation of *KRAS* mutations by inflammation leads to multiplication of pancreatic acinar cells, the apparent cell of origin for pancreatic cancer (Storz 2020, Paoli 2020, Kopp 2012). KRAS protein expression is hypothesized to be high enough for tumor initiation but low enough to evade apoptosis and senescence because of poor translation due to rare codon expression (Lampson 2013). The dividing cells may develop additional mutations due to: (a) relevant germline mutations (Pihlak 2017), which rewire the networks and make them more susceptible to instability; (b) reactive oxygen species developed through several mechanisms; (c) aging related DNA changes and (d) the effects of other super promoters. This ultimately leads to pancreatic intraepithelial neoplasia with subsequent progression towards malignancy.

Controls have not yet evolved to limit the impact of common *KRAS* mutations because: (a) these mutations are irrelevant to the evolutionary process as their impact occurs after the age of reproduction and nurturing of offspring (Simpson 1998), (b) natural selection typically operates on time scales of 1 million years (Uyeda 2011) and the risk factors associated with these mutations are recent - some were lethal until 100 years ago and not associated with pancreatic cancer (chronic pancreatitis, diabetes), and others did not widely occur until < 1,000 years ago (obesity, severe alcohol use, tobacco use, longer lifespan).

How random chronic stress acts as a super promoter for pancreatic cancer
Low levels of known risk factors or exposure to risk factors not yet categorized may also push physiologic networks towards malignant pathways, as discussed above. This includes chronic pancreatitis without histologic changes (Cobo 2018) or symptoms (Fujii 2019), "bad luck" or random mutations arising during DNA replication in noncancerous stem cells (Tomasetti 2015, Tomasetti 2017, Mehrotra 2020), germline changes of low frequency (Chang 2018, Shindo 2017), subclinical immune dysfunction and the proliferative effects of physiologic or mildly elevated insulin and the IGF pathway (see below).

If biologic networks follow the laws of self-organized criticality (Daniels 2018, Tsuchiya 2020), then network disturbances should follow a power law frequency distribution, with most having a small impact but rare disturbances causing an "avalanche" of change through interacting networks. Although counterintuitive, there may be no qualitative or quantitative difference between those disturbances causing minimal network changes and those leading to premalignant or malignant states (Bak, How Nature Works 1999).

How immune system dysfunction acts as a super promoter for pancreatic cancer
An intact immune system inhibits tumors that commonly arise but are clinically silent. For example, primary immunosuppressive disorders (Mortaz 2016), immunosuppressive infections (HIV, EBV) and therapeutic immunosuppression (transplantation) are associated with lymphoma (Shannon-Lowe 2017), Kaposi sarcoma, anal cancer (Lee 2016), skin cancer (Garrett 2017) and liver cancer (Silverberg 2011). However, no relationship has been found between these immunosuppressive conditions and pancreatic cancer.

Pancreatic cancer risk factors themselves may cause immune system dysfunction, including: (a) tobacco use, which impairs innate and adaptive immunity (Lee 2012, Qiu 2017) due in part to the inflammatory microenvironment it creates (Weissman 2020); (b) excess weight, which is associated with lower NK cell cytotoxic activity (Moulin 2008) and other immune system alterations that may reduce its ability to kill tumor cells, although there is considerable person to person variability (Elisia 2020); (c) aging, which is associated with immune system dysfunction due to low grade chronic inflammation (Keenan 2019) and impaired autophagy (Zhang 2016, Folkerts 2019); (d) germline changes in ABO antigens, which may facilitate immunosurveillance for malignant cells (Wolpin 2009) and (e) hormonal changes, including insulin resistance, which alter immune response (Ieronymaki 2019). On the other hand, allergic hypersensitivity is protective against pancreatic cancer, apparently through increased immune surveillance (Gandini 2005, Cotterchio 2014), as discussed above.

The process of pancreatic carcinogenesis features escape from immune surveillance by establishing an immunosuppressive microenvironment that hinders tumor cell eradication (Martinez-Bosch 2018, Gan 2020). Tumor cells evade the immune system through "camouflage and sabotage" as they acquire malignant characteristics (Poschke 2011), with a coevolutionary process that ultimately results in tumor escape (Ostrand-Rosenberg 2008). The dynamics of this 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).

