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Review

Evolution of transmissible cancers: An adaptive, plastic strategy of selfish genetic elements?

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SUMMARY

A growing number of studies have applied evolutionary and ecological principles to understanding cancer. However, few such studies have examined whether phenotypic plasticity—the ability of a single individual or genome to respond differently to different environmental circumstances—can impact the origin and spread of cancer. Here, we propose the adaptive horizontal transmission hypothesis to explain how flexible decision-making by selfish genetic elements can cause them to spread from the genome of their original host into the genomes of other hosts through the evolution of transmissible cancers. Specifically, we hypothesize that such cancers appear when the likelihood of successful vertical transmission is sufficiently low relative to the likelihood of successful horizontal transmission. We develop an evolutionary optimization model of this hypothesis, highlight empirical findings that support it, and offer suggestions for future research. Generally, phenotypically plastic selfish genetic elements might play an important role in the evolution of transmissible cancers.

INTRODUCTION

In his Pulitzer Prize-winning book, Siddhartha Mukherjee[1, p. xvii] refers to cancer as "the emperor of all maladies, the king of terrors." Indeed, of all major diseases, none is dreaded more than cancer for the simple reason that it is among the most challenging diseases to prevent and treat. Cancer is a large group of diseases that involve abnormal cell growth with the potential to spread to other parts of the body. Because cancers entail the proliferation of cells that are an integral part of their host's body, they are difficult to eradicate without damaging the host. Not surprisingly, cancers are responsible for a significant fraction of deaths (approximately 16% of human deaths worldwide or roughly 10 million deaths annually[2]). Notably, the cancer burden continues to grow.

Cancers are not restricted to humans. Among animals, cancers have been observed in all groups of vertebrates and many invertebrates.[3] Cancer-like phenomena have even been documented in fungi and plants, although they appear to be less lethal in plants than in animals.[3] In short, cancers and related phenomena occur across the Tree of Life.

Researchers have increasingly applied ecological and evolutionary principles to understand cancer's evolution, prevention, and treatment (e.g.,[4–9]). Critically, these principles have helped explain why cancers are so difficult to prevent and treat: Cancers are driven by the simple logic of natural selection, which favors entities that best propagate their distinctive characteristics into the next generation. Thus, selection among cell lines within a host organism can favor a line that pursues short-term proliferation into the next generation of cells at the expense of other lines.[7] Essentially, cancer's evolution is a testament to the power of natural selection.

At the same time, these evolutionary principles help explain the limits of cancer. Evolutionary theory predicts that differential over-replication by cell lines within an organism should be disfavored by selection acting at the level of the host organism. Because hosts with cancerous cells will generally reproduce less (owing to the harmful effects of cancer), cancer cells should have fewer opportunities than non-cancer cells to leave descendants in the next host generation. Indeed, the fact that cancer frequently causes the death of the host has led many to regard it as an evolutionary "dead end".[7,10] According to this perspective, cancer is best thought of as somatic cells evolving within one organismal generation.

Yet, this perspective ignores the possibility that cancer cells (or [onco]genes that trigger them) might spread infectiously from their original host organism to a new host.[6,11–15] The existence of such "transmissible cancers" expands the scope for selection to favor the evolution of cancer. Their existence even raises the possibility that cancer can be regarded as an adaptive strategy by "renegade" cells or genes.

Here, we develop these ideas to explain the evolution of transmissible cancers. We propose that flexible decision-making by "selfish" genetic elements (which we describe below) can cause these elements to spread from the genome of their original host into the genomes of other hosts through the evolution of transmissible cancers. We develop an evolutionary optimization model of this hypothesis, highlight

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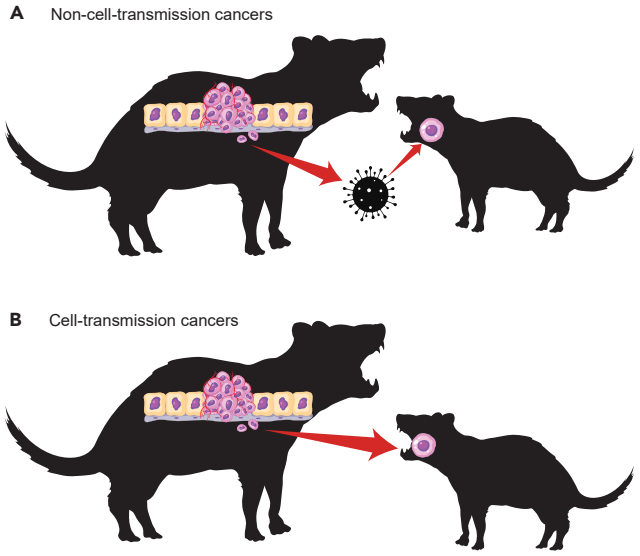

Figure 1. Two routes by which selfish genetic elements can spread through transmissible cancers

(A) First, a selfish genetic element might spread from its host's genome to a new host's genome via non-cell-transmission cancers. In this route, a selfish genetic element that triggers the proliferation of its host cell increases its copy number in tumors. This, in turn, enhances the likelihood that the genetic element will be picked up by a vector (e.g., a bacterium or virus) capable of infecting another host of the same or different species. This could eventually lead to the integration of the genetic element into the new host's genome.

(B) Alternatively, selfish genetic elements might spread from their host's genome to a new host's genome via cell-transmission cancers, where cancer cells move from the previous host to new hosts through direct contact between hosts.

empirical findings that provide preliminary support, and offer suggestions for future research. In doing so, we do not intend to provide an exhaustive literature review of our model's predictions. Instead, we aim to put forth a new idea in the hope that it will motivate tests of these predictions. But before outlining our model, we discuss its underlying premises and the evidence supporting each premise.

PREMISES OF OUR MODEL

Our hypothesis is based on three underlying premises. These are: (1) cancers can spread infectiously, (2) genes can be selfish, and (3) genes can be plastic. Below, we explain and justify each premise.

Premise #1: Cancers can spread infectiously

Although it is generally thought that the one redeeming feature of cancer is that it dies with its host, increasing evidence suggests that cancer can sometimes spread infectiously from its original host to a new host. This can occur through two main routes (Figure 1). First, and by far the more common of the two routes, cancer can be transmitted from one host individual to another through a vector, such as a virus (Figure 1A). For example, nearly all cervical cancers in humans are caused by certain strains of human papillomaviruses (HPVs), which are transmitted through sexual contact. When someone is infected with oncogenic types of HPV, the virus can transform normal cells in the new host into cancerous cells. Indeed, DNA from oncogenic HPV has been found in almost all cervical cancer biopsies.[16] Other viruses with oncogenic properties include adenovirus, herpesvirus, Epstein-Barr virus (EBV), and Rous sarcoma virus (RSV).[17]

The mechanism by which a virus transforms normal cells into cancerous cells appears to vary from one virus to another.[17] For example, in the case of HPV and RSV, the virus contains oncogenes that trigger cancer in the new host. In the case of EBV, the virus causes the proliferation of lymphoid cells that eventually remodel their genome so that the expression of the *c-myc* gene—a "master regulator" of cellular metabolism and proliferation[18]—becomes aberrantly high, transforming it into an oncogene. Although such viral-caused cancers are thought to account for a minority of all cancers (it is estimated that only 10–15% of cancers in humans are caused by viruses[17]), this is likely a conservative estimate when one considers that viral-caused cancers are hard to detect. Yet, for the reasons we describe below, such transmission might be more frequent than is currently recognized.

