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Cancer from an Evolutionary Perspective

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Abstract

There is an active research program currently underway, which treats cancer progression as an evolutionary process. This paper investigates the ways that cancer progression is like and unlike evolution in other contexts. The aim is to take a multi-level perspective on cancer, investigating the levels at which selection may be acting, the unit or target of selection, the relative roles of selection and drift, and the idea that cancer progression may be a by-product of selection at other levels of organization. The aim is to integrate data and theory from molecular biology and *in situ* studies of cancer progression, as well as dynamical models of cancer that represent progression as a multistage process.

Keywords: evolution, cancer, natural selection, multilevel selection, modeling

1. Introduction: Nothing in Cancer Makes Sense Except in Light of Evolution?

Dobzhansky (1973) wrote that "nothing in biology makes sense except in light of evolution." How can evolutionary thinking shed light on cancer? After all, cancer is ordinarily understood to be a case of failure of otherwise functional controls on cell birth and death. At first pass, this view seems fundamentally at odds with taking an evolutionary perspective on cancer. For, how can something that is an exemplary case of "dysfunction" count as an evolutionary process or product of adaptive evolution?

There are many ways of investigating cancer; this is in part because cancer is a product of many causes, both remote and proximate, acting at a variety of temporal and spatial scales. Different disciplines frame different questions about cancer initiation and progression, scaling up from proximate mechanisms to remote etiology. Molecular biologists identify molecular and genetic mechanisms that are associated with cancer, using either experimental work on cells in culture, gene knockout experiments, GWAS (genome wide association studies), proteomics, epigenomics, and transcriptomics. Geneticists, developmental and systems biologists develop models of genetic regulatory networks, to better understand how genes and their products act and interact in either preventing or advancing cancer progression. Multilevel models of interactive causal factors in cancer draw upon a variety of evidence from epidemiology, genetics, and developmental biology. The study of familial patterns of cancer incidence using classic Mendelian models can be used in concert with evidence from genetic and genomic investigations to identify genes or gene families associated familial cancer syndromes, such as Li Fraumeni syndrome. Epidemiological investigations into environmental risk factors in cancer, such as smoking, radiation exposure, or endocrine disruptors use case control, cohort, and ecological studies to tack risk exposure, find correlative body burdens of toxins, as well as rates of incidence of disease. Studies of

the immune system's and tissue microenvironment's roles in cancer complement this research, and have immense potential for therapy. Evolutionary perspectives are merely one additional approach, drawing upon evolutionary models or study of evolutionary history to better understand this complex and heterogeneous causal process.

However, Dobzhansky's dictum suggests a stronger thesis; that literally "nothing" in cancer makes sense absent an evolutionary perspective. To be sure, this claim may seem unduly strong. However, here are two suggestions of what someone defending such a view might have in mind. First, one could argue that what makes some organisms distinctively vulnerable to cancer is their belonging to one or another lineage in the tree of life. For instance, all and only multicellular organisms may get cancer. To "make sense" of cancer in a particular species, moreover, one needs to know how and why that lineage is distinctively vulnerable to cancer. Understanding a species' evolutionary history – e.g. the selective trade-offs they face in development and life history – can inform our understanding of how and why they are more or less vulnerable to cancer. For example, elephants are less vulnerable to cancer than humans because they have multiple copies of *p53*, likely an adaptation to the large number of replications of somatic cells in development (Abegglen, et. al., 2015).

Moreover, to understand cancer, one needs to understand that the emergence of multicellularity involved a compromise in fitness of parts, in service of collectives; cells had to come together and cooperate in service of the survival and reproductive success of the collective. Any collective of cells, especially collectives whose survival and reproductive success depends on functional organization, or "division of labor" among cells, are at least potentially vulnerable to breakdown in cooperative organization. Somatic cells divide and acquire mutations during our lifetimes; some of these mutations involve failures in regulatory pathways that ordinarily "enforce" functional organization, and thus cooperation. In this way, an evolutionary perspective – understanding how evolution of multicellularity required the emergence of cooperative organization, and understanding how and why multicellular organisms are thus distinctively vulnerable to failure – is essential to understanding cancer.

Second, advanced carcinomas in complex metazoans coopt signaling pathways that are ordinarily adaptive at the organismic level; this is a classic example of a cross-level byproduct. This process can only "make sense," in other words, given a multilevel perspective on evolution. On the multilevel perspective, any entity in the biological hierarchy with heritable variation that makes a difference to survival and/or reproductive success may be subject to selection. But, multilevel processes are subject to co-option and cross-level byproducts abound. Traits advantageous at one level or with respect to units of selection that are component parts of some a higher level can compromise (or enhance) fitness at other levels; classic examples are "jumping genes" or meiotic drive. Traits at the level of cells that ordinarily enhance fitness at the level of the organism is apoptosis, or programmed cell death. Some of the capacities that invasive cancer cells acquire (the capacity to invade and metastasize) are in fact unique features of metazoans (e.g., the capacity for cells to undergo a change in phenotype from epithelial to mesenchymal cells, or the epithelial-mesenchymal transition). So, understanding how metastasis is possible requires understanding the distinctive evolved features of metazoans. We will develop some of these considerations further, below.

There are at least three ways in which evolutionary perspectives shed light on cancer causation and potentially also unify diverse lines of inquiry in the biomedical sciences: comparative biology of cancer, evolutionary medicine, and evolutionary dynamics of cancer.

- First, we can compare different species and higher taxa, in order to understand what makes some lineages particularly vulnerable to cancer. In other words, comparative biology may help us identify mechanisms associated with cancer vulnerability, onset and progression, when they arose, where and why they are shared, as well as how they have diverged (Aktipis, et. al., 2015).[1]
- Second, we can look to unique features of our own evolutionary history in order to explain patterns of cancer incidence in humans, or identify distinctive causes of vulnerability to cancer in different human populations. For instance, why do women with lower parity have higher rates of cancer? Or, why are men more vulnerable to cancer than women? What aspects of our evolutionary history might explain these differences? (Gluckman, et. al., 2009; Stearns and Koella, 2008; Sun, et. al., 2014)
- Third and last, we can consider cancer progression itself as an evolutionary process, with corresponding evolutionary dynamics. We might develop theoretical models of this process, and link these models with empirical data (Frank, 2007; Wodarz and Komarova, 2015).