Using a systems biology approach (Koutsogiannouli 2013), we consider the immune system to be a collection of control mechanisms for pancreatic and other cancers that act during the entire process of carcinogenesis (Elebo 2020). Malignancy emerges due to an altered overall relationship, not just dysfunction in tumor cells (Haas 2019, Derbal 2018):

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

At a societal level, our public health and medical care systems act as a "behavioral immune system" (Schaller 2015) to reduce risk factors for pancreatic cancer, such as tobacco use, alcohol abuse

or excess weight. When these systems are dysfunctional and do not optimally promote public health, this causes malignancies in a similar manner as disruptions in the physiologic immune system.

How constitutive or high hormonal levels act as a super promoter for pancreatic cancer
Pancreatic carcinogenesis is associated with hyperinsulinism, insulin resistance and excess insulin like growth factor (IGF) production (Trajkovic-Arsic 2013, Avgerinos 2018, Brocco 2020). These hormonal changes are commonly associated with pancreatic cancer risk factors of excess weight (Malli 2017) and diabetes (Lam 2011). They are also associated with excessive alcohol use, which increases insulin resistance (Lindtner 2013, Oh 2018, Nygren 2017) and tobacco use, which may promote insulin resistance (Mukharjee 2020 but see Keith 2016) or reduced insulin sensitivity (Cureus 2016) but the precise mechanisms are unknown. Chronic inflammation due to a proinflammatory diet or excess weight may lead to insulin resistance (Chen 2015), but there is no documented association between insulin resistance and chronic pancreatitis (Kumar 2017, Niebisz-Cieślak 2010).

A high fat diet causes epigenetic changes that may promote obesity and diabetes in offspring (Huypens 2016), suggesting that it may promote insulin resistance in other contexts but whether diet itself is a risk factor for pancreatic cancer is controversial, as discussed above. A low calorie diet is associated with reduced levels of insulin and IGF (Hursting 2013) but the independent effects of diet, excess weight and diabetes are difficult to disentangle (Kolb 2017).

Relationships of hyperinsulinemia and insulin resistance with other pancreatic cancer risk factors are unclear. Germline changes in the ABO blood group are associated with type 2 diabetes (Legese 2020) but although there are numerous germline causes of hyperinsulinemia (Galcheva 2019), they are not known to promote pancreatic cancer. Insulin resistance affects the immune response (Ieronymaki 2019), which suggests that in the correct context, alterations in the immune system may provide feedback on insulin-IGF pathways (Patel 2013), although this is not documented. We hypothesize that random chronic stress does not affect insulin resistance because its metabolic pathways are more stable than those associated with malignant progression, although data is limited. Finally, although there are no known studies linking allergies to insulin resistance, obesity may be related to an increased risk of aeroallergen sensitization and allergic asthma through mechanisms relating to insulin resistance (Husemoen 2008).

Hyperinsulinemia, insulin resistance and IGF abnormalities promote proliferation and survival of acinar and ductal cells adjacent to islets, including transformed cells (Andersen 2017, Li 2019), which may be mediated by the mTOR pathway regulating cell growth, proliferation and cell death (Perry 2020). This mechanism may have similarities to how chronic or increased expression of estrogens and androgens cause breast (Dall 2017), endometrial (Rodriguez 2019) and prostate cancer (Liu 2020). Whether metformin, used to treat type 2 diabetes, reduces the risk of pancreatic cancer is controversial (yes-Gong 2014,Dong 2019; no-Malek 2013).

Although excess weight is associated with increased estrogen levels, which promote endometrial and breast cancer (Ding 2020. De Pergola 2013), systemic menopausal hormonal therapy with estrogens is actually associated with a reduced risk of pancreatic cancer (Sadr-Azodi 2017, Andersson 2018).

