How Lung Cancer Arises, Based on Complexity Theory

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- Abstract

- We hypothesized that studying cancer based on complexity theory instead of the traditional reductionist approach will yield new insights into understanding how cancer arises and, ultimately, more effective treatment options. This paper is the first in a series discussing each of the 20 leading causes of US cancer death and how they arise based on complexity theory. This report focuses on lung cancer and begins with a summary of complexity theory and a discussion of our hypotheses: that complexity theory is important in understanding cancer; that chronic cellular stress is the underlying cause of most cancer; and that lung cancer risk factors are better understood in this context. Finally, we discuss generalized treatment approaches based on complexity theory.

1 Introduction: complexity theory

A system is considered complex if the properties of the entire system are greater than the sum of the properties of each part of the system. Interactions between the parts lead to emergence of novel properties that cannot be predicted (1) and may be surprising (2) (page 19). In contrast, the traditional reductionist approach assumes that the behavior of the whole is equal to the sum of the behavior of the parts, that even the most complicated system is merely a combination of simpler systems (3) and that diseases are simply collections of flawed parts. Although rational, the reductionist approach has not led to adequate knowledge to substantially reduce cancer-related deaths.

We previously proposed that the following principles ("laws") of complexity theory and self-organization create a more robust framework for understanding the origins and dynamics of cancer:

1. In life, as in other complex systems, the whole is greater than the sum of the parts.

2. There is an inherent inability to predict the future of complex systems.

3. Life emerges from non-life when the diversity of a closed system of biomolecules exceeds a threshold of complexity.

4. Much of the order in organisms is due to generic network properties.

5. Numerous biologic stressors push cellular pathways toward disorder.

6. Organisms resist movement towards disorder through multiple layers of redundant controls, many related to cell division.

7. Cancer arises due to failure in these controls, with histologic and molecular characteristics related to the cell of origin, the nature of the biologic stressors, and the individual's germ line configuration [(4), with modifications].

2 Chronic cellular stress is the underlying cause of most cancer

We have proposed that chronic cellular stress causes most cancer cases by pushing susceptible stem or progenitor cells into a dysregulated and unstable network trajectory associated with increased and relatively uncontrolled cell division (5) [see also (6)]. Due to the complex nonlinear interactions that characterize living systems (7), we cannot predict which stressors will be associated with which malignant patterns, which cells will be affected, and which molecular pathways or gene products will be altered, although prior experience is instructive.

We have identified 9 chronic cellular stressors that commonly cause adult malignancy: chronic inflammation (due to infection, infestation, autoimmune disorders, trauma, obesity, diabetes and other causes); exposure to carcinogens; reproductive hormones; Western diet (high fat, low fiber, low consumption of fruit and vegetables); aging; radiation; immune system dysfunction; germ line changes and random chronic stress / bad luck. Individually or in combination, these stressors disrupt aspects of biologic networks that maintain homeostasis. Initially, the network changes may be minor but eventually large "catastrophes" of network change arise that are identifiable histologically or based on molecular patterns as premalignant or malignant (8). This model of how cancer arises excludes acute causes of cancer, when tumor cells are close to their genetic events, such as germ line changes in the young (9).

3 Lung cancer is the leading cause of US cancer death

Lung cancer is the leading cause of US cancer death, with 135,720 estimated deaths in 2020 or 22.4% of total cancer deaths (10) (page 17). It is the second most commonly diagnosed non-skin cancer in the US (after breast cancer), with an estimated 228,820 new cases in 2020. The death rate has declined by 51% since 1990 in men and by 26% since 2002 in women. From 2008 to 2017, the death rate decreased by 4% per year in men and 3% per year in women. Assuming continued decreases in smoking, annual US lung cancer deaths are projected to decrease to 50,000 in 2065 (11).

4 Lung cancer in never-smokers (nonsmokers)

We discuss lung cancer separately in smokers and never smokers based on striking differences in their epidemiological, clinical and molecular characteristics, which has led some authors to conclude they are distinct clinical entities (12, 13). Never smokers with lung cancer have a much higher predominance of women, more frequent Asian/Pacific Islander or Hispanic ethnicity, a higher frequency of adenocarcinoma, more frequent *EGFR* mutations and *ALK* rearrangements

and superior survival, even when adjusted for standard prognostic factors, as indicated in Table 1. These results are often discussed in terms of non-small cell lung cancer because small cell lung cancer is uncommon in never smokers, although its prevalence is increasing (14, 15).

5 Population attributable fraction

The population attributable fraction (PAF) is the projected reduction in death or disease if exposure to a risk factor is reduced to an alternative ideal exposure scenario, such as no exposure. Since lung cancer has multiple risk factors with synergistic interactions, PAFs often overlap and add up to more than 100 percent (16, 17). PAFs for specific lung cancer risk factors may vary greatly by geographical region due to differences in exposure. For example, household use of coal is a major risk factor for lung cancer in China but not elsewhere (18). We prefer to discuss PAF in terms of lung cancer incidence but some studies report PAF only for lung cancer deaths. Mortality is somewhat similar to incidence due to lung cancer's low five-year relative survival of 19% [(10), page 19 but see also (19) -PAF was higher for cancer mortality than for cancer incidence]. For Table 2, we attempted to use results common to several studies; when studies had varying PAFs, we used the lower figures. Many studies included the population as a whole (smokers and never smokers) but we separated out results for never smokers when available.