Each approach yields important insights. For instance, work on the comparative biology of cancer identifies common mechanisms associated with the prevention of cancer: mechanisms involved in inhibiting cell proliferation, regulation of cell death, division of labor, resource transport, and creation and maintenance of the extracellular environment (Askistis, et. al., 2015). Comparing and contrasting how tissue architecture, development, and other mechanisms of suppression of cancer-like growth across species can help cancer researchers identify targets of treatment or prevention of cancer. For instance, the relative absence of invasive cancer in the naked mole rat and blind mole rat may be due to a variety of mechanisms that enhance multicellular cooperation and suppress dysplastic growth, as well as unique features of the extracellular matrix, and relatively low metabolic rates. Understanding the operation of each factor's role in preventing disease in mole rats might help identify targets for intervention or tools for thinking about how best to prevent the advance of the disease in humans. Evolutionary thinking shapes this kind of research in (at least) two ways: first, in helping us understand the selective context, trade-offs, and thus origins of such traits, and second, in helping uncover their shared and disparate mechanistic bases. Knowing how a trait is realized (or, can be decomposed into parts, processes, etc.) in one organism can give us insight into how a trait can be decomposed or mechanistically realized in closely related organisms. Shared ancestry is (at least sometimes) good reason to suspect shared genetics and shared mechanistic and developmental bases for many traits (for a discussion of the logic behind this inference, see, e.g., Sober, 1991, and more recently: 2008).

[1] To be sure, comparative evolutionary biology is only one of several approaches to comparative biology; comparative molecular and developmental biology are also fruitful. But knowing the shared history of two organisms can help direct one to better identify and uncover shared molecular and developmental structures, and mechanistic bases.

Each approach also faces various challenges. Like comparative biology, evolutionary medicine is concerned with how differential vulnerability to cancer evolved. Evolutionary medicine's focus is largely on *human* vulnerability to disease and how features of our selective environment or selective trade-offs yielded these vulnerabilities. Testing hypotheses about the evolutionary past is difficult, to say the least. It requires a diverse array of evidence, and of course, often at best we can say that one or another hypothesis is most consistent with the widest array of evidence and theoretical considerations. Claims about how evolution shaped our vulnerability to disease have been contentious. Some have argued that such claims make "adaptationist" assumptions, i.e., assumptions that a given trait is adaptive, or selectively advantageous, founded on at best "just so" stories (Valles, 2011; see also Murphy, 2006).

However, there are better and worse such arguments; the best arguments consider not only the widest array of evidence, but also trade offs in fitness, as well as the role of constraints arising out of development and life history. Many arguments from evolutionary medicine concern trade-offs in fitness. For instance, traits adaptive early in life may yield fitness costs later in life. A vivid example is androgenic hormones; male hormones predispose men to higher prostate cancer risk, but they may also yield an advantage early in life, in terms of increasing sperm production, relative growth and size at sexual maturity, and thus (potentially) access to mates and resources. Of course, large size may be less of a fitness advantage in current environments; this may be a case of a "mismatch" between our ancestral and current contexts (see, e.g., Summers, et. al., 2008 for discussion). "Mismatch" hypotheses suggest that traits that may have been adaptive in the past leave us vulnerable to disease in our current environment. For instance, many advocates of evolutionary medicine have argued that women in the modern world are at higher risk of breast cancer because they delay or prevent pregnancy. This exposes them to more cycles of estrogen, which increases breast cancer risk. Presumably, higher rates of pregnancy reduced estrogen exposure in our evolutionary past. Of course, such hypotheses are contentious; there is always the potential for confounding causes (in this case, of increased cancer risk due to a variety of risk factors at work in modern society) (Greaves, 2000). Claims about human psychology, behavior and social conditions at work in our evolutionary past are particularly contentious (see, e.g., Adriens and DeBlock, 2011), because claims about our ancestral social environment are so difficult to substantiate. Nonetheless, evolutionary medicine can help us better understand patters of incidence of disease in different environments, while has the potential to inform practical applications. For instance, lactose intolerance is clearly tied to ancestral patterns of agriculture and milk consumption.

The last of the three approaches has already been applied in contexts of cancer treatment and prevention. For instance, evolution of multi-drug resistance is one of the major causes of cancer mortality. This is the case not only for standard chemotherapy, but also for targeted or "precision" drugs; such drugs can be more or less effective in different patients, and lose their effectiveness over time. With some caveats (see, e.g., Pisco, et. al., 2012), an evolutionary perspective on cancer may shed light on how drug resistance comes about.

In this paper, the focus will be primarily on the third approach. We will provide a brief summary of the basic presuppositions about cancer progression that one must accept in order to defend this view, as well as how this perspective fits into a multilevel perspective on evolution (Section 2), a brief discussion of several mathematical models that have been

developed to characterize this process (Section 3), the variety of empirical data that has been brought to bear on the theory (Section 4), and then discuss the broader implications of taking this perspective for cancer diagnosis and treatment (Section 5).

Section 2: The Evolutionary Perspective on Cancer Progression: A General Introduction

According to an ongoing research program, cancer arises from a Darwinian[2] process of mutation and selection among somatic cells (Greaves, 2000, 2007; Frank and Nowak, 2004; Merlo, et. al., 2006; Greaves and Maley, 2010). Cancer cells are cells that have acquired a series of somatic mutations and epigenetic alterations that allow them to escape regulation of cell birth and death, leading to disorderly growth, invasion, and metastasis. This is a long process that can start as early as the womb (Mori, et. al., 2002). Over the course of the average human's lifetime, there are many millions of cell divisions in the body. Thus, by chance alone, mutations and epigenetic changes occur. Some such mutations are associated with cancer: they may lead to chromosomal instability, failures of DNA repair, or failures in regulation of cell birth and death.