Risk factors frequently interact with each other
There is close interaction between risk factors on multiple levels. First, because the same behavior affects multiple risk factors, the effects may be difficult to dissociate from each other, as with diet, excess weight and diabetes. Second, many risk factors have synergistic effects: tobacco use accentuates the effects of excess weight, diabetes and chronic pancreatitis (Weissman 2020) and heavy alcohol use may potentiate the effect of poor diet and inflammation due to alcohol related chronic pancreatitis (Duell 2012b). Third, the mechanistic pathways of risk factors overlap. Each has the capability of promoting network instability, which can propagate similar to the effect of grains of sand dropped on a sand pile.

Treatment approaches for pancreatic cancer based on complexity theory
Current treatment for pancreatic cancer is ineffective. Complete tumor resection, possible only in the 20% of patients with localized disease, yields 5 year survival rates of only 18-24% (Pancreatic Cancer Treatment (PDQ®), accessed 14Feb21). In fact, microscopic seeding of distant organs frequently occurs before or simultaneously with tumor formation at the primary site by dormant cells that are later reactivated by chronic inflammation (Rhim 2012, Park 2020). Chemotherapy is primarily palliative - 2

current combination regimens for metastatic disease yield an overall survival of only 8-11 months (Chiorean 2020). Radiation therapy has no proven value and clinical trials are ongoing regarded targeted therapy and immunotherapy. Curative options at other sites, based on etiologies of immune system suppression or infection, are not applicable to the pancreas (Pernick 2017).

Treatment failure is predictable because it is based on reductionist principles (kill the tumor cells) that reflect an incomplete understanding of the biology of pancreatic cancer. Instead, curative treatment must target the network changes that are part of how this cancer arises. Specifically, these principles appear to be crucial:

I. Network medicine. Pancreatic cancer is a systemic disease (Sohal 2014). Tumors may begin with mutated genes but ultimately develop multiple dysfunctional cellular networks. In addition, large tumors are sustained by years or decades of supportive network changes throughout the body, called an altered systems biology (Koutsogiannouli 2013). Even if the tumor is destroyed by surgery, radiation or otherwise, networks outside the tumor typically will not revert to normal and may continue to create new tumors. Thus, focusing on "network medicine" and systemic changes is mandatory (Barabási 2011, Parini 2020).

II. Blocking multiple pathways. Disabling the activity of some dysfunctional networks requires combinations of treatments to block multiple pathways because these networks interact in a weblike manner and can readily bypass a single block in a particular pathway. We speculate that curative treatment will require at least 3 to 5 drugs to block pathways sufficiently to disrupt most key networks below, as is the case for many curable cancers in children and young adults (Mukherjee: The Emperor of All Maladies 2010).

III. Combinations of combinations of treatment. Pancreatic cancer is due to network dysfunction in the local tumor as well as in many key systemic networks affecting the tumor, including inflammation, the immune system and the insulin-IGF system. Normalizing or antagonizing each network may require a distinct treatment or combinations of treatments. Thus, curative therapy that affects all of these networks supporting the tumor may require combinations of combinations of treatment. This is more complicated than for childhood tumors, which are typically caused by inherited mutations (Kentsis 2020) and lack key systemic network changes.

IV. Monitoring key networks. Monitoring key networks which nurture and maintain the tumor is necessary to determine their current status, response to treatment and effect on patient survival. These key networks include: the inflammatory process in general, the microenvironment of the tumor and metastatic sites, unicellular networks that promote malignant behavior, embryonic networks that promote lack of cell differentiation and rapid growth, the immune system's antitumor capabilities, the insulin-IGF system and important germline networks affecting malignancy. This monitoring, analogous to therapeutic drug monitoring of antimicrobials for infectious diseases, should supplement existing radiologic and clinical studies that determine the size and extent of the known tumor. For each network, we must determine what biological molecules to monitor, how best to do so and how changes in their values should affect treatment. It may be useful to develop a cancer network score to predict prognosis and suggest future treatments, analogous to the TNM staging score.

V. Clinical trials. Extensive clinical trials will be needed to determine the effectiveness of individual treatments, combinations of treatments and combinations of combinations of treatments affecting these key networks, as well as their effect on tumor response and long term survival rates. Additional studies will determine how to reduce side effects and what adjustments to make for particular patients. The history of curative cancer therapy in children and young adults suggests that protocols originally thought to be too difficult to implement can be simplified and made more tolerable. Towards this end, every cancer patient should be enrolled in a clinical trial, a major change in the status quo.