In the first route described above, genetic material that causes cancer—not actual cancer cells themselves—is transmitted from one host to another. However, an alternative route occurs when cancer cells spread contagiously from the original host to a new host (Figure 1B).[6,11–13,19] Such transmissible cancers have persisted for centuries and even millennia in natural populations of eight different species[15]: two mammals[12,20–22] and six species of bivalves.[23] Here, we discuss transmissible cancers in mammals, which are the best studied.

The oldest known example of transmissible cancer occurs in dogs (*Canis lupus familiaris*). Canine transmissible venereal tumor (CTVT) is believed to have evolved from a single cell about 11,000 years ago and has been circulating in dogs since.[12,20,21] As its name implies, it is

spread by sexual intercourse. Dogs may be especially prone to transmissible cancers. Because they remain locked in sexual intercourse for half an hour or longer (often resulting in torn tissues), cancer cells have an extended opportunity to travel between hosts.[12,24]

Two transmissible cancers have been found in Tasmanian devils (*Sarcophilus harrisii*). Devil's facial tumors (DFT1 and DFT2) spread around the face and are often fatal.[22] Indeed, these tumors have nearly driven devils extinct.[25,26] DFT1 is thought to have originated in a single individual in the mid-1990s; DFT2 evolved more recently.

Devils may be vulnerable to transmissible cancers for at least two reasons. First, devils often bite each other, providing a path for cells to travel from one host to another. Second, devils are so genetically similar that a cancer cell injected from a cancerous individual into another individual might not be detected and destroyed by the second individual's immune system. A foreign cell is typically rejected through a vertebrate's self/nonself recognition immune system, as mediated by the major histocompatibility complex (MHC). However, extreme climatic events throughout the devil's evolutionary history severely reduced wild populations, leading to bottlenecking and low MHC diversity.[12] The idea that low host genetic diversity can favor transmissible cancers is supported by experiments in which a sarcoma was transmitted between inbred Syrian hamsters.[27]

In addition to these four naturally occurring transmissible cancers (CTVT in dogs, DFT1 and DFT2 in Tasmanian devils, and clam leukemia in bivalves), transmissible cancers might also occur in humans through at least three routes. First, cancers might be transmitted across individuals through the placenta, which is a highly permissive organ. Indeed, cancer cell transmission has been documented to occur through the placenta from mother to fetus.[28,29] In some cases, the infected child has survived to sexual maturity,[29] suggesting mother-to-fetal transmission could be an effective strategy for a cancer-causing genetic element to spread from one host to another. More generally, there are numerous instances of "microchimerism" in which cells from one individual cross the placenta and colonize another individual's body. For example, fetal cells have been found to stay in the mother's body (and vice versa) decades after birth.[30] Second, human choriocarcinomas are another example of a transmissible cancer.[31] Most are derived from trophoblastic cells of the conceptus (the embryo in the uterus) that invade and become metastatic in the maternal body. Third, an exogenous cancer-causing retrovirus might be passed from mother to offspring via breastmilk (the transmission of viruses from mother to offspring has been documented through breastfeeding[32]). All three routes could provide a pathway for transmissible cancers in humans and other placental mammals.

Given that so few transmissible cancers have been documented, this raises an important question: Are transmissible cancers rare, or are they relatively common but researchers have simply failed to detect them? Some have argued that transmissible cancers—especially those that involve the actual transfer of cancerous cells across hosts—are rare because they require a "perfect storm" of factors to come together.[14] Such factors include tumor tissue properties that promote the shedding of large numbers of malignant cells, tumor cell plasticity that permits their survival in a new host, and host behavior and genetics that render new hosts susceptible to invading cancer cells.[6] The infrequent confluence of such tumor and host traits might explain the rarity of transmissible cancers. It is also possible that cancers with the potential to become contagious are often so lethal that they have few, if any, opportunities to spread to new hosts before the original host dies.

Alternatively, transmissible cancers might be more common than currently recognized, and researchers have failed to detect them, for at least two reasons. First, such cancers are likely hard to detect, especially in natural populations. Second, researchers might have devoted little effort to looking for transmissible cancers because plausible theoretical arguments for why such cancers should evolve (such as what we provide here) have been lacking.

Premise #2: Genes can be selfish

Darwin conceived natural selection as a "struggle for life" between organisms[33, p. 61]. According to Darwin, if individuals differ in their characteristics, and if this variation is associated with differential fitness (meaning some individuals produce more offspring because of their distinctive characteristics), then those individuals will experience natural selection—the nonrandom, differential survival or reproduction of individuals that differ in their characteristics. Furthermore, if these characteristics can be passed to offspring, the population will evolve by natural selection.

Starting in the 1960s, however, some evolutionary biologists began to ask if individual organisms are the only biological entity on which selection can act and promote adaptations.[34,35] This reframing of how natural selection works was based on the observation that multicellular organisms consist of a nested hierarchy of levels of biological organization: genes in cells, cells in organisms, organisms in groups, and so on. In principle, any collection of "entities" (e.g., genes or cells) that exhibit variation, differential fitness, and heritability should be capable of undergoing evolution by natural selection; that is, they should be capable of serving as a "unit" or "level" of selection.[36–41] Here, we focus on genes as a level of selection.

The most compelling evidence that genes can serve as a level of selection comes from the occurrence of "selfish genetic elements."[42] Selfish genetic elements are pieces of DNA that enhance their transmission at the expense of the rest of the genome and even their host organism. Note that in describing these elements, we follow convention and use the word "selfish" to emphasize that the phenotypic effects of these elements enhance their own propagation in the genome.[35,43,44] This gives the *appearance* that these genetic elements are "behaving" to maximize their transmission at the expense of other elements.[35,43,44] Nevertheless, it is important to keep in mind that phrases such as "selfish genetic elements," "adaptive strategy," and similar phrases are metaphors (as, indeed, is the phrase "natural selection"). Moreover, we refer to these DNA sequences as "elements"—and not genes—because they may not be actual genes. For example, they may be transposable elements.

As it turns out, all genomes—most especially those of sexually reproducing species—are vulnerable to such elements.[45–47] Indeed, selfish genetic elements have been documented in all major taxonomic groups, from bacteria and fungi to plants and animals.[46,48] One of the main

ways selfish genetic elements promote their transmission is through a process known as "meiotic drive." With meiotic drive, genetic elements subvert the mechanisms of proper segregation during meiosis to obtain greater than Mendelian transmission at the expense of their homologs.[49] We emphasize that these genetic elements enhance their transmission during meiosis not by encoding useful traits for their host but by simply performing actions that violate the rules of normal Mendelian segregation in which all alleles are equally likely to end up in the pool of gametes. These actions include: (1) increasing the speed with which cells containing the element divide during gamete formation, (2) producing toxins that kill any gamete cells not containing the element, and (3) ensuring that the element ends up in an egg cell and not a polar body, which generally cannot be fertilized.[46] Regardless of the precise mechanism, the result of these actions is to increase the frequency of the selfish genetic element in the gamete pool.