Estimations of mutation rates per gene per cell division are about 10^{-7}. One question that an evolutionary or "dynamic" perspective on cancer can shed light on is whether the somatic mutation rate (the rate at which mutations are acquired in somatic cells) is high enough to eventuate in cancer during the lifetime of the average individual. There is some disagreement about this in the literature; some argue that it is sufficient; indeed, some contend that we should be surprised that cancer does not occur more often (Tomlinson, et. al., 1996; Sieber, et. al., 2003). Others disagree (Loeb, 1991, 2011), and argue that a "mutator phenotype" needs to come on the scene first, accelerating cancer development. Settling this debate is not easy: one needs to know not only how many mutations are necessary or typical for a cancer cell to eventuate, and the typical rate of mutations, but also have some sense of how effective the immune system and interactions between cancer-precursor cells and the tissue microenvironment may be in halting cancer progression. In addition, tissue architecture, or, the hierarchical subdivision of cells into stem and differentiated cells, could also play an important role in preventing the advance of disease. That is, most cells with mutations that may otherwise have yielded cancer are prevented from doing so for a variety of reasons. How many such incipient cancer cells are there?

According to one recent study, 18-32% of normal skin cells in the average sun exposed adult have clonal populations of cells with 2-3 "driver" mutations (at a density of ~140 driver mutations per square centimeter) (see, Martinocerana, et. al., 2015). There is, in other words, a "vast reservoir" of mutations in healthy normal cells, but most such cells do not eventuate

[2] I am here following Godfrey-Smith's (2009) sense of a "minimal" Darwinian population; this is any population where there are heritable variations in fitness in a population (see also, e.g., Lewontin, 1970). A population that is undergoing changes due to such heritable variations in fitness is undergoing a "Darwinian" process. Godfrey-Smith argues that there are more or less "paradigmatic" cases of Darwinian populations; for instance, higher heritability is one condition that is optimal for selection. So also is greater availability of variation for selection to act, etc. This idea is (roughly) similar to a minimal sense of what makes a population "evolvable" (see, e.g., Pigliucci, 2008).

in cancer. This naturally leads to a question: Why don't we get cancer more often than we do? When we do, what are the main reasons why? What can cause some such clonal populations of cells to become cancer? Are the causes primarily cell-intrinsic? Are most pre-cancerous cells so unstable that they eventually die on their own? Does their relative success have to do with competitive interactions between cells? Or, are there population-level interactions between clonal populations or subpopulations, or perhaps between whole tumors for multifocal lesions? In other words, at what "level," or between what entities might such interactions take place? Could natural selection be acting at multiple "levels"?

In normal tissue, contact inhibition, tissue architecture, and various other mechanisms control cellular growth and prevent overgrowth of cells. How and when cells are born and die – i.e., the particular mode of regulation of growth – is very specific to the type of tissue. Epithelial cells in the skin or colon, for instance, regularly slough off and die over the course of a lifetime; in contrast, bone growth and renewal is relatively slow post-adolescence. Cancer occurs when the tissue-specific signals that regulate cell birth and death fail. What enables cancers to escape these regulatory signals? What most cancer researchers will say is that the primary causes are chromosomal alterations, or, the acquisition of mutations or epigenetic changes to cells that give them distinctive capacities (or, perhaps better: incapacities): such as the capacity to resist apoptosis, attract a blood supply, or continue to divide.

But, while this explanation describes properties of cancer cells; cancer itself is not simply a disease of cells. That is, whether populations of such cells eventuate in cancer has to do with interactions between cells and the tissue microenvironment. What evolutionary approaches to cancer investigate is whether differences in cells and populations of cells descended from common ancestors are more or less successful at persisting and eventuating in disease. This has to do not only with cell-intrinsic features, but population level features: population size, mutation rates, death rates, genetic heterogeneity, etc. These differences in populations of cells may make some populations more or less "evolvable." Population level features of certain tissue types or tissue architectures may be more vulnerable to cancer. For instance, populations with stem cell hierarchies may be more (or less) vulnerable to cancer, depending upon the features of the stem cells, (whether they divide in one way or another), as well as the relative number of stem cells. That is, an evolutionary approach to cancer is not simply a matter of understanding properties of cancer cells, but dynamic properties of populations of such cells in interaction with the "ecology" of the tissue microenvironment.[3]

[3] I prefer not to take a dogmatic stance regarding what cancer is "ultimately" a disease "of." Cancer is a disease of cells, but it is also (at least in some cases) a heritable disorder, a disease of genes, the immune system, tissue architecture, stem-like cells, development, tissue disorganization, viral infection, environmental toxins, and much else besides. All of these factors are causally relevant to explaining cancer in its diversity. Cancer is an enormously heterogeneous set of disease processes, with very different causes, acting at a variety of temporal and spatial scales. Philosophers (and scientists) error when they attempt to reduce all these causal explanations to a single scale or single theoretical framework (see, e.g., Wimsatt, 1972, reprinted in 2007). Thanks for reviewers for challenging me to address this concern. See, e.g., Nathan, M. (2014) for a fascinating discussion of how (and how not) to think about the molecular environment as an "ecosystem."

Once a population of cells has become invasive, evolutionary approaches to cancer progression explore how competition among cancer cells or cell lineages within a tumor for space and resources affects cancer progression. Or, they might investigate the possibility of cooperative interactions between cell lineages, and between the tumor and the tissue microenvironment, and how these cooperative interactions could be selected for. A variety of different theoretical models, as we will see below, have been used to investigate these questions.

What presuppositions about cancer does this approach make? All start with the assumption that multicellular organisms are a product of a long history of evolution, from solitary replicators to networks of replicators enclosed within compartments, from genes to chromosomes, from prokaryotic cells to eukaryotic cells containing organelles, from unicellular to multicellular organisms, and from solitary organisms to colonies. These are sometimes called the "major transitions" of evolution (Maynard Smith and Szathmary, 1995). In each of these transitions, entities capable of surviving and reproducing autonomously aggregated into a single, larger unit, and a new level of biological organization. In order for this transition to happen, it was necessary for individual units to benefit in some way from participation in collectives. Cancer, on this view, illustrates that cooperative organization in biology is always an unstable compromise. That is, the mechanisms that reinforce cooperation in collectives are subject to breakdown. As long as there are entities with heritable variation in fitness within any collective, the collective is vulnerable to "defection" from within. Cancer is a vivid example of breakdown in cooperative organization of cells and tissues, due to the acquisition of a series of mutations and epigenetic and genomic changes – changes that allow cancer cells to become relatively "autonomous." According to the evolutionary perspective, then, cancer is both a byproduct and process of evolution: cancer cells are populations of cells that have acquired one or more mutations. Such populations may eventually yield the cancer phenotype: self-sufficiency of growth, failure to respond to apoptotic signals, acquisition of a blood supply, etc. Insofar as these variations are heritable and make a difference to the relative fitness of cells, cancer progression is driven (in part) by natural selection on heritable variations in these precancerous cells, cancer cells, and cell lineages. These interactions take place within the "ecology" of the tissue microenvironment. This ecology is shaped both by the circulating molecules, and tissue architecture.