6 Attributable risk factors for lung cancer

6.1 Tobacco (smoking)

We discuss the traditional risk factors for lung cancer in the entire population (smokers and never smokers) and in never smokers in the context of the 9 chronic cellular stressors in declining order of population attributable fraction. The American Cancer Society attributes 80% of US lung cancer deaths in 2020 to tobacco [(10), page 17], comparable to a report from the US Surgeon General using 2005-2009 data (82.4% of lung cancer deaths in adults 35 years or older (20) Table 12.4, page 660). Other countries report similar attributable fractions except in Korean women, who have a low prevalence of smoking (19), see Table 3. Risk increases with quantity and duration of smoking. Quitting reduces the risk as the interval lengthens for not smoking. Cigar and pipe smoking also increase the risk (21, 22), although the PAF has not been calculated. E-cigarettes, which deliver nicotine as an aerosol without tobacco or the burning process, have not been definitively associated with human lung cancer. However, acute inhalation disturbs human lung homeostasis in healthy individuals (23) and is carcinogenic to murine lung and cultured human bronchial epithelium (24)**.**

Tobacco smoke promotes lung cancer through carcinogen exposure, chronic inflammation, radiation, premature aging, germ line changes and possibly immune system dysfunction. It contains at least 70 known carcinogens including aldehydes (25), ammonia, aromatic amines, arsenic, benzopyrene, cadmium, formaldehyde, polycyclic aromatic hydrocarbons and tobacco specific nitrosamines (26), which act through several mechanisms. First, tobacco carcinogens may undergo metabolic activation leading to the formation of DNA adducts (27). This process, generally catalyzed by cytochrome P450 enzymes, occurs as reactive intermediates bind covalently to the nitrogen and oxygen atoms of DNA bases [(28), **Figure 5.1**]. These DNA adducts may evade repair systems and cause miscoding during DNA replication when DNA

polymerase directs the placement of an incorrect DNA base opposite the adduct. This may lead to the accumulation of permanent somatic mutations in *KRAS* and *TP53* genes and ultimately to clonal overgrowth. These carcinogens also undergo metabolic detoxification, which excretes carcinogen metabolites into water soluble, generally harmless forms via catalysis by glutathione S transferases and UDP glucuronosyl and sulfo-transferases (20) (page 149). The balance between carcinogen activation and detoxification is determined partly by genetic polymorphisms and appears to affect cancer susceptibility; individuals with a higher activation and lower detoxification capacity have a greater risk for smoking related cancer (28) (Chapter 5).

Second, nicotine and nitrosamines in tobacco smoke or their metabolites bind directly to cellular receptors including beta adrenoceptors, EGFR and insulin-like growth factor receptor, leading to activation of protein kinases, growth receptors and other pathways, which can contribute to carcinogenesis (29).

Third, tobacco smoke promotes lung cancer via chronic inflammation. Tobacco smoke has a synergistic effect with other respirable particulates in generating reactive oxygen species and catalyzing redox reactions in human lung epithelial cells (30). Although protected by enzymatic and nonenzymatic antioxidant defenses, tobacco smoke may cause an imbalance of pro-oxidants and antioxidants in the cellular environment, which leads to oxidative stress and increased production of mediators of pulmonary inflammation that may promote DNA damage, inhibition of apoptosis, activation of proto-oncogenes, lipid peroxidation of cellular membranes, and telomere shortening (31).

Fourth, radioactive polonium 210 in cigarette smoke causes lung cancer due to alpha particle deposits in the lungs (32, 33).

Fifth, smoking is associated with hypomethylation of CpG sites in the *AHRR, F2RL3* and other genes (34, 35), even in individuals with a short smoking history (36). *AHRR* is the repressor of the aryl hydrocarbon receptor, a key regulator of relationships between the cell and the external environment including dioxins and polycyclic aromatic hydrocarbons (37). *F2RL3* (*PAR4*) encodes a protein involved in inflammatory reactions and blood coagulation and is a very strong predictor of lung cancer risk and mortality, particularly at older ages (38).

Sixth, smoking may induce autophagy and premature aging in the host stromal microenvironment, which promotes anabolic tumor growth (39).

Seventh, inherited variants in nucleotide excision repair genes, whose products detect and remove bulky DNA lesions induced by tobacco smoke in the respiratory tract, may predispose to smoking-related lung cancer (40, 41), particularly squamous cell carcinoma in some populations (42).

Finally, smoking may suppress the immune system by impairing innate and adaptive immunity (43, 44).

Complexity theory suggests that we cannot predict the short- or long-term impact of even a "simple" carcinogen on lung epithelial cells due to the relative stability of biologic pathways and their nonlinear interactions with each other. Thus, the impact of decades of exposure to 7,000 substances in tobacco smoke (20) (page 154), many with multiple physiologic actions, cannot be

precisely determined. They likely promote network changes in a myriad of different pathways at multiple sites within the lungs (45-47). For example, analysis of a poorly differentiated lung adenocarcinoma showed more than 50,000 single nucleotide variants (48), and a small cell lung cancer cell line had 22,910 somatic mutations (49). This level of mutations likely overwhelms the capacity of the DNA repair pathway, both due to their magnitude and because mutations may damage the repair pathways themselves. Tumor growth may be countered by a vigorous response involving DNA repair and immune surveillance but ultimately, as with HIV virus attacked by T cells, the balance may shift so that the disease process gains the upper hand (50).

Why do never smokers with non-small cell lung cancer (NSCLC) have longer survival than smokers with NSCLC? We speculate that decades of exposure to large numbers of carcinogens in tobacco smoke creates tumors that are more multifocal and aggressive, features traditionally associated with poorer survival. In addition, smoking-related tumors and their microenvironment may have more unstable behavior at the molecular or cellular network level, even if not detectable by histology.