Premise #3: Genes can be plastic

Finally, genes can be "plastic", meaning they can be expressed conditionally. Although "phenotypic plasticity"—the ability to respond differently to different environmental circumstances—is generally regarded as a property of individual organisms,[50–54] many genes can respond differently to different environmental circumstances the same way many organisms can. Indeed, the fact that genes can be expressed only under certain circumstances forms the basis for our modern understanding of development.[55] For instance, the production of different cell types within a multicellular organism—skin cells, blood cells, etc.—and their organization into tissues and organs involves differential gene expression. Thus, the genes in skin cells are the same as those in the blood precursor cells. What makes these two types of cells different are the genes that are activated (i.e., expressed). The mechanisms involved in such differential gene expression are well established[55] and involve genes responding to signals from outside the genome.[56]

However, genes are capable of more complex conditional strategies than merely generating different cell types.[44] Haig's "strategic gene" framework[44,57,58] holds that some genes can facultatively alter their expression to increase their chances of being transmitted to the next generation given their current circumstances. A compelling example comes from studies of "genomic imprinting." Although most genes are expressed similarly whether they are inherited from the mother or the father, imprinted genes are expressed differently depending on whether they are maternally derived or paternally derived. Epigenetic processes, such as DNA methylation and histone modification, mediate such genomic imprinting. These epigenetic marks are established ("imprinted") in the germline of the parents and are then maintained through mitotic cell divisions in the somatic cells of the offspring.[59]

Haig et al. suggested that genomic imprinting evolves from parent-offspring conflict.[60] In many species (such as mice), a female mates with several males during her lifetime. This means a maternally derived gene in any one female's offspring is more likely to have copies in future offspring (because the mother remains the same) than a paternally derived gene (because different offspring from the same female might have different fathers). Thus, genomic imprinting would be favored to allow paternally derived genes to demand more resources from the mother than maternally derived genes in the same offspring.

Support for this idea comes from studies of two antagonistic genes in mice.[61] One gene, *insulin-like growth factor 2* (*Igf2*), is paternally imprinted, meaning it is expressed only when inherited from the father (it is silent when inherited from the mother). This gene encodes IGF-II, an insulin-like polypeptide that helps extract resources from the mother during pregnancy. Opposing the effects of *Igf2* is a maternally imprinted gene, *insulin-like growth factor 2 receptor* (*Igf2r*). This gene encodes a receptor that degrades the product of *Igf2*, minimizing the resource extraction from the pregnant mother. Therefore, these two genes are in a "tug-of-war," with *Igf2* working to extract resources from the mother and *Igf2r* resisting this extra investment and saving resources for the female's future offspring.[61] The existence of genomic imprinting suggests that genes can use flexible "decision-making" to maximize their transmission in the gene pool. Such adaptively flexible gene expression appears to be widespread.[62,63]

Having outlined our premises, we now turn to our hypothesis for the evolution of transmissible cancers, which we have dubbed the "adaptive horizontal transmission hypothesis."

THE ADAPTIVE HORIZONTAL TRANSMISSION HYPOTHESIS

Traditionally, cancer has been regarded as a maladaptive breakdown of cell division regulation in multicellular organisms; i.e., the breakdown is simply a physiological machinery failure, often later in life due to the accumulation of mutations in genes regulating cell division.[1] According to this view, which we label as the null model, cancer is not caused by any entity whose long-term reproductive interests are advanced by runaway cell division. In the null model, the only evolutionary process is simply some version of somatic evolution occurring within an individual, as in the population analogy (e.g.,[64,65] but see[66]).

However, a neglected (and untested) possibility is that cancer reflects an adaptive and phenotypically plastic strategy employed by selfish entities, i.e., selfish genetic elements residing within tumor cells (Figure 2). For example, runaway cell division leading to tumor formation may be caused by a selfish genetic element that is sometimes favored to invest in its horizontal transmission to the genomes of other organisms via bacterial or viral vectors, as opposed to vertical transmission through the offspring of the host organism in which it resides. Such horizontal transmission might be promoted through tumor formation. Tumors dramatically increase the number of cells containing the selfish element, thereby increasing the element's chance of being picked up by bacterial or viral vectors and ultimately transmitted to the genomes of the same or other organisms. Such a strategy optimally would be phenotypically plastic: the selfish element most favored would be one that conditionally triggers cancer only when its likelihood of successful vertical transmission is sufficiently low relative to the likelihood of successful horizontal transmission (Figure 2).

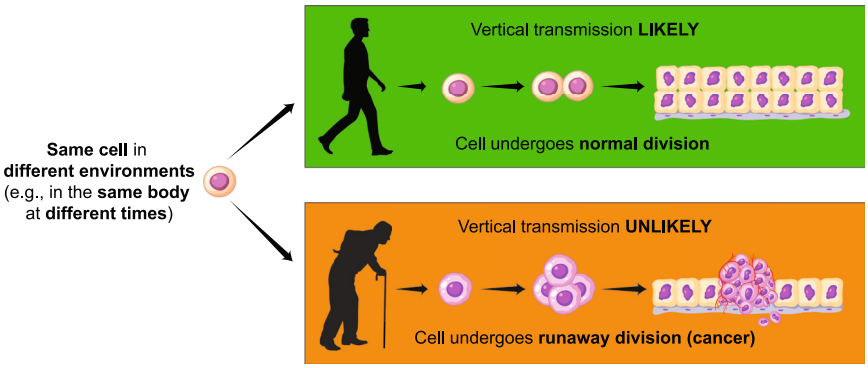

Figure 2. Flexible decision-making by selfish genetic elements can cause them to spread through the evolution of transmissible cancers

When vertical transmission of the selfish genetic element becomes unlikely, a selfish genetic element causes a normal cell to become cancerous. Through such plastically induced cancer, the element increases its chances of being spread horizontally from the genome of the original host into that of a new host through a transmissible cancer.

We propose that the latter theoretical idea, which we call the "adaptive horizontal transmission hypothesis" (developed in an evolutionary optimization model below), could apply broadly to both the evolution of (1) cell-transmission (CT) cancers, in which it is cancer cells (the latter containing the selfish genetic elements promoting the cancer) that are being transmitted from one organism to another in horizontal transmission, and (2) non-cell-transmission (NCT) cancers, in which it is the cancer-causing selfish genetic elements that are moving via bacterial or viral vectors from the genome of their original multicellular host into genomes of other hosts of the same or different species. (An interesting but untested possibility with features both of CT and NTC cancers is that horizontal transmission might occur if shed host cells containing a virus are picked up by another host with subsequent transfer of the virus into the other host's cells.)

Increasing evidence suggests that many, if not most, cancers are driven by the accumulation of mutations in long-lived stem cells that replenish tissues after the earlier stem cells differentiated into the organism's original tissues during development.[67,68] Our model could be seen as applying to flexible decision-making by selfish genetic elements in stem cells, both the stem cells responsible for the original construction of organismal tissues and the leftover stem cells that replenish such tissues later in an organism's lifetime (the latter being particularly susceptible to cancer origination).

Cell-transmission (CT) cancers

In CT cancers, cancer cells move from the previous host to new hosts through direct contact between hosts (Figure 1B). In these cases, the selfish genetic elements causing the cancers are triggering the proliferation of copies of themselves in tumors, and cancerous cells in these tumors are known to move into new hosts via direct contact (as described above). Such cancers are characteristically highly transmissible.

Such selfish genetic elements face the decision of how much to invest in horizontal transmission to another host versus vertical transmission to the host's offspring. There is a clear trade-off in the decision: Investment in horizontal transmission is likely to come at the expense of the likelihood of successful vertical transmission because tumor formation is likely to impair the host's ability to produce future offspring (which may be potential new hosts for the cancer cells through direct transmission; e.g., see[29]). This trade-off is a central feature of our evolutionary model of optimal investment in horizontal versus vertical transmission below.