VI. Strong public health programs. A curative treatment strategy should create strong public health programs to promote pancreatic cancer risk reduction, develop more effective screening programs and ensure that all patients get optimal medical care. Risk factor reduction includes behavioral changes to decrease pancreatic cancer risk such as reducing smoking, excess weight and alcohol abuse and encouraging a healthy diet and exercise (European Code Against Cancer, accessed 14Feb21). At a

societal level, our public health and medical care systems act as a "behavioral immune system" (Schaller 2015) to reduce cancer risk factors. Our physiologic immune system prevents numerous cancers from being clinically evident, as discussed above. Similarly, a well run public health system that promotes risk factor reduction and early detection will prevent many cancers from arising (Schüz 2019). As changes to personal behavior reduce cancer incidence, a higher percentage of cases will be attributable to random chronic stress, which may shift our perspectives and create opportunities to understand these cases better, as demonstrated with nonsmoking related lung cancer (Thomas 2020).

We should also develop more effective programs for identifying premalignant or malignant lesions in both high risk patients and current patients being monitored for relapse. Unfortunately, there are no simple tests to detect premalignant pancreatic cancer lesions (Guo 2016). Screening for malignancy consists of computed tomography scans, magnetic resonance imaging or endoscopic ultrasonography (Owens 2019). Since tumors arise and are maintained due to alterations of local and systemic networks, we suggest creation of a pancreatic cancer risk calculator, similar to that used for cardiovascular disease, which uses a combination of screening tests for the various super promoters, markers of tumor cell dissemination in blood, assessment of key networks described above and other high sensitivity and high specificity tests (Yu 2016, Nakatochi 2018).

At an individual level, optimal medical care promotes the reduction of behavioral risk factors, earlier detection of disease and increased use of effective treatments not available to those with inadequate care, poor performance status or severe comorbidities (Kelly 2016, Maclay 2017).

Based on the risk factors and super promoters discussed above, we have identified these key network issues to be addressed by curative treatment:

1. Kill as many primary tumor cells as possible. High tumor cell kill is important because tumor cells: (a) directly damage tissue and organ systems, interfering with their function. Human physiology is based on interdependence between tissues and organ systems with substantial redundancy. However, as cancer damages tissues and organs, this redundancy diminishes and physiologic functions necessary to maintain life start to fail; (b) reproduce and replace other tumor cells killed by treatment and (c) have diverse strategies to sabotage physiologic control mechanisms that normally prevent cells from traversing malignant pathways; thus, each tumor cell death may eliminate a different tumor strategy.

2. Attack multiple targets within local tumor networks. Curative treatment for pancreatic cancer should build on our success in curing cancer in children and young adults, including childhood leukemia, Hodgkin lymphoma and testicular cancer. These cancers are caused by inherited or constitutional cancer predisposition or developmental mutations (Kentsis 2020) and exhibit a limited number of somatic tumor mutations (Sweet-Cordero 2019). Although they typically have no prominent risk factors and show no field effects, curative therapy still requires combinations of 3-5 effective treatments with different mechanisms of action, mixed and matched for maximum effect (Mukherjee: The Emperor of All Maladies 2010; see N'Guessan 2020 for combination chemotherapy trial for pancreatic cancer). Multiple agents are necessary because biologic pathways are weblike, not linear, allowing cancer cells to bypass important steps blocked by antitumor agents (Nollmann 2020, Ozkan-Dagliyan 2020). Curing pancreatic cancer may require even more treatment diversity due to: (a) its complex and heterogeneous mutational landscape (Rice 2019, Samuel 2011, Juiz 2019), (b) the field effects generated by cancer promoters / risk factors acting over decades of exposure and (c) associated systemic network changes that also must be addressed by treatment (discussed below)

Drug combinations may be more effective than single agents in general, not just for cancer therapy (Mokhtari 2017). Determining whether drug combinations are synergistic, additive or antagonistic is time consuming, but "deep learning," other computational approaches and modeling methods may help screen possible combinations for effectiveness (Preuer 2018, Sidorov 2019). Combining different types of therapy may also be effective; for example, regional hyperthermia combined with radiotherapy may kill cancer stem cells (Oei 2017) and improve survival (Fiorentini 2019).

3. Move local tumor cell networks into less lethal states. Curative treatment, in addition to killing large numbers of tumor cells through multiple mechanisms, should include therapies to create less hazardous network states in tumor cells that survive this treatment (Heudobler 2019). A theoretical framework to

move malignant networks from cancer attractors to a less hazardous state has been described (Huang 2013, Kim 2017, Zhou 2016). Network altering treatments, even if successful in disrupting cancer attractors, typically cannot move malignant or premalignant cells back to their normal physiologic state, but they can push them towards alternative states with reduced malignant properties. Examples include retinoids for acute promyelocytic leukemia and childhood neuroblastoma (Nowak 2009), progestin for endometrial hyperplasia (Gallos 2013) and other lineage reprogramming agents (McClellan 2015, Gong 2019). For tumors with no known effective treatments, constant perturbation of networks with drugs that destabilize the existing state may move cancer attractors towards a more differentiated or less hazardous state (Cho 2016, Kim 2017).

4. Disrupt the inflammatory process, which plays a central role in promoting and sustaining carcinogenesis. This includes: (a) triggering pro-resolution pathways which are typically initiated at the beginning of the physiologic inflammatory process (Fishbein 2020, Park 2020); (b) mimicking the halting mechanisms associated with wound healing (Shah 2018, Kareva 2016) and liver regeneration (Abu Rmilah 2019) and (c) using COX2 inhibitors, other NSAIDs or other anti-inflammatory agents to diminish inflammation associated with pancreatic cancer (Wang 2019, Zappavigna 2020, Sun 2019, Choi 2019). Disrupting the inflammatory process will also diminish its ability to promote tumor growth, acinar to ductal metaplasia, reactive oxygen species and glycolysis, described above. In addition, it will affect the key networks discussed below relating to immune system dysfunction, a tumor supportive microenvironment, activation of unicellular networks and activation of embryonic networks.

5. Disrupt the microenvironment that nurtures tumor cells at primary and metastatic sites. The 5 super promoters produce a microenvironment which nurtures mutated cells, steers cellular networks towards malignant pathways (Mbeunkui 2009), helps them escape immune surveillance (Labani-Motlagh 2020) and ultimately promotes invasion by activating cells to mimic physiologic "invasion" of wounded epithelium through the extracellular matrix (Bleaken 2016, Coussens 2002). Tumors require a fertile "soil" for the cancer "seeds" to grow (Fidler 2003, Tsai 2014), as exemplified by Hodgkin Reed-Sternberg cells, which produce cytokines that assist tumor cell survival and proliferation (Wang 2019). Similarly, pancreatic tumor cells produce cytokine IL1β and proinflammatory factors, essential for establishing a tumor supportive microenvironment (Das 2020, Huber 2020). From a network perspective, there is a complex crosstalk among cancer cells, host cells and the extracellular matrix (Sounni 2013, Sperb 2020). We recommend combinatorial therapy to normalize the microenvironment by targeting the vasculature, inflammation, fibroblasts and the extracellular matrix (Mpekris 2020). For example, anti-VEGF or anti-VEGF receptor treatment can normalize vasculature by reducing vascular permeability (Gkretsi 2015). Normalizing the microenvironment may also enhance drug delivery and effectiveness (Polydorou 2017, Stylianopoulos 2018) or make existing tumors or intermediate states more susceptible to immune system attack (Ganss 2020).

It is also important to disrupt the microenvironment of possible metastatic sites. In the pancreas, tumor cell spread often occurs even before a primary malignancy arises. Typically, these cells would die at secondary sites, but the malignant process preconditions the otherwise hostile microenvironment of the secondary site so it can sustain their colonization (Houg 2018).