6.2 Secondhand smoke

According to the US Surgeon General, secondhand smoke (passive smoking, environmental smoke) caused 4.6% of US lung cancer deaths in all adults (smokers and never smokers) 35 years or older as of 2005-2009 [(20) Table 12.4, page 660]. In Alberta, Canada, in 2012, 5.2% of lung cancer cases were attributed to passive smoking (51) (Table 5). Considering only never smokers, Sisti determined that the PAF for secondhand smoke for lung cancer cases in North America / Europe / China was 8.2% / 10.3% / 12.4% in men and 5.6% / 14.3% / 24.1% in women (18). Although male and female nonsmokers with lung cancer have similar clinical features, women have a much higher incidence of environmental tobacco smoke exposure than men [78.6% versus 21.4%, (52)].

Secondhand tobacco smoke is a mixture of aged, exhaled mainstream smoke and diluted sidestream smoke. The International Agency for Research on Cancer (IARC), the specialized cancer agency of the World Health Organization, has classified secondhand tobacco smoke exposure as a carcinogen [(53), Involuntary Smoking, Section 5.5]. Sidestream and secondhand smoke contain more than 50 carcinogens including benzene, 1,3-butadiene, benzo[*a*]pyrene and 4-(methylnitrosamino)1-(3-pyridyl)-1-butanone (54). There is no apparent threshold dose for respiratory carcinogens, at least in active smokers (55). Passive smoking causes a significant increase in urinary levels of metabolites of NNK, a tobacco specific lung carcinogen (56). The pooled evidence suggests a 20 - 30% increase in lung cancer risk from secondhand smoke exposure due to living with a smoker (57). The mechanism of action is presumed similar to that in smokers.

6.3 Random chronic stress/bad luck

Lung cancer in never smokers causes an estimated 20% of annual US lung cancer deaths (58) and is considered by some a distinct disease from that in smokers (13, 59). In the US, at 30,000 annual deaths, it would be the seventh most common cause of cancer death after lung cancer in smokers and cancer of the colon, pancreas, breast, liver and prostate (10). The lung cancer death

rate for never smokers is comparable to death rates for leukemia and endometrial cancer in women and to esophageal, kidney and liver cancer in men (55).

The proportion of NSCLC cases worldwide in never smokers varies from 8 – 10% of lung cancer cases in the US (55, 60) (includes all lung cancer histology) to 22.4% in Portugal (61), 32.4% in Singapore (62) and 38.0% in Korea (63). The death rate of never smokers from lung cancer appears to be stable [(64), but see (65)] but the proportion of never-smoking patients with lung cancer has been increasing. For example, NSCLC in never smokers in Japan has increased from 15.9% of cases in the 1970s to 32.8% of cases in the 2000s (12), most likely due to a reduction in smoking-related lung cancer (55).

We attribute the major cause of lung cancer in never smokers to be random chronic stress / bad luck, accounting for 50 – 70% of these cases in North America and Europe. This is calculated as 100% minus the attributable risk of known factors. These "no risk factor" lung cancers may be due to known risk factors which are neglected by researchers because their impact is typically small when compared with smoking, such as (a) chronic obstructive pulmonary disease (COPD); (b) pneumonia, HIV, HPV, tuberculosis or other infections; (c) unrecognized radon exposure; (d) unrecognized exposure to secondhand smoke, air pollution or other carcinogens; (e) Western diet; (f) aging; (g) germ-line variations that confer an increased cancer risk; and (h) obesity, which is not a traditional risk factor for lung cancer but is associated with chronic inflammation.

Self-organized criticality explains the impact of minor risk factors. Although dropping a large amount of sand onto a sandpile may cause an avalanche, it may also be caused by a single grain of sand in the correct context (66). Similarly, trivial risk factors arising in a particular context of chronic stressors may cause an avalanche of network changes leading to cancer.

We propose that there is a baseline rate of lung cancer due to random chronic stress / bad luck which specifically excludes the effects of known risk factors and is usually overshadowed by the massive risk associated with cigarette smoking. We estimate this baseline rate as 2 cases per 100,000 men and women per year, compared with the current age adjusted US incidence of lung cancer of 54.2 cases per 100,000 (67). This estimate is based on the lowest incidences observed worldwide of 1.7 per 100,000 in Western Africa [(68, 69); see also (70)]. This baseline rate is comparable to US rates of lung cancer before the popularization of tobacco in World War I, reported as less than 5 per 100,000 (71), although historical rates need to be interpreted with caution due to subsequent changes in how lung cancer is diagnosed [(72), Appendix C, Tobacco-Smoking and its Interaction with Radon]. The lung may be more susceptible to cancer from environmental toxins and other chronic stressors than other organs due to its large surface area of 70 m^2 (73).

Tomasetti and Vogelstein also claim that lung cancer in nonsmokers is mainly due to the bad luck of random mutations arising during DNA replication in normal, noncancerous stem cells that might interact with existing risk factors; these effects also cause variation in cancer risk among tissues [(74, 75) but see (76, 77)].

6.4 Radon exposure

In the US general population, indoor radon exposure causes 9.9 – 14.1% of lung cancer deaths in men and 10.8 – 15.3% of lung cancer deaths in women (72) (**Table ES-2**). Data on lung cancer cases (not deaths) attributable to radon exposure is not available. Worldwide estimates show wide variations. Kim et al. showed general population attributable risks of 4% in the Netherlands, 5 – 13% in France, 7.8 – 16% in Canada and 20% in Sweden (78). Gaskin provided estimates for 66 countries using 3 different models, ranging from 4.2% in Japan to 29.3% in Armenia (79). In Korea, the PAF for lung cancer due to long term radon exposure varied from 6.6% in men and 4.7% in women in one study (80), to 12.5 – 24.7% (men plus women) in a different study based on different models (81). Some researchers believe that radon-induced lung cancer deaths may be overestimated by 9 – 26% due to an association of diesel engine exhaust with lung cancer (82), although others disagree (83, 84).

In never smokers, the PAF for radon exposure (males 18.9 – 25.8%, females 19.7 – 26.9%) is double that for ever smokers [males 8.7 – 12.5%, females 9.6 – 13.7%, (72), **Table ES-2**]. However, the lifetime risk of radon-induced lung cancer death at an exposure level of 4 pCi/L is only 7 per 1,000 for never smokers compared with 62 per 1,000 for ever smokers (85). With a lifetime exposure of 10 pCi/L, the risk of radon-induced lung cancer is only 18 per 1,000 for never smokers compared with 150 per 1,000 for ever smokers. These differences are apparently due to a marked synergistic interaction between smoking and radon; most radon-related deaths among smokers would not have occurred if the victims had not smoked (85).

Radon is a tasteless, colorless and odorless gas produced naturally from radium in the decay series of uranium and is considered a Group 1 carcinogen by IARC. Studies of underground miners of uranium and other ores have established exposure to radon progeny as a cause of lung cancer (86, 87). Radon decay into polonium causes both alpha particle bombardment of bronchial epithelium and precipitation of polonium. Alpha particles carry enough energy to produce a high rate of double strand DNA breaks compared with other types of ionizing radiation (88), generating damage that is difficult to repair and ultimately producing mutations (89). Alpha particles also produce reactive oxygen intermediates that may damage DNA. The cause of the synergy between smoking and radon is not well understood (72) **(Appendix C**).

6.5 Occupational, including asbestos

Lung cancer is the most common cancer associated with occupational exposure (90). Estimates of the proportion of lung cancer caused by occupational exposure through independent or shared causal pathways range widely because of differences in industrial settings but 10% has been proposed as a reasonable average for the general population (17). Known exposures that cause lung cancer include radon (discussed above), asbestos, tar and soot, chromium, cadmium and nickel (17, 88, 91), as well as cooking oil (92). In a general population, an association was found even at low exposures of asbestos, crystalline silica and nickel-chromium (93). Data for women may be insufficient to calculate stable estimates due to lower exposure (94). Arsenic in drinking water also causes lung cancer (95) but not at low levels (96, 97).

Asbestos is a mineral silicate containing iron, magnesium and calcium around a core of silicon dioxide. Cigarette smoking potentiates the effect of asbestos and other occupational lung carcinogens according to some (98, 99) but not all (100) researchers. In one study of asbestos exposure in North Americans working with insulation, lung cancer deaths were increased 3.6x in

nonsmokers with asbestos exposure; 7.4x in nonsmokers with asbestos exposure and asbestosis; 10.3x in smokers without asbestos exposure; 14.4x in smokers with asbestos exposure; and 36.8x in smokers with asbestos exposure and asbestosis (101).

In general, the findings on occupational risk factors in never smokers appear to parallel those in smokers, although many studies of occupational exposure and lung cancer either do not stratify results by smoking status or include very small numbers of never smokers, leading to imprecise risk estimates (18, 55). As a result, a PAF for occupational risk for never smokers is not available.

Occupational agents have varied mechanisms of action that may be nonlinear by themselves and in combination with smoking. For example, asbestos exposure causes immunosuppression through enhancement of regulatory T cells, impairment of CD4+ T cells and impairment of killing activities of CD8+ cytotoxic T lymphocytes and NK cells (102, 103) and its persistence in lung tissue causes chronic inflammation. Immunosuppression and chronic inflammation are chronic stressors that cause cancer in an indirect manner (104), mediated in part through oxidative stress (105). The common localized inflammatory actions of tobacco smoke and asbestos may explain their additive effects while additional tobacco-related carcinogens and iron-related catalysis in asbestos may account for synergistic effects (99).

6.6 Outdoor air pollution

In 2013, the IARC classified outdoor air pollution and particulate matter (PM) as Group 1 carcinogens causing lung cancer [(106), see also (107, 108)]. Doll and Peto previously estimated that 1 – 2% of lung cancer cases were related to air pollution (90) but some suggest this estimate is too low (109). In Alberta, Canada 1.9 – 5.7% of incident lung cancer cases were estimated in 2012 to be attributable to PM2.5 outdoor air pollution (particulate matter ≤ 2.5 μm in aerodynamic diameter) (110). Additional studies confirming the association between outdoor air pollution and lung cancer include: (a) in US female nurses exposed to PM2.5, both never smokers and former smokers who quit at least 10 years previously had a hazard ratio of 1.37 compared with those not exposed (111); (b) in Korea, the adjusted odds ratio was 1.09 for a ten-unit increase in PM10 and 1.10 for a ten-unit (parts per billion) increase in nitrogen dioxide (112); and (c) a worldwide study showed a relative risk of lung cancer based on exposure to PM2.5 of 1.09 in Asia, 1.06 in North America and 1.03 in Europe (113). In addition, in US nonsmokers, an increased risk of lung adenocarcinoma was observed for each 10 $\mu g/m^3$ increment in ambient PM2.5 concentrations, particularly in those without nonmelanoma skin cancer and who spent more than 1 hour per day outdoors (114). Data were insufficient to calculate the PAF for outdoor air pollution and lung cancer (18, 55).

Exposure to traffic-related air pollution also increases the risk of lung cancer, based on a meta-analysis of studies of nitrogen oxides, sulfur dioxide and fine particulate matter (115). Other studies have found relationships between lung cancer and nitrogen dioxide as a proxy for traffic sourced air pollution exposure (116, 117) and between residential proximity to major roadways in Italy and lung cancer mortality (118).

The lungs are exposed daily to oxidants generated by air pollutants including inhalable quartz, metal powders, asbestos, ozone, soot, tobacco smoke and particulate matter. These substances

promote oxidative stress, which causes pulmonary inflammation and is associated with carcinogenesis (30). In addition, the air pollutant benzo(a)pyrene is a carcinogen that induces DNA methylation alterations, which may affect lung cancer development and progression (119).

6.7 Tuberculosis

No known study has calculated the PAF for tuberculosis and lung cancer in the general population. However, tuberculosis has been associated with an increased lung cancer risk in Finnish male smokers [hazard ratio 1.97, (120)], Korean adults [(hazard ratio 1.37 in men and 1.49 in women, (121)], Korean male smokers [relative risk 1.85, (122)], Taiwanese patients with latent tuberculosis infection [hazard ratio 2.69, (123)], Taiwanese patients with tuberculosis post-inhaled corticosteroids for asthma [hazard ratio 2.52, (124)] and never-smoking Asian women [odds ratio 1.31, (125)], while no association was found in Lithuanian patients (126). In never smokers, Sisti estimated the PAF of lung cancer due to tuberculosis as 1.1% in North America, 2.4% in Europe and 12.7% in China (18).

The apparent mechanisms are markedly prolonged chronic inflammation (even in patients who receive treatment) and pulmonary scarring (120, 127).

6.8 Germ line variations / family history

Many studies have documented an increased risk of lung cancer due to family history or genetic predisposition (128, 129). Genetic interactions between oncogenesis-related genes may also play an important role (130). Sisti determined the attributable risk in never smokers, but the results varied by geography: North America 2.0%; Europe 1.2%; and China 2.9% (18).

Genetic factors are masked by the overwhelming influence of smoking and to a lesser extent radon, occupational exposure, air pollution, coal burning and tuberculosis. Individuals with a first-degree relative with lung cancer have a 1.5x increased risk after adjusting for smoking and other potential confounders, with the association strongest for those with a family history in a sibling (131).

Polymorphisms of numerous germ line markers have been associated with lung cancer. They include inflammatory markers C reactive protein (132, 133) and *NFKB1*, a transcription factor activated by proinflammatory cytokines which regulate gene expression, apoptosis and cell proliferation (134). Other genetic polymorphisms associated with increased lung cancer risk include: (a) alpha1 antitrypsin: nonsmokers with the SS genotype had an increased risk due to reduced anti-protease protection against neutrophil elastase and other proteases, promoting emphysema (135); in another study, carriers had a 70 to 100% increased risk and may have constituted 11% of lung cancer patients (136); (b) ACYP2, important in membrane pumps such as the Ca/Mg ATPase in the sarcoplasmic reticulum of skeletal muscle (137); (c) Glypican 5, implicated in cell proliferation and morphogenesis and a possible tumor suppressor (138, 139); (d) *NQO1*, which prevents benzo(a)pyrene related DNA adducts (140); and (e) telomerase related genes *TERT* and *TERC* (141). For adenocarcinoma, 2.5 – 4.5% of patients carry germ line variants in DNA repair pathway genes *ATM*, *TP53*, *BRCA2*, *EGFR* and *PARK2* that have been linked to cancer risk in Mendelian syndromes (142).

A very rare syndrome of germ line *EGFR* T790M mutations targets never smokers; carriers have a 31% risk of lung cancer (143); T790M may be a weak oncogene by itself but requires a secondary mutation to potentiate cancer development. Of note, lung cancer in never smokers is associated with an increased prevalence of tumor-related *EGFR* mutations (144).

The diversity of gene polymorphisms associated with lung carcinoma confirms the importance of complexity theory in carcinogenesis. Important polymorphisms occur not only in genes associated with DNA repair (*ATM*, *TP53, NQO1*), which prevent DNA adduct formation (*NQO1*) or which affect telomerase (*TERT* and *TERC*) but also in genes that produce growth factors (*EGFR*), mediate inflammation (C reactive protein, *NFKB1*), are part of connective tissue (Glypican 5) or membrane pumps (*ACYP2*) or promote emphysema (alpha1 antitrypsin). These polymorphisms cause network alterations over decades, which may affect additional networks and promote carcinogenesis in the correct cellular context.

6.9 Chronic obstructive pulmonary disease (COPD)

Chronic stressors associated with a small PAF in never smokers include COPD and pneumonia. Sisti attributed 0.4% of lung cancer in never smokers in North America to COPD, compared with 0.6% in China (18). No estimate was calculated in European populations, and no attributable risk has been calculated for smokers. This association is strongest in those with emphysema (145, 146), often identified on CT scan (147-150).

The increased risk of lung cancer in patients with COPD appears to be due to airway obstruction assessed with FEV1 (151, 152), although some authors believe the association is largely explained by smoking (153). Current and former smokers with COPD may disproportionately benefit from lung cancer screening (154).

COPD is characterized by an excessive inflammatory and oxidative stress response that may contribute to its association with lung cancer (155). As COPD progresses, activated leukocytes release proteases and free radicals. Reactive oxygen species cause DNA damage and alter regulatory proteins involved in host immunity and tumor suppression. Statins may protect against lung cancer in COPD patients by attenuating pulmonary and systemic inflammation (156). In addition, dysregulated immune function is implicated in the pathogenesis of COPD and may alter host immunosurveillance that plays an important antitumor role during the evolutionary course of lung cancer (157). The lung microbiome and genetic susceptibility may also be important (158).

6.10 Pneumonia (chronic inflammation)

Due to the high incidence of lung cancer in never smokers, a relationship has been sought with other factors, including infections. In North America, a modest 0.2% of lung cancer in never smokers is attributed to pneumonia [(18); see also (159), (160), and (161) but see also (162)]. *Chlamydia pneumoniae* infection shows a consistent relationship with an odds ratio of 1.5, but no attributable risk has been calculated (163, 164). This relationship may be due to the disruption of the host proteome by *C. pneumoniae* proteins (165, 166).

6.11 Indoor air pollution – never smokers

The IARC has concluded that household combustion of coal causes lung cancer (167). Sisti attributed 19.9% of lung cancer cases in Chinese women who were never smokers to household use of coal (18), which is common in low and medium resource countries (55) and is associated with poorly ventilated kitchens. Burning coal generates respirable particles and many carcinogens including benzo[a]pyrene, formaldehyde and benzene.

6.12 Aging

Many risk factors for lung cancer have no quantified population attributable risk, including aging, diet, HIV, HPV, obesity and cannabis smoking. Advanced age is the most important risk factor for cancer overall and for many individual cancer types. According to SEER, the median age of US cancer diagnosis is 66 years for all anatomical sites; for lung cancer, the median age is 70 years (168).

Aging promotes carcinogenesis in several ways. First, aging is associated with specific epigenetic modifications that may contribute to aberrant chromatin conformation and stability as well as somatic mutation (169). Determining “intrinsic epigenetic age acceleration” may predict lung cancer incidence (170). Second, aging provides more time for chronic stressors to exert their effects through the progressive accumulation of mutations and other network alterations (171). Third, aging is associated with immune system dysfunction and chronic inflammation, known chronic stressors which causes malignancy (172, 173). Fourth, aging affects regulation of microRNAs, which may promote lung cancer initiation and progression by affecting cell proliferation (174). Finally, although not described specifically in the lung, aging may promote cancer through effects on tissue microenvironment (175).

Metformin, resveratrol and Rhodiola have both anti-aging and anti-cancer effects by altering evolutionarily conserved nutrient sensing pathways, including IGF1 signaling, mTOR, AMPK and sirtuins (176, 177). These agents not only reprogram energy metabolism of malignant cells but also target normal postmitotic cells by suppressing their conversion into senescent cells.

6.13 Diet

In the US, diet is closely linked to cancer in the colon and breast but is so closely entangled with smoking that it is difficult to discern an independent effect (17, 178). No PAF has been calculated for diet and lung cancer (18) although Doll and Peto estimated a 20% reduction in lung cancer with a change in diet (90), particularly consumption of more vegetables and perhaps fruit, which was confirmed by subsequent studies (179-181). It is difficult to unravel the relative importance of each constituent, and the protective effect may result from multiple factors (182). Diets deficient in whole grains, vegetables and fruits are often “pro-inflammatory," and are associated with reactive oxygen and nitrogen species which damage DNA and promote genetic instability, insulin resistance and blunted immune response (183-185).

6.14 HIV

HIV-positive patients have an increased risk of lung cancer due in part to tobacco use and aging. Whether HIV is an independent risk factor is controversial [yes: (186, 187); no: (188)]. Lung cancer is the most frequent non-AIDS defining cancer (189) and the leading cause of cancer death in people with HIV receiving antiretroviral therapy (190). Low CD4/CD8 ratios and

cumulative episodes of bacterial pneumonia appear to promote lung cancer in this setting, most likely through immune dysfunction and chronic inflammation (191).

6.15 HPV

Recent reports and meta-analyses suggest that HPV infection significantly increases the risk of lung cancer [(192, 193) but see (194)]. Possible transmission routes into the lung are via coexisting cervical (192) and nasopharyngeal lesions or through inhalation (195). The HPV E6 and E7 oncogenic proteins may affect *TP53* and *RB* genes in bronchial epithelium as they do at other sites.

6.16 Abdominal obesity

Abdominal obesity based on waist circumference is associated with increased lung cancer risk among never, former and current smokers (196), although increased body mass index (BMI) has surprisingly been associated with a reduced risk [(197, 198) but see (199)]. The mechanism for the association between abdominal obesity and lung cancer is poorly understood but may involve associated metabolic disturbances such as hyperinsulinemia, sex hormone-binding globulin and unbound androgens and estrogens (196), as well as associations between obesity and smoking.

6.17 Cannabis / marijuana smoking

A New Zealand study found that the highest tertile of cannabis use was associated with a 5.7x increased risk of lung cancer, after adjustment for confounding variables including cigarette smoking (200). A study in Tunisia, Morocco and Algeria, three areas with high prevalence of cannabis consumption, found a 2.4x increased risk after adjusting for tobacco smoking and occupational exposure [(201) but see (202)]. The mechanism may be the production of carcinogens (tar, polyaromatic hydrocarbons) and inflammation of distal airways (203).

7 Treatment approaches to lung cancer based on complexity theory

Traditional lung cancer treatment is based on tumor histology and molecular testing and consists of surgery, chemoradiation therapy, targeted therapy and immunotherapy (204). Overall five-year survival rates vary by histology (6% for small cell lung cancer versus 24% for non-small cell lung cancer) as well as tumor stage [57% for localized disease (16% of cases), 31% for regional disease, and 5% for disseminated disease] (10).

Current treatment is based on reductionist principles, namely killing tumor cells where they exist. However, this approach does not consider cancer as a complex system [(2) (page 17)]. Our approach is to focus on the dysfunctional cellular networks that caused the primary tumor, that may cause additional cancers in adjacent tissue, and that may play a role in treatment resistance.

Complexity theory suggests that curative treatment must combine multiple strategies that affect network behavior. Our strategies are as follows:

I. Successful treatment should kill as many tumor cells as possible. This is important because tumor cells: (a) directly damage tissue and organ systems, interfering with their function; (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, so each tumor cell death may eliminate a different tumor strategy. In addition, since dead tumor cell debris may stimulate tumor growth, it may be necessary to enhance its endogenous clearance (205).

II. Curative treatment must address tumor heterogeneity. Curative therapy for childhood leukemia, Hodgkin lymphoma and testicular cancer requires combining effective treatments based on different mechanisms of action with techniques that minimize side effects (206). However, curing lung cancer may require more diverse combinations of treatment. Curable cancers typically affect the young, have no prominent risk factors and show no field effects. In contrast, lung cancer has a median age of 70 years, has major risk factors of tobacco and secondhand smoke and demonstrates prominent field effects. Its high degree of molecular heterogeneity (47, 207) is due, in part, to the high mutation load induced by tobacco use (46).

III. Reduce chronic stressors related to personal behavior, which may cause network changes that ultimately lead to cancer. These chronic stressors interact to reinforce each other in unpredictable ways to alter network pathways in the cells. As the magnitude of any individual stressor is reduced, the interactions are markedly reduced, and the networks may revert towards a more stable state (208).

Behavioral changes that reduce chronic stressors causing lung cancer include smoking cessation, reducing exposure to secondhand smoke, eating a healthier diet, maintaining a healthy body weight, home radon testing [see (209)] and reducing exposure to pollution or occupational hazards.

IV. Counteract the effects of chronic stressors. It is important to halt network changes unaffected by personal behavior, such as random chronic stress / bad luck, germ line changes or aging, as well as those caused by past personal behavior, although this is often difficult. Currently, we are unable to reverse damage caused by even simple lung carcinogens such as radon's alpha particles, which directly damage DNA in respiratory epithelium. This apparently linear process has elements of complexity because radon progenies may be nonuniformly distributed within the airway (210).

Tobacco smoke, unlike radon gas, contains multiple carcinogens that act both independently and synergistically at numerous targets within a cell. It also triggers chronic inflammation which promotes carcinogenesis via still different pathways. Although this diversity makes it difficult to identify effective strategies to counter its effects, we suggest detecting and countering the activated inflammatory process associated with many chronic stressors (tobacco, overweight, diet) may be useful. Possible future goals are enhancing immune system detection and destruction of premalignant and malignant cells or quarantining them analogous to the calcification of tuberculosis (211).

V. We should attempt to move cancer networks into less lethal states. Kauffman has indicated that a complex network of thousands of mutually regulating genes in normal cells typically produces a stable equilibrium state called an attractor, which corresponds to gene expression profiles specific to each cell type and which stabilizes cellular networks against common perturbations [(212); see also (213)]. Attractors have been analogized to a low energy

state or valley on a topographic diagram that pulls in cells with similar network configurations [(214), **Figure 1**]. Malignant cells may exhibit gene expression profiles called cancer attractors that pre-exist in healthy genomes but are normally not accessible, analogous to dangerous cliffs that are avoided by well-planned highways (215). Chronic cellular stress, in the correct cellular context, may move cellular networks from physiologic attractor states to intermediate malignant states and ultimately to cancer attractors.

A theoretical framework for determining what molecular targets to treat to move malignant networks to a less hazardous state has been described (216-218). However, the dynamic nongenetic heterogeneity of tumor cells makes them moving targets and drives replenishment of the tumor with surviving, nonresponsive cells (216, 219). Although the nonlinear functioning of gene regulatory networks makes prediction difficult, it has been suggested that network rewiring could be accomplished by constant perturbation of networks with drugs which destabilize the existing state and move them towards a more differentiated or less hazardous state (220).

It may be helpful to investigate these agents or pathways that move malignant networks towards more benign states:

(a) maturational agents, such as retinoids used in acute promyelocytic leukemia (221);

(b) myeloid differentiation promoting cytokines or lineage reprogramming agents (222-224);

(c) factors that halt the wound-healing process (225, 226), end rapid cell division in embryogenesis (227) or limit prion-like effects that induce malignant behavior in neighboring cells (228, 229);

(d) countering cytokines that assist tumor cell survival and proliferation (230); and

(e) factors regulating interactions between unicellular and multicellular processes (231, 232). Due to the apparent incompatibility of simultaneous activation of unicellular and multicellular processes, promoting the activation of multicellular network programs may limit unicellular processes associated with malignancy (231).

VI. Novel treatments might take advantage of fine tuning in physiologic cells 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 (233), immune checkpoint inhibitors that target the large mutational burden of aggressive tumors (234, 235) and treatments directed towards other aspects of chaotic or unstable states such as cell to extracellular matrix detachment (236).

VII. Targeting the microenvironment that nurtures tumor cells may have therapeutic value by interfering with the complex crosstalk between cancer cells, host cells and the extracellular matrix (237, 238), by normalizing aberrant properties (239), and by disrupting the fertile “soil” necessary for the cancer “seeds” to grow (240). Normalizing the microenvironment may enhance drug delivery and effectiveness (241, 242) or make existing tumors or intermediate states more susceptible to immune system attack.

VIII. Better screening is important, both for premalignant and malignant lesions, to reduce missed cancers or premalignant lesions. This includes computer-aided detection in low-dose CT scans for lung cancer (243). Priorities for screening should be based on known individual germ line variations, coexisting diseases and other risk factors.

IX. Promoting rational medical care is important. Better health makes it easier to detect signs and symptoms associated with malignancy. It also improves performance status, which expands treatment options (244).

8. Summary

We have reviewed the origins of lung cancer based on complexity theory. Important findings include: (1) the diversity of carcinogens and their prolonged period of exposure likely create a field effect involving a myriad of different pathways at multiple sites within the lungs; (2) smoking promotes lung cancer through chronic inflammation as well as carcinogens, affecting varied pathways; as a result, curative treatment may require more diverse strategies than usual for aggressive tumors; (3) non-small cell lung cancer in never smokers versus smokers may represent a less aggressive disease with superior survival; (4) random chronic stress / bad luck causes an estimated 50 – 70% of lung cancer in never smokers and a baseline incidence of lung cancer worldwide of 2 cases per 100,000; since there are no known chronic stressors to halt, it may be prudent to try to detect and counter any existing inflammatory process; (5) based on the cancer attractor model, it may be possible to use biomolecules in existing physiological processes to steer tumor cells into less lethal cellular pathways; and (6) it is important to identify and minimize existing patient chronic stressors to prevent recurrence and production of new tumors.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Tables

Table 1 - Characteristics of Lung Cancer Patients in Never Smokers versus Ever Smokers

Cho 2017 (63) (Korea, non-small cell lung cancer, 2011-2014)

Women: 83.7% versus 5.6%
Adenocarcinoma: 89.8% versus 44.9%
EGFR mutations: 57.8% versus 24.4%
ALK rearrangements: 7.8% versus 2.8%
Two-year overall survival: 75.8% versus 49.8%

Clément-Duchêne 2016 (60) (US, lung cancer, 2003-2005)

Women: 62.5% never versus 36.2% former versus 40.1% current smokers
Asian/Pacific Islander: 15.2% never versus 3.7% former versus 2.4% current smokers
Adenocarcinoma: 61.3% never versus 35.6% former versus 28.1% current smokers
Median survival: 507 days never versus 330 days former versus 323 days current smokers

Dias 2017 (61) (Portugal, non -small cell lung cancer, 2011-2015)

Women: 74% versus 7%
Adenocarcinoma: 93% versus 65%
EGFR mutations: 36% versus 8% (type of *EGFR* mutation also different)
ALK rearrangements: 26% versus 4%

Santoro 2011 (245) (Brazil, non-small cell lung cancer, 2005-2009)

Women: 68% versus 32%
Adenocarcinoma: 70% versus 51%
Median survival: 22.1 versus 14.9 months

Toh 2006 (62) (Singapore, non-small cell lung cancer, 1999-2002)

Women: 68.5% never versus 12% current versus 13% former smokers
Adenocarcinoma: 69.9% never versus 39.9% current versus 47.3% former smokers
Adjusted hazard ratio for death is 1.3 for smokers versus never smokers

Yano 2008 (12) (Japan, non-small cell lung cancer, 1974-2004)

Women: 85.8% versus 11.2%
Adenocarcinoma: 87.8% versus 49.1%

Superior overall and cancer specific survival in never smokers (see article)

Table 2 - Population Attributable Fraction of Lung Cancer

	Smokers and Never Smokers	Never Smokers
Tobacco (smoking)	80%	Not applicable
Secondhand smoke	5%	North America: men, 8.2%, women, 5.6%
Random chronic stress / bad luck	Not available	50-70%
Radon	10%	Men: 18.9 - 25.8% Women: 19.7 - 26.9%
Occupational	10%	Not available
Outdoor air pollution	1-2%	Not available
Tuberculosis	Not available	North America: 1.1% Europe: 2.4% China: 12.7%
Germline / family history	Not available	North America: 2.0% Europe: 1.2% China: 2.9%
Chronic obstructive lung disease	Not available	North America: 0.4% China: 0.6%
Pneumonia	Not available	North America: 0.2%
Indoor air pollution (women)	Not available	China: 19.9% (household use of coal)

Unspecified attributable risk: aging, diet, HIV, HPV, abdominal obesity, cannabis / marijuana smoking.

References in text

Table 3 - Population Attributable Fraction of Lung Cancer Due to Tobacco by Country

Country	Attributable fraction of lung cancer	Reference
USA	2020: 80% of deaths	**Cancer Facts & Figures 2020**, page 17
Australia	2010: 83.5% of cases in men, 73.7% of cases in women	**Pandeya 2015**, **Table 3**
Canada	2012: Alberta, 75.6% of cases	**Grundy 2017; Poirier 2016**
Germany	2018: 89% of cases in men; 83% of cases in women	**Mons 2018**
Greece	1992-2013: 89% of deaths in men; 78% of cases in women	**Sifaki-Pistolla 2017**
Korea	2009, 53.3% of cases in men; 5.2% of cases in women	**Park 2014**, **Table 3**
United Kingdom	2015, 81.9% of cases in men; 75% of cases in women	**Brown 2018; Parkin 2011**

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