Non-cell transmission (NCT) cancers

In the much more prevalent NCT cancers, the selfish genetic element is not in a cancer cell that is directly transmitted to another host but in the original host's genome itself (Figure 1A). In this case, we propose that the selfish genetic element triggering the proliferation of the host cell containing it increases its copy number in tumors. This increase in copies exposed to the environment increases the chance that the selfish genetic element will be picked up by some vector (e.g., a bacterium or virus) capable of infecting another host of the same or different species (even after the death of the host, during bacterial decomposition), leading eventually to the integration of the selfish genetic element into the genome of the new host. Importantly, bacteria are known to acquire DNA from external sources, including environmental DNA through transformation and directly from other cells through conjugation.[69] Both sources provide a potential mechanism for bacteria to acquire selfish genetic elements predisposing tumor formation. In addition, growing evidence shows that bacteria can transfer their DNA to eukaryotes.[70]

According to our proposed hypothesis, NCT cancers are transmitted to other hosts, but such transmission would be slower and much less easily detected than in the case of CT cancers. A possible exception to the latter is in the interesting case of HPV cancers, in which the HPV virus infects new hosts through sexual contact (see above). Genes from the HPV virus subsequently become integrated into the host genome and produce proteins that cause (1) genomic instability (enhanced mutability) of the host genes, increasing the chance that host genes affecting the regulation of cell division will be disrupted in their actions leading to runaway cell division; and (2) production of new virions within host cells.[71] Thus, the putative selfish genetic element in HPV both causes tumor formation and production of new virions capable of infecting new hosts through sexual contact, leading to rates of infection much higher than is observable for other NCT cancers. The result

is that HPV cancers are much more frequently observed to be transmissible than are other NTC cancers in which the putative selfish genetic elements aren't associated with linked genes encoding the vectors for their horizontal transmission.

The idea that widespread tumor formation in NCT cancers reflects adaptive investment of selfish genetic elements in horizontal versus vertical transmission hinges critically on the plausibility of the notion that such elements have some mechanism for "tracking'" the likelihood of their hosts engaging in vertical transmission through reproduction in the future. We can envision four theoretical mechanisms by which this could plausibly occur.

First, such a genetic element capable of triggering runaway cell division could be closely linked to mutable stretches of DNA that regulate the expression of the selfish genetic element. When a certain number of mutations accumulate in the latter linked mutable region, the expression of the selfish element could be dramatically increased. Since the number of accumulated mutations should be higher in older host organisms, this provides a simple mechanism for selfish elements to "assess" cues associated with host age and, thus, the likelihood of its own vertical transmission.

Second, the putative selfish genetic element may be sensitive to the activity of distant genetic regulators, either in the same cell in which it resides or in different cells. When a sufficient number of mutations accumulate in these regulators, the selfish genetic element responds by triggering tumor formation.

Third, the selfish genetic element may itself enhance the mutation propensity in host genes that control cell division. Over time, enough mutations accumulate in the latter host genes to trigger runaway cell division and tumor formation. In this way, the selfish element can effectively increase its copy number in tumor cells, again causing tumor formation with a higher probability in older hosts with a reduced likelihood of vertical transmission. These tumors will be enriched in selfish genetic elements. There is evidence that the third mechanism might operate in HPV-related cancers, in which HPV DNA integrated into the host genome produces proteins (E6 and E7) that augment host genomic instability.[72]

Finally, the putative selfish genetic element may be sensitive to the levels of circulating hormones associated with age and reproductive state. This mechanism seems plausible, given that many genes are sensitive to the presence of hormones. Indeed, many hormones work by activating transcription factors, which in turn help initiate gene expression.

As in the case of CT cancers, selfish genetic elements in NCT cancers face the decision of how much to invest in horizontal transmission to another host via tumor formation versus vertical (genetic) transmission through the host's offspring (non-genetic transmission, e.g., transmission of an exogenous virus through the placenta[73] is not considered). Note that this decision by a selfish genetic element assumes that the latter is in the genome of a multicellular host, since the tumor-initiating option requires multicellularity. In contrast, a selfish genetic element in a viral genome lacks a tumor-formation option and is forced to invest only in the production of replicate virions, which then infect other hosts (or perhaps other cells within the original host). This means that viral selfish genetic elements invest everything in "offspring" production, but these offspring must be transmitted to other hosts. In the latter case, the distinction between vertical and horizontal transmission disappears. For this reason, we make it clear that our adaptive horizontal transmission hypothesis assumes that the selfish genetic element making the decision resides at least initially in a multicellular host.

There is a clear trade-off in the decision to invest in vertical versus horizontal transmission for a selfish genetic element that is in the genome of a multicellular host: Investment in horizontal transmission is likely to come at the expense of the likelihood of successful vertical transmission because tumor formation often impairs a host's future ability to produce offspring. As in CT cancers (see above), this trade-off is central to our evolutionary model of optimal investment in horizontal versus vertical transmission.

AN EVOLUTIONARY OPTIMIZATION MODEL OF INVESTMENT IN HORIZONTAL VERSUS VERTICAL TRANSMISSION

We present a simple evolutionary optimization model of how much a selfish genetic element should invest in its horizontal versus its vertical transmission by appropriately altering host physiology, with such investment depending on such factors as the age and fecundity of the host in which it resides (see Table 1 for a list and description of all model parameters.). The model predicts several known features of cancers. In particular, cancers should be expressed more frequently in older adult host organisms since older organisms exhibit a declining probability of vertical transmission. The model leads to several other testable predictions that may unveil some of the currently unexplained properties of cancers.

The model is as follows. First, the probability of successful horizontal transmission for an infectious, cancer-causing pathogen is the probability that it will infect a new host who is not an offspring of the current host. The probability of horizontal transmission for a selfish genetic element in the genome of a host is the probability that it will be transmitted to another host (not necessarily in the same species as the current host) by being picked up by a vector such as a bacterium or virus and becoming integrated into the new host's genome. The probability of successful vertical transmission for an infectious, cancer-causing pathogen is the probability that it will infect a new host who is an offspring of the current host. The probability of successful vertical transmission for a selfish genetic element in the genome of a host is the probability that it will be genetically transmitted to an offspring of the current host. We assume that a pathogen or genetic element's investment in horizontal transmission trades off with its success in vertical transmission (and vice versa).

Let p = the proportional allocation of available host resources into physiological structures or actions (e.g., tumor formation) that promote horizontal transmission of the selfish genetic element responsible for the cancer. In horizontal transmission, we assume that investment in tumor formation specifically increases the probability of encountering vectors capable of horizontally transmitting the selfish genetic element. Let $1 - p$ be the proportional allocation of available host resources into the promotion of vertical transmission of the selfish genetic element/pathogen, capturing the assumed trade-off between investments into horizontal versus vertical transmission. In vertical transmission, we

Table 1. Model variables and meanings

Variable	Meaning
P	Fraction of the total host resource that is allocated to horizontal transmission
k_h	Intrinsic difficulty of horizontal transmission
k_v	Intrinsic difficulty of vertical transmission
$h = \frac{p}{p+k_h}$	Probability of successful encounter with a vector capable of horizontal transmission
t_h	Probability that an encountered vector successfully transmits the selfish element to another host
f_v	Probability that the focal selfish genetic element in a surviving host will successfully be transmitted to a host's offspring
$W = t_h h + f_v v$	Overall fitness of the selfish genetic element

assume that the investment specifically increases the host's survival and, in so doing, increases the expected number of future offsprings of the host.

The probability h of a successful encounter with a vector capable of horizontal transmission is assumed to be equal to $h = \frac{p}{p+k_h}$, where k_h is a constant that controls how fast the probability of exposure to a horizontally-transmitting vector rises with the fractional investment p in horizontal transmission. Thus, as the fractional investment increases, the probability h of encountering a horizontally transmitting vector increases monotonically with an upper asymptote of 1.0. Likewise, the probability of host survival (and thus, the likelihood of vertical transmission) v is assumed to be equal to $\frac{1-p}{(1-p)+k_v}$, where k_v is a constant that controls how fast the host's survival rises with increasing fractional investment $1\text{-}p$ in vertical transmission. The latter monotonically increases to an upper asymptote of 1.0. The constants k_i can be thought of as the intrinsic difficulty, due to constraints outside of the selfish element's control, of increasing the probability of tactic success by increasing the fractional allocation to tactic success. For example, k_h is a constant that will decrease as the availability of relevant vectors capable of horizontal transmission increases. Similarly, k_v is a constant that will increase as host mortality factors outside of the control of the selfish genetic element become stronger.

The overall fitness W of the selfish genetic element/pathogen facing the decision is simply equal to

$$W = t_h h + f_v v \qquad \text{(Equation 1)}$$

In Equation 1, t_h is the probability that the encountered vector successfully transmits the selfish element to another host, and f_v is the probability that the focal selfish genetic element in a surviving host will be successfully be transmitted to a host's offspring.

A fitness maximizing intermediate optimal fractional investment p^* in tactic 1 will satisfy $\frac{dW}{dp} = 0$ for $0 < p^* < 1$. The formula for p^* is complicated, but when it is substituted into the probability of encounter with a vector capable of horizontal transmission ($=h^*$), the resulting expression quickly yields some testable predictions. For example, after the latter substitution, it can be shown that

$$dh^* / dt_h = \frac{\sqrt{(f_v/t_h)k_h k_v}}{2t_h(1+k_h+k_v)} > 0 \qquad \text{(Equation 2)}$$

It follows from Equation 2 that the probability of encounter with a vector capable of horizontal transmission, given an optimal fractional allocation to such transmission, will increase as t_h increases. This occurs because as t_h increases, the individual will increase its fractional allocation to horizontal transmission, which automatically increases the observed probability of success in such transmission. It is empirically useful to cast the prediction in this way, because probabilities of successful transmission can be much easier to measure (at least indirectly) than are levels of fractional allocation.

Likewise, it can be shown that

$$dh^* / df_v = -\frac{\sqrt{(f_v/t_h)k_h k_v}}{2f_v(1+k_h+k_v)} < 0 \qquad \text{(Equation 3)}$$

It follows from Equation 3 that the probability of encounter with a vector capable of horizontal transmission, given an optimal fractional allocation to such transmission, will decrease as f_v increases. From Equations 2 and 3 together, it can be inferred that as the ratio t_h/f_v increases, the observed probability of successful horizontal relative to that of vertical transmission should increase.

Similarly, it can be shown that

$$dh^* / dk_h = -\frac{\frac{\sqrt{(f_v/t_h)}(1+k_h+k_v)k_v}{\sqrt{k_h k_v}} + 2\left[1+k_v - \sqrt{(f_v/t_h)k_h k_h}\right]}{2(1+k_h+k_v)^2} \qquad \text{(Equation 4)}$$

The right-hand side of Equation 4 can be shown to be negative if $h^* > 0$. Thus, the probability of success of horizontal transmission, given an optimal fractional allocation to such transmission, will decrease as k_h increases. In other words, the probability of success of horizontal transmission, given an optimal fractional allocation to promote it, will decrease the greater the intrinsic difficulty of horizontal transmission. It follows that a reduced availability of horizontally transmitting vectors will reduce the investment in horizontal transmission.

Likewise, it can be shown that

$$dh^* / dk_v = \frac{\frac{\sqrt{(f_v/t_h)}(k_v - k_h - 1)k_v}{\sqrt{k_h k_v}} + 2k_1}{2(1+k_h+k_v)^2} > 0 \quad \text{(Equation 5)}$$

Thus, the probability of success of horizontal transmission, given an optimal fractional allocation to such transmission, will increase as the intrinsic difficulty of vertical transmission, k_v, increases.

The optimal fraction allocation to horizontal transmission, p^*, will be greater than zero if

$$t_h / f_v > \frac{k_h k_v}{(1+k_v)^2} \quad \text{(Equation 6)}$$

Thus, at least some allocation to horizontal transmission is favored if the ratio t_h/f_v is sufficiently large to exceed the right side of Equation 6.

Similarly, the optimal fraction allocation to horizontal transmission, p^*, is equal to 1 if

$$(t_h / k_v) > \frac{(1+k_h)^2}{k_h k_v} \quad \text{(Equation 7)}$$

Thus, complete allocation to horizontal transmission is favored if the ratio t_h / k_v is sufficiently large to exceed the right side of Equation 7.

PREDICTIONS OF THE ADAPTIVE HORIZONTAL TRANSMISSION MODEL

A summary of model predictions and supporting evidence is given in Table 2. The first main model prediction is that investment in horizontal transmission via tumor formation should increase as the likelihood of vertical transmission (i.e., offspring production) decreases.

Thus, cancers should be most likely to arise when the likelihood of vertical transmission is lower, as when organismal fertility declines with age. If the selfish genetic elements causing cancers can have phenotypically plastic effects, we would further expect these elements to be most likely to trigger cancers when there are physiological indicators of facultative loss of expected fertility and also to refrain from triggering cancers when there are indicators of facultative increases in expected fertility. The predictions of the plasticity version of the adaptive horizontal transmission hypothesis are particularly intriguing because such predictions do not easily or strongly follow from the standard null model.

Substantial evidence exists that cancers occur more frequently in later life.[74] Indeed, in humans, age is the greatest risk factor for cancer. At a mechanistic level, this makes sense because there's more time for cells to be damaged in older individuals, making any mutation(s) that causes cancer more likely to occur. However, fertility also declines in older individuals.[80] This could explain why older stem cells responsible for replenishing an organism's tissues later in life are particularly susceptible to cancer origination: Selfish elements in such older stem cells might, in effect, be sensitive to factors that correlate with the organism's age (such as hormonal cues or metabolic byproducts in the body), and conditionally trigger tumor formation (see the last mechanism hypothesized for conditional expression of selfish genetic elements in NCT cancers discussed above). Alternatively, as in the third mechanism for conditional expression of selfish elements in NCT cancers discussed above, a selfish genetic element might actually cause genetic instability in the genes around it in the same stem cell (including instability in genes controlling the regulation of stem cell division), leading eventually to cancer origination in older stem cells.

Other evidence strongly suggests a link between cancer susceptibility and the likelihood of vertical transmission. For example, married couples tend to have overall lower cancer rates than unmarried individuals,[75] which is consistent with the prediction that a higher expectation of vertical transmission is expected to reduce cancer risk. Moreover, there is evidence that cancer origination becomes more likely in specific tissues when local cues are associated with contexts associated with increases or decreases in expected fertility. For example, breast cancers are less likely when there is a higher rate of breastfeeding, which is an indicator of increases in expected fertility.[76] More generally, female fertility is negatively associated with cancer rates.[81] However, one finding that violates the prediction of an inverse relationship between cancer risk and vertical reproduction probability is that ovarian removal can reduce the risk of breast cancer,[70] possibly due to the removal of the breast-cancer predisposing effects of estrogen in human females. Since estrogen can trigger cell division in breast tissue, such an effect is more consistent with the null model of cancer origination than with the adaptive horizontal transmission hypothesis. Nevertheless, overall, the number of births is negatively associated with breast cancer risk in human females.[82] In men, medical conditions causing undescended testes (lowered expected vertical transmission probability) can yield a 40-fold increase in the rate of testicular cancer,[78] further in support of the prediction of the adaptive horizontal transmission hypothesis.

Intriguingly, prostate cancers are less likely the greater the frequency of ejaculations[77] (a proxy for the likelihood of vertical transmission). Although one might contend that the prostate gland is so well shielded from the environment that it would preclude any horizontal transmission from this organ, the prostate is a frequent target of infections (e.g., it is estimated that 70% of men suffer bacterial infections of their

Table 2. Summary of predictions and supporting evidence for the adaptive horizontal transmission hypothesis

General prediction of the adaptive horizontal transmission hypothesis	Supporting evidence
Cancer risk should be inversely related to the probability of vertical transmission.	1. Cancer risk rises with increasing age, when fertility declines.[74] 2. Cancer risk is lower for married than unmarried couples.[75] 3. Breast cancer is less likely with a higher rate of breast feeding.[76] 4. Prostate cancer risk declines with more frequent ejaculations[77] and testicular cancer risk appears to increase in undescended testes.[78]
Cancer risk should be inversely related to the intrinsic difficulty of horizontal transmission.	Cancer risk is especially high in skin and linings of the digestive, respiratory, and urogenital tracts, likely associated with high vector encounter rates.[79]

prostate at some point in their lives[83]). These infections are caused when bacteria get in the prostate when urine flows backward through the urethra (vesicoureteral reflux).[83,84] Thus, this suggests that a selfish genetic element could be transmitted to and from the prostate through horizontal transmission via urine.

What about the special case of menopause in women? Are post-menopausal (i.e., post-reproductive) women at higher risk of cancers? We could find no evidence that menopause is associated with increased cancer rate beyond the increase characteristic of older female age. However, menopause is thought to have evolved to redirect maternal investment in offspring to investment in the rearing of grand-offspring and other extended kin.[85] Since these extended kin will also tend to share copies of the selfish genetic elements with the mother, it is possible that cancer risk in the mother is not further enhanced after menopause because such cancer would reduce the mother's ability to care for the extended kin and thus be disfavored by kin selection.

A second model prediction is that the investment in horizontal transmission will decrease the greater the intrinsic difficulty of horizontal transmission. Different predictions arise for NCT versus CT cancers. For NCT cancers, a key factor that should vary inversely with the intrinsic difficulty of horizontal transmission is the availability of competent horizontally transmitting vectors (i.e., increased availability of the latter is predicted to increase the investment in horizontal transmission). In CT cancers, a higher frequency of direct contact with other hosts is expected to lower the intrinsic difficulty of horizontal transmission and thus increase the investment in horizontal transmission. Interestingly, CT cancers are associated with tissues characterized by a high frequency of contact with hosts, such as oral tissues (through oral contact) or genital areas (through sexual contact). NCT cancers, by contrast, appear especially likely to arise in long-lived, tissue-replenishing stem cells that give rise to epithelial tissues in vertebrates, i.e., cells that line organs and are part of structural tissues.[86] Such tissues comprise the skin and linings of the digestive, respiratory, and urogenital tracts, which are also plausibly tissues experiencing a relatively high rate of exposure to pathogens since the cells in these tracts are especially equipped to activate the immune response.[79] Thus, the tissue distribution of cancer propensity is itself consistent with the predictions of the adaptive horizontal transmission model. This interpretation is an alternative to the null model explanation that cancers are prevalent in epithelial tissues (carcinomas, malignancies of epithelial tissue, account for 80–90% of all cancer cases in humans) simply because of their relatively high rates of turnover with a consequent higher risk of tumor-initiating mutations. However, the latter null model hypothesis would seem to predict that tissues experiencing the highest total turnover rates would be most susceptible to cancers. In contrast, although blood cells account for nearly 90% of the total cell turnover rate,[87] blood cancers account for only 10% of cancer incidence.[88] Thus, the null model explanation has difficulties.

Given the consistency of the model predictions with several known aspects of cancers, including those that the null model does not predict, we propose that the adaptive horizontal transmission hypothesis is worthy of additional tests. Particularly intriguing would be to identify the nature of the putative selfish genetic element(s) generating cancers and the potential molecular mechanisms by which such elements assess and respond to indicators of the likelihood of vertical transmission.

FUTURE DIRECTIONS

Whether flexible decision-making by selfish genetic elements causes transmissible cancers is currently unknown. Thus, future research is needed to test this idea by addressing the following issues.

First, more research is needed to determine how common transmissible cancers are, particularly in natural populations. Although some have argued that transmissible cancers are rare because they require an unlikely confluence of events to occur,[14] they may be more common than currently recognized, and we have simply failed to detect them. Indeed, if phenotypically plastic selfish genetic elements play an important role in the evolution of transmissible cancers, then such cancers might be more common than is generally recognized. Under this hypothesis, transmissible cancers might be considered an adaptive strategy.

Second, are any such selfish genetic elements that cause transmissible cancers capable of flexible (i.e., plastic) expression, and if so, what mechanism(s) affect such expression? As noted above, our hypothesis assumes that selfish genetic elements have some mechanism for tracking the likelihood of their hosts engaging in vertical transmission through reproduction in the future. We also described four theoretical mechanisms by which this could plausibly occur. More studies are needed to evaluate each of these theoretical mechanisms.

Third, additional studies are needed to determine if our model explains the disparity in cancers between animals and plants. The general absence of cancer metastasis in plants is thought to result from the difficulty of cancer cell movement throughout the plant because the rigid

cell walls make such movement difficult, even though plants sometimes develop local tumors such as galls or crowns. Such a barrier indicates that the intrinsic difficulty of horizontal transmission is higher in plants than in multicellular animals. Thus, according to our model, there should, therefore, be a lower tendency for neoplasias to be initiated in plant than in animal tissues. Indeed, such propensity appears to be lower in plants, owing to the greater "supracellular" control of cell division in plants than in animals, primarily through strong external control of cell division by the phytohormones auxin and cytokinin in plants.[89] We propose that the greater apparent external control of cell division in plants reflects adaptive restraint by potentially selfish genetic elements in plant cells, rather than stricter control imposed by more powerful external cell division regulators in plants than in animals. Such greater restraint by selfish genetic elements in investing in horizontal transmission in plants is predicted by our model, but it requires further tests.

Conclusions

That evolutionary thinking can shed light on cancer is uncontroversial. Like most organismal features, cancer is subject to evolution by natural selection, which favors entities that best propagate their distinctive characteristics into the next generation. Viewed through this lens, cancers are considered cheaters of multicellular development that enjoy a short-term selective advantage despite a long-term selective disadvantage to their host organism. By killing its host, cancer cannot benefit over the long term from the uncontrolled propagation it causes. For this reason, cancer is usually regarded as an evolutionary dead end and not an adaptive strategy.

However, some cancers can spread infectiously from their original host organism to a new host, thereby expanding the range of possibilities by which selection can favor cancer's evolution. Although these transmissible cancers are often viewed as "oddball" cases, they might represent an adaptive strategy by selfish genetic elements. Indeed, flexible decision-making by selfish genetic elements might cause such elements to spread from the genome of their original host into the genomes of other hosts through the evolution of transmissible cancers. Future research is needed to clarify the incidence and causes of transmissible cancers to determine if their occurrence is shaped by changing conditions in their immediate host environment; most notably, changes in the likelihood that their host can reproduce vertically.

Limitations of the Study

As noted above, we did not intend to provide an exhaustive literature survey. Instead, we have sought to put forward an idea and a theoretical model that we hope will motivate future research. In doing so, we might have unintentionally missed previous studies that are relevant to our hypothesis.

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AUTHOR CONTRIBUTIONS

Conceptualization, H.K.R. and D.W.P.; Model development, H.K.R.; Writing, H.K.R. and D.W.P.; Funding acquisition, D.W.P.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Mukherjee, S. (2010). The Emperor of All Maladies: A Biography of Cancer (Charles Scribner).
2. World Health Organization (2024). Cancer. https://www.who.int/health-topics/cancer#tab=tab_1.
3. Aktipis, C.A., Boddy, A.M., Jansen, G., Hibner, U., Hochberg, M.E., Maley, C.C., and Wilkinson, G.S. (2015). Cancer across the tree of life: cooperation and cheating in multicellularity. Philos. Trans. R. Soc. Lond. B Biol. Sci. *370*, 20140219. https://doi.org/10.1098/rstb.2014.0219.
4. Crespi, B., and Summers, K. (2005). Evolutionary biology of cancer. Trends Ecol. Evol. *20*, 545–552. https://doi.org/10.1016/j.tree.2005.07.007.
5. Dujon, A.M., Aktipis, A., Alix-Panabières, C., Amend, S.R., Boddy, A.M., Brown, J.S., Capp, J.-P., DeGregori, J., Ewald, P., Gatenby, R., et al. (2021). Identifying key questions in the ecology and evolution of cancer. Evol. Appl. *14*, 877–892.
6. Ujvari, B., Gatenby, R.A., and Thomas, F. (2016). The evolutionary ecology of transmissible cancers. Infect. Genet. Evol. *39*, 293–303. https://doi.org/10.1016/j.meegid.2016.02.005.
7. Shpak, M., and Lu, J. (2016). An evolutionary genetic perspective on cancer biology. Annu. Rev. Ecol. Evol. Syst. *47*, 25–49. https://doi.org/10.1146/annurev-ecolsys-121415-032109.
8. Ågren, J.A., and Scott, J.G. (2023). Viruses, cancers, and evolutionary biology in the clinic: a commentary on Leeks et al. 2023. J. Evol. Biol. *36*, 1587–1589. https://doi.org/10.1111/jeb.14232.
9. Frank, S.A., and Yanai, I. (2024). The origin of novel traits in cancer. Trends in Cancer. S2405-8033(24)00145-6.
10. Gardner, A. (2015). The genetical theory of multilevel selection. J. Evol. Biol. *28*, 305–319. https://doi.org/10.1111/jeb.12566.
11. Dujon, A.M., Gatenby, R.A., Bramwell, G., MacDonald, N., Dohrmann, E., Raven, N., Schultz, A., Hamede, R., Gérard, A.L., Giraudeau, M., et al. (2020). Transmissible cancers in an evolutionary perspective. iScience *23*, 101269. https://doi.org/10.1016/j.isci.2020.101269.
12. Murchison, E.P. (2008). Clonally transmissible cancers in dogs and Tasmanian devils. Oncogene *27*, S19–S30. https://doi.org/10.1038/onc.2009.350.
13. Ní Leathlobhair, M., and Lenski, R.E. (2022). Population genetics of clonally transmissible cancers. Nat. Ecol. Evol. *6*, 1077–1089. https://doi.org/10.1038/s41559-022-01790-3.
14. Tissot, S., Gérard, A.L., Boutry, J., Dujon, A.M., Russel, T., Siddle, H., Tasiemski, A., Meliani, J., Hamede, R., Roche, B., et al. (2022). Transmissible cancer evolution: the under-estimated role of environmental factors in the "perfect storm" theory. Pathogens *11*, 241. https://doi.org/10.3390/pathogens11020241.
15. Bramwell, G., DeGregori, J., Thomas, F., and Ujvari, B. (2024). Transmissible cancers, the

genomes that do not melt down. Evolution *78*, 1205–1211. https://doi.org/10.1093/evolut/qpae063.
16. zur Hausen, H. (2002). Papillomaviruses and cancer: from basic studies to clinical application. Nat. Rev. Cancer *2*, 342–350. https://doi.org/10.1038/nrc798.
17. Bouza, E., Martín Jiménez, M., Alemany, L., Arribas, J., Bañares, R., Barragán, M.B., Eiros Bouza, J.M., Felip, E., Fernández-Capetillo, O., Gracia, D., et al. (2021). Overview of virus and cancer relationships. Position paper. Rev Esp Quimioter *34*, 525–555. https://doi.org/10.37201/req/058.2021.
18. Dang, C.V., Resar, L.M., Emison, E., Kim, S., Li, Q., Prescott, J.E., Wonsey, D., and Zeller, K. (1999). Function of the c-Myc oncogenic transcription factor. Exp. Cell Res. *253*, 63–77. https://doi.org/10.1006/excr.1999.4686.
19. Metzger, M.J., and Goff, S.P. (2016). A sixth modality of infectious disease: contagious cancer from devils to clams and beyond. PLoS Pathog. *12*, e1005904. https://doi.org/10.1371/journal.ppat.1005904.
20. Ní Leathlobhair, M., Perri, A.R., Irving-Pease, E.K., Witt, K.E., Linderholm, A., Haile, J., Lebrasseur, O., Ameen, C., Blick, J., Boyko, A.R., et al. (2018). The evolutionary history of dogs in the Americas. Science *361*, 81–85. https://doi.org/10.1126/science.aao4776.
21. Baez-Ortega, A., Gori, K., Strakova, A., Allen, J.L., Allum, K.M., Bansse-Issa, L., Bhutia, T.N., Bisson, J.L., Briceño, C., Castillo Domracheva, A., et al. (2019). Somatic evolution and global expansion of an ancient transmissible cancer lineage. Science *365*, eaau9923. https://doi.org/10.1126/science.aau9923.
22. Pye, R.J., Pemberton, D., Tovar, C., Tubio, J.M.C., Dun, K.A., Fox, S., Darby, J., Hayes, D., Knowles, G.W., Kreiss, A., et al. (2016). A second transmissible cancer in Tasmanian devils. Proc. Natl. Acad. Sci. USA *113*, 374–379. https://doi.org/10.1073/pnas.1519691113.
23. Hart, S.F.M., Yonemitsu, M.A., Giersch, R.M., Garrett, F.E.S., Beal, B.F., Arriagada, G., Davis, B.W., Ostrander, E.A., Goff, S.P., and Metzger, M.J. (2023). Centuries of genome instability and evolution in soft-shell clam, *Mya arenaria*, bivalve transmissible neoplasia. Nat. Can. (Ott.) *4*, 1561–1574. https://doi.org/10.1038/s43018-023-00643-7.
24. Rebbeck, C.A., Thomas, R., Breen, M., Leroi, A.M., and Burt, A. (2009). Origins and evolution of a transmissible cancer. Evolution *63*, 2340–2349. https://doi.org/10.1111/j.1558-5646.2009.00724.x.
25. Hamede, R., Lachish, S., Belov, K., Woods, G., Kreiss, A., Pearse, A.M., Lazenby, B., Jones, M., and McCallum, H. (2012). Reduced effect of Tasmanian devil facial tumor disease at the disease front. Conserv. Biol. *26*, 124–134. https://doi.org/10.1111/j.1523-1739.2011.01747.x.
26. Lachish, S., Jones, M., and McCallum, H. (2007). The impact of disease on the survival and population growth rate of the Tasmanian devil. J. Anim. Ecol. *76*, 926–936. https://doi.org/10.1111/j.1365-2656.2007.01272.x.
27. Brindley, D.C., and Banfield, W.G. (1961). A contagious tumor of the hamster. J. Natl. Cancer Inst. *26*, 949–957. https://doi.org/10.1093/jnci/26.4.949.
28. Greaves, M., and Hughes, W. (2018). Cancer cell transmission via the placenta. Evol. Med. Public Health *2018*, 106–115. https://doi.org/10.1093/emph/eoy011.
29. Tolar, J., and Neglia, J.P. (2003). Transplacental and other routes of cancer transmission between individuals. J. Pediatr. Hematol. Oncol. *25*, 430–434.
30. Bianchi, D.W., Zickwolf, G.K., Weil, G.J., Sylvester, S., and DeMaria, M.A. (1996). Male fetal progenitor cells persist in maternal blood for as long as 27 years postpartum. Proc. Natl. Acad. Sci. USA *93*, 705–708. https://doi.org/10.1073/pnas.93.2.705.
31. Ning, F., Hou, H., Morse, A.N., and Lash, G.E. (2019). Understanding and management of gestational trophoblastic disease. F1000Res. *8*. F1000 Faculty Rev-428. https://doi.org/10.12688/f1000research.14953.1.
32. Hino, S. (2011). Establishment of the milk-borne transmission as a key factor for the peculiar endemicity of human T-lymphotropic virus type 1 (HTLV-1): the ATL Prevention Program Nagasaki. Proc. Jpn. Acad. Ser. B Phys. Biol. Sci. *87*, 152–166. https://doi.org/10.2183/pjab.87.152.
33. Darwin, C. (2009). In The Annotated Origin: A Facsimile of the First Edition of On the Origin of Species (The Belknap Press of Harvard University Press).
34. Dawkins, R. (1976). The Selfish Gene (Oxford University Press).
35. Ågren, J.A. (2021). The Gene's-Eye View of Evolution (Oxford University Press).
36. Keller, L. (1999). Levels of Selection in Evolution. Princeton University Press.
37. Lloyd, E.A. (2020). Units and levels of selection. In The Stanford Encyclopedia of Philosophy, E.N. Zalta, ed., p. 2020. https://plato.stanford.edu/archives/spr2020/entries/selection-units/.
38. Sober, E. (1984). The Nature of Selection (University of Chicago Press).
39. Lewontin, R.C. (1970). The units of selection. Annu. Rev. Ecol. Systemat. *1*, 1–18.
40. Okasha, S. (2006). Evolution and the Levels of Selection (Oxford University Press).
41. Suárez, J., and Lloyd, E.A. (2023). Units of Selection. In Elements in the Philosophy of Biology (Oxford University Press).
42. Werren, J.H., Nur, U., and Wu, C.I. (1988). Selfish genetic elements. Trends Ecol. Evol. *3*, 297–302.
43. Grafen, A. (2003). Fisher the evolutionary biologist. The Statistician *52*, 319–329.
44. Haig, D. (1997). The social gene. In Behavioural Ecology: An Evolutionary Approach, J.R. Krebs and N.B. Davies, eds. (Blackwell Scientific Publications), pp. 284–304.
45. Werren, J.H. (2011). Selfish genetic elements, genetic conflict, and evolutionary innovation. Proc. Natl. Acad. Sci. USA *108*, 10863–10870. https://doi.org/10.1073/pnas.1102343108.
46. Burt, A., and Trivers, R.L. (2006). Genes in Conflict: The Biology of Selfish Genetic Elements (Harvard University Press).
47. Hurst, G.D., and Werren, J.H. (2001). The role of selfish genetic elements in eukaryotic evolution. Nat. Rev. Genet. *2*, 597–606. https://doi.org/10.1038/35084545.
48. Jaenike, J. (2001). Sex chromosome meiotic drive. Annu. Rev. Ecol. Systemat. *32*, 25–49.
49. Sandler, L., and Novitski, E. (1957). Meiotic drive as an evolutionary force. Am. Nat. *91*, 105–110.
50. Pfennig, D.W., editor (2021). Phenotypic Plasticity and Evolution: Causes, Consequences, Controversies (CRC Press).
51. West-Eberhard, M.J. (2003). Developmental Plasticity and Evolution (Oxford University Press).
52. Pigliucci, M. (2001). Phenotypic Plasticity: Beyond Nature and Nurture (Johns Hopkins University Press).
53. Sultan, S.E. (2015). Organisms and Environment: Ecological Development, Niche Construction, and Adaptation (Oxford University Press).
54. DeWitt, T.J., and Scheiner, S.M. (2004). In Phenotypic plasticity: Functional and conceptual approaches (Oxford University Press).
55. Barresi, M., and Gilbert, S.F. (2023). Developmental Biology, 13th ed. (Oxford University Press).
56. Nijhout, H.F. (1990). Metaphors and the role of genes in development. Bioessays *12*, 441–446.
57. Haig, D. (2012). The strategic gene. Biol. Philos. *27*, 461–479.
58. Haig, D. (2020). From Darwin to Derrida: Selfish Genes, Social Selves, and the Meanings of Life (MIT Press).
59. Wood, A.J., and Oakey, R.J. (2006). Genomic imprinting in mammals: emerging themes and established theories. PLoS Genet. *2*, e147. https://doi.org/10.1371/journal.pgen.0020147.
60. Moore, T., and Haig, D. (1991). Genomic imprinting in mammalian development: a parental tug-of-war. Trends Genet. *7*, 45–49.
61. Haig, D., and Graham, C. (1991). Genomic imprinting and the strange case of the insulin-like growth factor II receptor. Cell *64*, 1045–1046. https://doi.org/10.1016/0092-8674(91)90256-x.
62. Grishkevich, V., and Yanai, I. (2013). The genomic determinants of genotype x environment interactions in gene expression. Trends Genet. *29*, 479–487.
63. Yanai, I., and Lercher, M. (2016). The Society of Genes (Harvard University Press).
64. Gerstung, M., Jolly, C., Leshchiner, I., Dentro, S.C., Gonzalez, S., Rosebrock, D., Mitchell, T.J., Rubanova, Y., Anur, P., Yu, K., et al. (2020). The evolutionary history of 2,658 cancers. Nature *578*, 122–128. https://doi.org/10.1038/s41586-019-1907-7.
65. Jassim, A., Rahrmann, E.P., Simons, B.D., and Gilbertson, R.J. (2023). Cancers make their own luck: theories of cancer origins. Nat. Rev. Cancer *23*, 710–724. https://doi.org/10.1038/s41568-023-00602-5.
66. Gatenby, R.A., and Brown, J. (2017). Mutations, evolution and the central role of a self-defined fitness function in the initiation and progression of cancer. Biochim. Biophys. Acta Rev. Canc *1867*, 162–166. https://doi.org/10.1016/j.bbcan.2017.03.005.
67. Hanahan, D., and Weinberg, R.A. (2000). The hallmarks of cancer. Cell *100*, 57–70. https://doi.org/10.1016/S0092-8674(00)81683-9.
68. Hanahan, D., and Weinberg, R.A. (2011). Hallmarks of cancer: the next generation. Cell *144*, 646–674. https://doi.org/10.1016/j.cell.2011.02.013.
69. Chen, I., Christie, P.J., and Dubnau, D. (2005). The ins and outs of DNA transfer in bacteria. Science *310*, 1456–1460. https://doi.org/10.1126/science.1114021.
70. Lacroix, B., and Citovsky, V. (2016). Transfer of DNA from bacteria to eukaryotes. mBio *7*, e00863-16. https://doi.org/10.1128/mbio.00863-00816.
71. Münger, K., Baldwin, A., Edwards, K.M., Hayakawa, H., Nguyen, C.L., Owens, M., Grace, M., and Huh, K. (2004). Mechanisms of human papillomavirus-induced oncogenesis. J. Virol. *78*, 11451–11460. https://doi.org/10.1128/jvi.78.21.11451-11460.2004.

72. Williams, V.M., Filippova, M., Soto, U., and Duerksen-Hughes, P.J. (2011). HPV-DNA integration and carcinogenesis: putative roles for inflammation and oxidative stress. Future Virol. *6*, 45–57. https://doi.org/10.2217/fvl.10.73.
73. Haig, D. (2012). Retroviruses and the placenta. Curr. Biol. *22*, R609–R613. https://doi.org/10.1016/j.cub.2012.06.002.
74. White, M.C., Holman, D.M., Boehm, J.E., Peipins, L.A., