Curing Cancer – Part 7 – Random chronic stress / bad luck as a major cause of cancer

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This is my seventh essay about curing cancer based on the principles of complexity theory. This essay discusses random chronic stress / bad luck, a major cause of pancreatic cancer (**Pernick 2021**) and lung cancer in nonsmokers (**Pernick 2018**).

Key concepts discussed are: (1) random chronic stress / bad luck is a major cause of cancer at some sites; (2) cancer often develops through rare bursts of activity in cells and their networks, not in a gradual, step-wide manner; (3) cancers due to random chronic stress may have better survival and other clinical differences compared with cancers due to traditional risk factors; and (4) due to the presence of random chronic stress, cancer will always be with us, although we can prevent some cases, we can detect it earlier and we can treat it more effectively.

What is random chronic stress / bad luck?

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 1 per 100 million nucleotides after error correction occurs (**Pray 2008**); (b) errors in how DNA is organized or modified by epigenetic events (**Wikipedia-Cancer epigenetics**, accessed 26Jan21); (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**); (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 erroneously included in the category of random chronic stress / bad luck.

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.

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**).

How does cancer due to chronic random stress differ from other cancers?

Cancer due to random chronic stress differs from cancers caused by traditional risk factors, such as cigarette smoking, in two important ways. First, the rate of cancer due to random chronic stress is much lower. We previously estimated the rate of lung cancer due to random chronic stress at 2 cases per 100,000 men and women per year, compared with the current age adjusted US incidence of lung cancer, due primarily to cigarette smoking, of 54 cases per 100,000 (**Pernick 2018**). However, random chronic stress may account for 50-70% of lung cancer cases in nonsmokers in North America and Europe (**Pernick 2018**). For pancreatic cancer, random chronic stress is also estimated to cause 2 cases per 100,000 people per year (age standardized) compared with the current age standardized rate of 7.7 in Europe and 7.6 in North America (**Pernick 2021**; **Rawla 2019**); it may be the most common risk factor for pancreatic cancer, accounting for 25-35% of US cases (**Pernick 2021**).

Second, clinical characteristics of resulting cancers may be different. For lung cancer, there are striking differences between the epidemiological, clinical and molecular characteristics of lung cancer in cigarette smokers (80-90% of cases) compared with never smokers that have led some authors to conclude that they are distinct clinical entities (**Yano 2008, Smolle 2019**). Never smokers with lung cancer have a higher predominance of women, more frequent Asian/Pacific Islander or Hispanic ethnicity, a higher frequency of adenocarcinoma histology, more frequent *EGFR* mutations and *ALK* rearrangements and superior survival

when adjusted for standard prognostic factors (**Pernick 2018**). Never smokers with lung cancer may have a higher predominance of women and Asians because these groups make up a larger percentage of never smokers (**Tsai 2008**).

For pancreatic cancer, cigarette smoking is also associated with higher death rates and poorer survival (**Ben 2019**, **Yuan 2017**). However, unlike lung cancer, pancreatic cancer has other risk factors causing a high percentage of cases, namely non O blood group, excess weight and type 2 diabetes, as well as less prominent risk factors of excessive alcohol use, diet, family history / genetic and chronic pancreatitis (**Pernick 2021**). To date, we are not aware of any studies comparing clinical and molecular characteristics of pancreatic cancer patients with and without these risk factors.

There are two reasons that patients with lung or 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.

Second, 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**).

Why cancer will always be part of our world

The American Cancer Society does great things, but its **mission statement**, "The American Cancer Society's mission is to save lives, celebrate lives, and lead the fight for a world without cancer" (accessed 31Jan21) is irrational. Even if we could totally eliminate all cancer risk factors, the presence of random chronic stress / bad luck would ensure a steady rate of new cancer cases. A realistic strategy is not to eliminate cancer but to try to prevent cases by reducing risk factors, detecting cases earlier and developing more successful treatment.

My next essay will discuss immune dysfunction, one of five "super promoters" of cancer into which most risk factors can be categorized: chronic inflammation, DNA alterations (somatic or germline), random chronic stress, immune system dysfunction (individual or societal) and hormonal effects.