Implicit in this approach is a "multilevel" perspective: this is the idea that selection can in principle operate at more than one level in the biological hierarchy, provided each level of analysis consists of populations of entities with heritable variation, and such variation makes a difference to relative survival or reproductive success of the selected entities. This idea is not controversial, nor is it new; indeed, Darwin himself imagined that selection could occur both at the individual and the group level (cooperative social groups, he thought, might have a fitness advantage over collectives where every man south his own advantage). A corollary of this view is that traits adaptive at one level of organization can be coopted at another level. Put more generally, evolutionary processes at one level of analysis can affect evolutionary processes at other levels of organization, either by constraining available trajectories, or providing traits that can be "coopted" toward new ends. Cancer is a vivid example: traits that are otherwise advantageous at the organismic level can be coopted by cancer. To be clear, this is not the claim that a single "event" is caused by selection acting (simultaneously) at two levels; but that the same process can be described as a process of

selection at one level (that of cells) and as a byproduct of selective processes (in the past) at another level (that of the organism as a whole). (For discussion of multilevel selection, and in particular, the possibility of cooption and cross-level byproducts, see, e.g., Okasha, 2007.)

Multilevel selection theory has been used to explore how cooperation or multicellular interactions evolve. For instance, it's generally believed that altruistic or cooperative behaviors are unlikely to evolve, because individual level selection will override "group" selection. The higher rates of turnover of individuals as opposed to groups means that a "free rider" can always invade a group with a high level of cooperation, thus preventing the overall increase in cooperation. Multilevel selection theory has been deployed in order to explain how 'major transitions' in evolution could have come about (Michod 1997, Michod and Herron, 2006; Maynard Smith and Szathmary 1995; Frank 1998; Okasha, 2006). Cooperative behaviors leading to the emergence of such collective benefits can be found today, even among organisms ordinarily understood to be solitary and self-interested. For instance, bacteria join together in service of production of what is sometimes called a "public good," such as access to nutrients, or escape from predation (West, et. al., 2007). Such collectives are always subject to "free riding" and "defection" from within; it's always possible that an individual could take advantage of a collective resource and either fail to cooperate, or use that resource to benefit itself at the expense of its cohort. Cancer is yet one more example.

This picture of cancer represents cancer progression as the process of selection within a population of cells in an individual organism, or, in a tumor, where competition might occur for space, resources, or simple capacity to divide at relatively high rates. Cancer progression could, however, involve selective processes operating at a variety of levels of organization. Indeed, these are not mutually exclusive options. For instance, there may be competition between clonal populations of pre-cancerous cells in somatic tissue. Some such populations may acquire an advantage relatively early or late that enable it to outcompete neighboring tissue and acquire cancerous phenotype earlier. Or, competition could occur between subpopulations of cells within a tumor, for access to space or resources. Tumors are often composed of relatively heterogeneous subpopulations of cells, some of which have acquired mutations that enable them to survive in unoccupied niches. For instance, hypoxia is a capacity to survive without access to oxygen; some cancer cell lineages acquire mutations that enable them to survive in relatively oxygen-poor environments. Such lineages might outcompete other lineages in certain environments. Moreover, whole tumors might perturb the environment in ways that are optimal for their survival, by producing products that are toxic to the normal cells with which they compete for space and resources. Alternatively, they might make it difficult for neighboring early stage tumors to grow and survive.

What are some of the more contentious assumptions of this model? First, selection requires heritable variation in fitness; and, cancer cells have far less than perfect heritability. Many cancer cells are characteristically "CIN-ful," that is, they have "chromosomal instability." This is when replication is imperfect, because the mechanisms that control cell mitosis have broken down. As a result, many cancer cells have huge chromosomal duplications and inversions. Selection cannot act as effectively on entities with low heritability. Second, cancer cell populations are characteristically short-lived, because they are either quickly subject to attack from the immune system, or "drift" to extinction because of relatively small population sizes and low variation. Moreover, cancer cells' "adaptations" are not very

sophisticated, but may involve a single phenotypic change, such as failure to respond to a specific apoptotic signal (Germain, 2012). This is very far from paradigmatic cases of complex adaptation, such as the compound eye or vertebrate limb. Most populations of proto-cancer cells have relatively low "evolvability": they simply die off because of intrinsic failures due to excessive chromosomal instability. By and large, the evolution of complex adaptations requires ample heritable variation in fitness, high levels of heritability, complex selective environments with distinctive ecological features, or local adaptive niches, and time. All of these are lacking in cancer. Even "successful" cancers (eventually) kill their host. Only rarely have cancers that survive the death of the host arisen in nature; canine viral cancers, for instance, appear to be an example. Thus, if cancer is an evolutionary process, it is a particularly short-lived one.

These are not necessarily devastating objections to the evolutionary perspective on cancer, however. As Godfrey-Smith (2009) has argued, the extent to which a population of entities approaches the "paradigmatic" case of Darwinian evolution is a matter of degree. A paradigmatic case has ample heritable variation, high heritability, and significant differences in fitness due to intrinsic rather than extrinsically varying, "contingent" circumstances. Only in such cases can selection make a more significant difference to the distribution of variation in a population than drift. Cancer cells have – admittedly – low heritability, but the heritable variation that they do have can (and does) make a difference to survival and reproductive success. This is evident in the emergence of chemotherapy resistance. And, though evolution in cancer cell populations is short term, short-term evolutionary change is – arguably – still evolution. After all, most species in the history of life have gone extinct. So also, most precancerous lesions may be a particularly vivid example of a short-lived evolutionary process. While there can be multiple "showers" of metastases, which are more or less successful in variable environments, by and large, even successful metastatic cancers are short-lived – at least from a geological perspective. So, cancer is a particularly short-lived evolutionary process; but, so is most evolution in "solution"; the typical processes of cell division and growth that occur in culture in most laboratories in experimental evolution. Nonetheless, even in a single short lived cycle of selection on dividing cells in culture, adaptations can be acquired and take over relatively quickly (see, e.g., Lenski, et. al., 1991).

Section 3: Mathematical Models of Tumorigenesis

Mathematical models of cancer's dynamics vary in terms of their explanatory targets – or the questions they are used to investigate. Their assumptions thus vary, and, so also, their "realism," or representativeness of various aspects of the complex process of tumorigenesis. Mathematical models are deliberate simplifications (though of course all models are, to a greater or lesser extent). Indeed, when building a model, mathematical biologists often start with the simplest possible scenario, and gradually add in complications as relevant to the case at hand. Detailed information about the variety of initiating conditions, constraints, and mechanistic bases of cancer is not necessarily of relevance to a dynamical model of cancer progression. A model may be very effective at representing one aspect of a dynamic process, or addressing one very specific question. Of course, cancer is a massively heterogeneous, complex causal process. Thus, any simple model will be in some sense a deliberate fiction.

However, as Wimsatt (1987) has argued, "false models" may lead to "true theories." That is, deliberate simplifications of complex processes can yield important insights about what outcomes can be expected under what initial conditions. While key assumptions of one's model should be at least consistent with our best scientific understanding of cancer causation and progression, it is permissible in model building to deliberately represent the system falsely (cf. Love and Nathan, 2015). That is, provided that the falsehoods in question are irrelevant or, instrumentally useful, many models contain overt and explicit falsehoods. For instance, one can define equilibrium conditions (when it's known that in nature, such conditions never or very rarely obtain), or one can identify what is expected for extreme cases on a continuum, or, under highly idealized circumstances. Such models provide a baseline or "null" case, so that departures from the null can be explained as expected, due to the presence of X, Y, or Z conditions. Whether a model is successful ultimately depends upon one's purposes. These vary from merely theoretical to practical. What matters is whether the model can answer the question we care about, or, alternatively, whether it provokes new lines of investigation, or suggests hypotheses worth exploring further. No model is intended to cover or represent all possible cancers. The aim is often conditional generalizations. That is, under the following conditions, what might we expect for systems of this type?

There are deterministic and stochastic models, individual-based or "cellular automaton" models, optimality models, models of competition, spatial dynamics, and hierarchical dynamics. One can use a model to explore different questions about different kinds of populations of cancer cells with different hierarchical structures, due to the presence of stem-like cells. Such models are used to pose different kinds of questions, test various hypotheses, and simulate different aspects of cancer progression. Over the course of the latter half of the 20th century, as new information about cancer incidence, initiation, progression, and molecular biology became available, new models with more sophisticated targets were developed. The first mathematical (or formal) models of cancer's dynamics were developed long before the molecular mechanisms or genetic mutations associated with cancer were well understood. Starting in the 1950s, these models represented cancer progression as a rate-limited multistage process, drawing upon epidemiological data – specifically, patterns of cancer incidence. Thus, for instance, Armitage and Doll (1954) developed dynamical models that predicted patterns of cancer incidence; essentially, they argued that since cancer incidence increases as a power of age, cancer progression is a product of a multi-stage, rate-limited process of acquisition of mutations. Today, models of cancer progression are more sophisticated, and involve the use of different kinds of mathematical tools – ranging from ordinary differential equations to agent-based approaches to elaborate simulations of spatial growth dynamics. We will consider two examples from the recent literature: a simple model of competition between two cell populations, and a more complex model of the evolution of chemotherapy resistance.

The former model is applicable to early stages of development of two "proto-cancer" cell populations. As we saw in section 1, above, most such populations do not progress to invasive disease. This model explores what features enable some cell populations to succeed in progressing. The second model examines how evolution of chemotherapy resistance is dependent on a variety of factors: treatment with one or more chemotherapeutic drugs, population size, birth and death rates of cells, and mutation rates. In the following section,

we will see how various models of cancer have been applied to specific observations, or how data has been brought to bear on the models.

The simplest possible model of cancer competition dynamics represents two populations of incipient cancer cells; these populations might vary in a number of ways, but we'll consider the case of "stable" versus "unstable" populations. Stable cells have wildtype or relatively normal somatic mutation rates. Unstable cells have the "mutator" phenotype – or, they are characterized by a lack of appropriate DNA repair mechanisms, and so have elevated rates of mutation. They accumulate mutations faster than normal somatic cells. Under what circumstances will such unstable cells come to dominate stable cells? In order to answer this question, we need to know some of the fitness trade-offs associated with stability v. instability. We might predict that stable cells with intact repair systems face a cost; DNA repair takes time. Cell-cycle arrest and repair results in overall slower rate of growth in stable populations than unstable populations. On the other hand, unstable cells suffer from high levels of DNA damage – they bear a larger proportion of mutations, many of which would be expected to be deleterious. Using such a set of differential growth equations, one can represent competitive interactions between such populations as a function of their intrinsic replication rate, mutation rate, and rate of DNA repair. Such models yield a variety of interesting results. As Wodarz and Komarova explain, "If the intrinsic replication rate of the mutator (M) is higher than that of the stable cells (S), then a high DNA hit rate can select for stable cells (S)," but a low DNA hit rate selects for genetic instability (M). However, the reverse is the case if the intrinsic growth rate of stable cells is higher than unstable cells. In other words, we can use such models to represent the relative fitness of cell types given the costs and benefits of high rates of mutation, v. DNA repair.

Of course, this is a very simple model, and we also might wish to consider a variety of further complications, appropriate to different contexts or stages of cancer progression. In early stages of cancer progression – e.g., before an incipient population of cells becomes a tumor – genetic instability may be relatively more advantageous than in later stages. This is because "mutators" might be more likely to acquire mutations that enable escape of the variety of controls on cell division in the tumor microenvironment – e.g., apoptotic signals. On the other hand, too many mutations will result in a highly unstable cell, and perhaps eventually in high rates of cell death.

Or, we can model the effects of chemotherapy on stable and unstable populations of cells, given different assumptions about apoptotic response in such populations. Wodarz and Komarova (2014) show that if we assume apoptotic response is intact in both such populations (i.e., if cells shut down provided a sufficient number of mutations is acquired), at high DNA hit rates, the mutator cells with the faster instrinsic rate of growth will overcome stable cells. On the other hand, with low DNA hit rate, stable cells will overcome mutators. The reverse is true when apoptosis is impaired. This has important implications for chemotherapy. Chemotherapy can induce a high DNA hit rate, by impairing DNA repair mechanisms. So, in populations of healthy cells, we can expect chemotherapy to select for genetic instability and induce tumors. On the other hand, where apoptotic response is weak, chemotherapy may reverse progression and increase the fitness of stable cells.

Competition models such as these represent the two populations as co-evolving, with two differential equations representing their intrinsic replication rate, mutation rate (assuming all

mutations are deleterious), and chance of DNA repair – or rate of arrest of replication and repair. This results in a set of coupled equations, where competition between two such populations is a function of rate or replication, can predict and explain the behavior of populations of co-evolving cells both before and during chemotherapy.

More sophisticated models can represent the emergence of drug resistance in a tumor or in leukemia, for one or more drugs. Such models might start with a simple set of assumptions: e.g., we can imagine that the population size of a tumor or leukemia cells in the body is N, the growth rate of cells as L and the death rate as D. L>D corresponds to clonal expansion. Mutations can lead to the generation of cell types that are resistant. Let the mutation rate be u; assume resistant cells proliferate, and the rate of death of the wild-type (non-resistant) to be H. We can use this simple mathematical model to predict when and how quickly resistance will evolve in one specific type of leukemia (CML), depending on the stage of growth, or, given treatment with one or more drugs. This can help us to predict when treatment failure is likely, and so, which kinds of combination therapy will be most effective, and at what stages. Chronic myeloid leukemia has three stages: a chronic phase, (which is unsymptomatic) the accelerated phase, and the blast crisis. The latter stages are associated with a very rapid rate of increase in undifferentiated cells.

So, on the basis of these models, Wodarz and Komarova (2005, 2014) have shown that depending upon initial population size of cells in a cancer, treatment failure is expected to occur when turnover rates of cells is high, and mutation rates are high. Larger tumors evolve resistance more quickly, even with a relatively low rate of turnover. On the other hand, resistance can arise at lower tumor sizes if rate of turnover of cells (D) is high. They predict that combination therapy will prevent treatment failure except when a cancer has a high turnover rate, or resistance mutations can be generated at rates several orders of magnitude higher than the physiological mutation rate. They extend the model to cases where there is complex tumor architecture (tumor stem cells), as well as cross resistance to multiple chemotherapies. In fact, the model was predictive: they offered treatment schedules that maximize the chances of successful therapy, given different sizes of tumor or stages of CML. The model could be extended to consider further complications, such as tumor stem cells or hierarchical structure of cell lineages in a tumor.

What do these models illustrate about (a) the value of approaching cancer from an evolutionary perspective, and (b) the nature of modeling in science? There are (at least) three general conclusions we can draw from such cases. First, as mentioned above, cancer can and should be understood as a dynamic process of change, in populations of cells undergoing complex interactions with their surrounding environment. This is – broadly understood – a "Darwinian" process of natural selection, one involving changes in proportions of distinct phenotypes and genotypes, over time. At the same time, we know that this process is far more complex, which can be disrupted or influenced by a variety of factors both remote and proximate; e.g., "drift" or chance factors to do with proximity to a blood supply, or features of the tissue architecture, could "accidentally" case a population of otherwise highly 'fit' cancer cells to die off. Or, byproducts of selection at other levels of organization can either be coopted in cancer, or (as is far more often the case) halt progression. Second, of course, the evolutionary perspective is a kind of idealization. Cancer is far from the "paradigmatic" case of adaptive evolution. Nonetheless, thinking about cancer from an evolutionary perspective can help us discover new hypotheses worth

testing, both about our distinctive vulnerability to cancer, and the dynamics of cancer progression. Third, the case illustrates how modeling is a process of picking out what we take to be causally significant factors given some target or phenomenon of interest. Whether it is chemotherapy resistance, or the emergence of hypoxic cells, we can use evolutionary modeling to represent the dynamics of the emergence of these traits in cancer. Of course, each cancer is genetic and epigenetically unique, and each cancer's environment is likewise unique. So, while some of the conclusions of these models can be generalized across distinct cases, this is of course "all else being equal."

What kind of knowledge we gain from using evolutionary modeling to represent the dynamics of the emergence of these traits in cancer? First, at minimum, this is predictive knowledge. That is, we can use evolutionary models to predict and describe the dynamics of populations of cancer cells, and the emergence of complex tumors as in part a product of dynamic interactions between cells, cell lineages, and the tumor microenvironment, and in part, a byproduct of organismic adaptations. That is, these models help predict when and why cancer progresses or fails to progress. Second, if one takes selection and drift to be causes of changes in populations over time, these models do not merely describe, but also explain. That is, to the extent that these models are accurate representations of cancer, they are not merely providing predictive, but also causal knowledge.[4]

Does adopting the evolutionary perspective on cancer progression require that we jettison other perspectives? I.e., does suggesting that cancer can be understood in this way require setting aside causal explanations from epidemiology, developmental biology, or genetics? In my view, it does not. All of these perspectives are important for understanding the complex causes of cancer. Cancer is a case study in complex causation; there are both remote and proximate causes of cancer, operating at very distinct temporal and spatial scales. In my view, it is a mistake to exclusively take one approach to cancer causation as "correct." Indeed, as several others have argued, the history of cancer research has been a history of a search for the "magic bullet" – one "essential" or most important cause (Mukherjee, 2011). But, the closer we look, the more heterogeneous the causes of cancer. So, while a search for one unified causal basis of cancer may have been a fruitful research strategy, it is a mistake to infer from the success of this strategy that causes acting at one temporal or spatial scale, or one disciplinary approach, can or should supplant all others.

Section 4: Empirical Data

Formal models of cancer progression and evolution have been developed for decades, and these models were revised or updated as new epidemiological, molecular, and clinical data became available. The simplest models of cancer as a rate-limited process of acquisition of somatic mutations, for instance, were developed more or less based on epidemiological patterns of cancer incidence, which rises by and large as a power of age (Armitage and Doll, 1954). More recently, a wide array of data from molecular biology, immunology, genomics,

[4] In my view, Stephens (2004), Millstein (2006), and Forber and Riesman, (2007), (among others) have argued persuasively that selection and drift may be viewed as causes of evolution. Such a view is consistent with a variety of theories of causation. Addressing this debate at any length, however, would go well beyond the scope of this paper.

and clinical medicine, has been used to either provide more precise parameters, or test applications of mathematical models of cancer's evolutionary dynamics.

The most vivid examples of these are efforts as sequencing tumors and metastases to better understand the dynamics of progression, either within a single patient, or across classes of patients with a common cancer type or subtype. For instance, Campbell, et. al., (2010) sequenced the genomes of 13 patients' pancreatic adenocarcinomas, to identify somatically acquired genomic rearrangements, and explore clonal relationships among metastases. Navin, et. al., (2011) used heterogeneous breast tumors to study human tumor progression, arguing that they "still contain evidence of early and intermediate subpopulations in the form of the phylogenetic relationships." Navin et. al., developed algorithms to compare the genomes of tumor subpopulations within patients to assess their divergence, and to identify genetic elements that may be involved in tumor progression. Genomic tools such as expression profiling, array-based copy number analysis, high-throughput DNA sequencing, and DNA methylation analysis have accelerated the accumulation of data about cancers and how they evolve. A variety of generalizations have arisen out of this research, generalizations that may in turn be useful in developing more detailed models of cancer progression, and in developing more targeted methods of prevention and treatment.

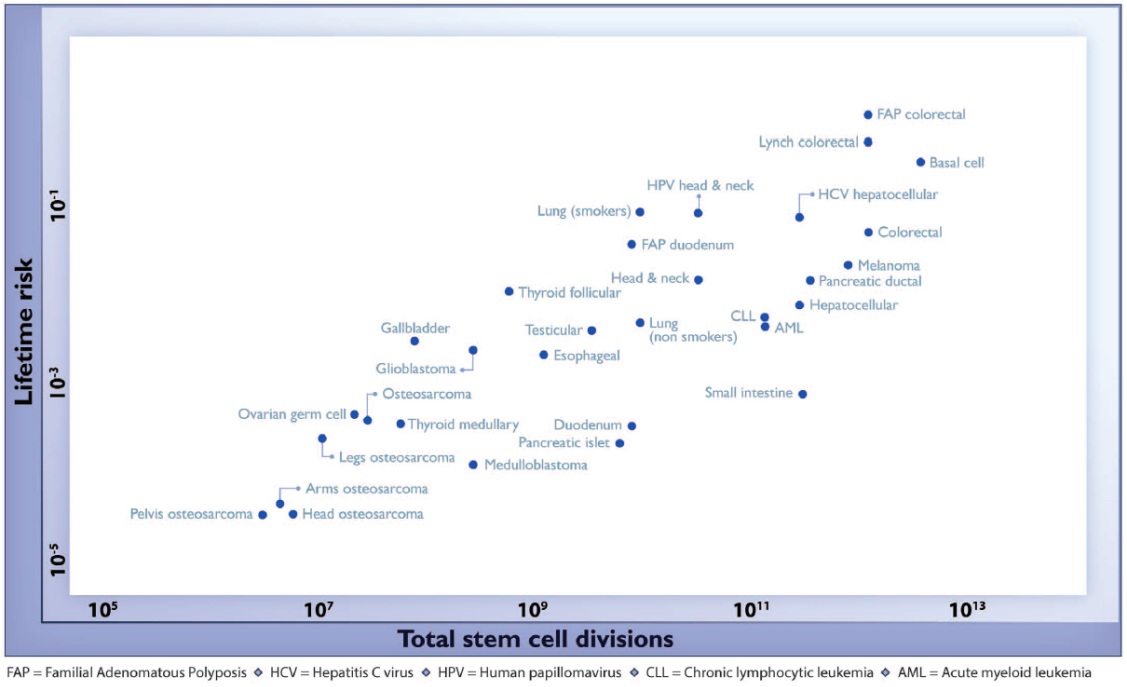
- For example, while it has long been known that cancers can be enormously heterogeneous, it is possible now to not only observe pathological heterogeneity, but also measure the extent of genetic heterogeneity in a tumor, and even track the historical progression of multiple different subpopulations of cells. Though, histological heterogeneity does not imply genetic heterogeneity, or vise versa (Navin, et. al., 2011).
- Some tumors are relatively "monogenomic" (consisting of an apparently homogeneous population of tumor cells with highly similar genome profiles throughout the tumor mass), whereas others are "polygenomic" (containing multiple tumor subpopulations that can be distinguished and grouped by similar genome structure). (cf. Navin, et. al., 2011)
- This heterogeneity suggests that genome-wide association studies derived from multiple samples of single regions of a given tumor type or subtype (e.g., in the typical tumor biopsy) may not be representative of the entire tumor when subpopulations are anatomically segregated. This suggests that more comprehensive genomics of cancer should be based on multiple rather than single samples from a tumor.
- Campbell, et. al., (2010) and Navin, et. al., (2011) both show that major chromosomal events and amplification of cancer genes and occur predominantly in early cancer development rather than the later stages of the disease.
- Campbell, et. al., (2010) also suggest that there is ongoing, parallel and even convergent evolution among different metastases, and also organ-specific branches, suggesting site-specific metastatic evolution.
- In all such studies, there were also patterns of change and distinctive types of mutations and chromosomal alterations typical of distinct cancers, arising in distinct tissue types.

In sum, these studies suggest a variety of insights of relevance to both theoretical understanding of cancer, and cancer diagnosis and treatment. A careful study of the

distribution of variation in cancers of distinct types may assist in predicting how and whether cancers are likely to progress. Data on subpopulations in a tumor and their spatial organization can be used to refine and explore theories of cancer progression, patterns of growth, migration, and metastasis. Such patterns also suggest interesting questions worth exploring further. For instance, are more heterogeneous tumors more likely to generate more or more successful metastases? Which particular mutations in which tumors are likely to yield metastases in which remote sites? How do subpopulations in a tumor evolve or coevolve? How does clonal architecture shape tumor progression? In what ways are metastases preadapted to distinctive remote locales? How do metastatic cells evolve and coevolve in novel environments?

There have also been interesting studies of how the tissue microenvironment prevents cancer, and which kinds of alterations to the tissue microenvironment promote cancer. For instance, inflammatory environments are by and large tumorigenic. Experimental work on radiation and various other insults (wounding) to the tissue microenvironment can, in fact, initiate cancer. On the other hand, the appropriate tissue architecture, or the normalization of signal transduction pathways appears to suppress cancer (Bissell and Hines, 2011). Cancer has been called the "wound that never heals," because the cancer cells initiate an inflammatory response and attract cells from the immune system that in part assist the cancer in attracting a blood supply and building up stromal tissue. That is, inflammatory cells are mobilized in response to signals emanating from the tumor microenvironment. Modeling this dynamic process has yielded some important predictions, and even novel treatments; for instance, the recognition that the immune system has a very specific response to cancer has led to the development of checkpoint therapies that take advantage of the body's own immune system. For a review, and discussion of the role of modeling in this process, see, Merlo, et. al., 2006.

Other work on the role of tissue architecture in preventing cancer has leant support to models of differential cancer risk in different tissue types. Recently, Tomasetti & Vogelstein, argued in a rather provocative paper (2014) that "only a third of the variation in cancer risk *among tissues* is attributable to environmental factors or inherited predispositions. The majority is due to "bad luck," that is, random mutations arising during DNA replication in normal, noncancerous stem cells." (Assumes somewhat artificial partitioning of causes.) Their argument, it turns out, was a very simple mathematical argument, drawing upon data showing that the frequency of a given cancer type appears to correlate with the tissue architecture of the tissue of origin in which that cancer occurs. In other words, we know that cells divide and mutations happen, but some tissues have more stem cell divisions than others. They conclude that cells that divide more often have more mutations. This is consistent with the observation that tissues with more stem cell divisions and more mutations are more frequently subject to cancers. (see figure 1, below)



FAP = Familial Adenomatous Polyposis ◆ HCV = Hepatitis C virus ◆ HPV = Human papillomavirus ◆ CLL = Chronic lymphocytic leukemia ◆ AML = Acute myeloid leukemia

Fig. 1. The relationship between the number of stem cell divisions in the lifetime of a given tissue and the lifetime risk of cancer in that tissue. Values are from table S1, the derivation of which is discussed in the supplementary materials.

This is a very simple linear regression model, however, and some have argued that there are exceptions to the general rule.

Indeed, exceptions to these general law-like claims about cancer progression are to be expected. Cancer is a massively heterogeneous disease, due to the fact that where, when, and how cancer arises in different tissues, and due to different remote and proximate causes, yields a widely disparate pattern of incidence and progression. Some cancers progress relatively quickly, due to massive chromosomal aberrations that occur early on in cancer progression, what some scientists call "chromothripsis." (Jones, et. al., 2012). However, this observation does not (per se) counter the idea that cancer progression is an evolutionary process; some evolutionary processes occur more quickly than others.

Some have argued that tumor stem cells complicate the evolutionary picture of cancer. However, there is no reason (in principle) why tissue architecture in a tumor could not be modeled using an evolutionary dynamic perspective. The only difference is that instead of using a model of growth such as exponential or logistic growth of clonal populations, one might represent a tumor composed of multiple cell lineages, some dividing and differentiating, and others dividing indefinitely. Different tumors have different pathways to progression, and representing this complexity requires looking to different kinds of modeling strategies. Thus, instead of modeling "gain of function" mutations (oncogenes) or "loss of function" mutations (tumor suppressor genes), in relatively uniform populations, one might models interactions between different subpopulations. For instance, in stem cell-driven tumors, stem cells need to acquire the capacity to overcome inhibition of cell division by differentiated cells. One can represent the dynamics of escape of stem cells from this inhibition using various feedback models with coupled differential equations for stem cells and differentiated cells.

Section 5: Clinical Implications

The above modeling strategies have a variety of implications for the clinic:

- First, as we saw above, knowing the population dynamics of the emergence of chemotherapy resistance are enormously valuable for designing a treatment schedule. Thus, assessing the size, mutation rate, and particular mutations of a tumor or leukemia can assist in decisions as to when and how to treat, with one or more drugs. Or, one can determine when and how radiation therapy is more or less likely to eventuate in secondary cancers.
- Second, using such models, one can in principle act to prevent cancer by adjusting the conditions under which cancers progress.
- Third, one might use evolutionary models to predict the likely progression of a tumor of a given size with given features, and thus provide more precise prognoses, as well as better timed and targeted therapies.
- Indeed, one might better predict which cancers are unlikely to progress, and so when it is better to engage in less aggressive treatment.

More generally, thinking of cancer as an evolving and co-evolving population of cells reinforces a fundamental insight about cancer and our vulnerability to cancer. First, cancer is a process, not a state of affairs. This insight is essential to understanding how better to prevent and treat cancer. Knowing that cancer is a process with variable natural histories suggests that when we screen, we need to be sensitive to the possibility that not all cancers progress uniformly to metastasis. This means that some cancers or precancerous lesions should not be intervened upon; less is sometimes more, and viewing cancer from an evolutionary perspective shows us why. Second, the evolutionary perspective on cancer reinforces the idea that ecology or tissue microenvironment of a cancer is enormously important; we need to devote more time and attention to why cancer does not progress, and which environments are less tumorigenic. This might lead to better preventive measures, and less aggressive intervention when it is far too late. Last but not least, the evolutionary perspective can also shed light on why some of us are more or less vulnerable to cancer, given our different trade-offs in life- history traits, and different mechanisms for regulation.

These considerations have larger import for both philosophy, and the clinic. First, as I hope to have shown, they illustrate the important role of modeling in biology, and in the biomedical sciences in particular. Models (however idealized) help us identify and isolate causally relevant factors in cancer progression. Moreover, we've seen that these models often have very specific targets; they are not intended to be "complete" explanations of cancer, but only pick out factors relevant to specific outcomes of interest. Second, such outcomes have of course broader relevance to clinical practice. The better we can get at identifying which cancers are more likely to progress more rapidly, or evolve resistance to chemotherapy, the better position we are in to intervene earlier, provide patients with information, and (ideally) develop targeted, effective interventions.

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