6. Disrupt the microenvironment that promotes an embryonic state in some tumors, which is associated with aggressive tumor behavior. In the microenvironment of the fertilized egg, as discussed above, coordinated network activity ultimately moves embryonic related networks towards mature, differentiated phenotypes. However, the non coordinated super promoters generate more unstable network activity that does not resolve, including cells with embryonic properties such as dedifferentiation, rapid cell division and migration (Ambrosini 2020). Maturational agents such as retinoids used in acute promyelocytic leukemia (Madan 2020) or myeloid differentiation promoting cytokines or lineage reprogramming agents (McClellan 2015, Gao 2019, Gong 2019) can reprogram networks to induce maturation. In addition, agents that halt rapid cell division in embryogenesis (Kermi 2017) may be useful.

7. Repair or interfere with the immune system dysfunction which coevolves with pancreatic carcinogenesis. The immune system consists of a web of interacting networks whose effectiveness is systematically degraded with malignant progression. Immune dysfunction in pancreatic cancer is typically not just the failure of one particular pathway (Karamitopoulou 2020). Curative treatment should attempt

to improve immune system function with combinatorial therapy that targets multiple aspects of immune dysfunction (Sodergren 2020).

8. Promote the activation of gene networks supporting stable, multicellular processes and suppress networks promoting unicellular processes that support malignant type behavior. Activation of multicellular network programs may limit unicellular processes associated with malignancy (Trigos 2018). Alteration of the physiologic balance between multicellular and unicellular networks may be triggered by inflammation and DNA alterations, as described above. This balance may be restored by drugs that specifically turn on machinery in multicellular networks by stimulating mesenchymal to epithelial transition (MET inducers) (Gaponova 2020), which then reactivates epithelial regulatory genes, turns off the motility machinery for invasion and causes cells to re-express apical-basal polarity (Hay 1995). In addition, treatment can target the weaknesses of cancer cells based on the atavistic theory (Lineweaver 2014) by applying a specific cellular stress that is readily dealt with by healthy cells using evolved capabilities or multicellular programming but not by cancer cells with predominantly unicellular programming. This includes “lethal challenges” of high dose methotrexate with leucovorin rescue (Howard 2016) or targeting other aspects of chaotic or unstable states, such as cell-extracellular matrix detachment (Crawford 2017).

9. Target the hyperinsulinemia or insulin resistance that promotes tumor growth. Possible strategies include the use of metformin (Wan 2018) or other drugs, as well as weight loss, exercise, a healthier diet and reducing alcohol and tobacco use. It appears that one block in these networks may be sufficient to normalize them, in contrast to the 3-5 blocks required for tumor cell networks.

10. Antagonize germline changes that promote malignant behavior. As recommended by the National Comprehensive Cancer Network (Daly 2020) and American Society of Clinical Oncology (Stoffel 2019), all pancreatic cancer patients should undergo genetic testing. Results can be used to determine targeted therapy to kill tumor cells (Zhu 2020) or to move premalignant or malignant cells into less harmful pathways. In addition, research should continue to determine common germline changes that promote pancreatic cancer through changes to networks affecting inflammation, DNA repair, cell cycle stabililty, immune systemic dysfunction or through other means.

11. Attempt to reduce personal behavior that activates the super promoters. In conjunction with the promotion of strong public health programs discussed above, a simple but important treatment component is to halt or at least reduce behavior that increases super promoter network activity, which may also reduce synergistic effects with other networks, causing reversion towards a more stable state (Kauffman, At Home in the Universe, 1995). For pancreatic cancer, this likely will reduce the incidence of new tumors and possibly could be synergistic with other therapy at targeting existing disease and improving survival (Jentzsch 2020). This risk factor reduction can be thought of as mechanisms through which etiologic fields can be attenuated throughout the body, preventing cancer occurrence and progression (Lochhead 2015).

Summary

Complexity theory recognizes that countering a systemic disease such as pancreatic cancer requires optimizing all factors affecting it, even if not directly part of the malignant process. We have identified aspects of patient health and disease that should be targeted towards providing cure. Prevention is important but random chronic stress still is the major risk factor and at this time cannot be prevented. Strategies should also focus on the other super promoters identified: chronic inflammation, DNA alterations, immune system dysfunction (individual and societal) and constitutive or increased expression of the insulin-IGF system. Treatment should be focused on all aspects of the tumor identified, with monitoring of key networks and with clinical trials to ensure optimal treatment of this devastating disease.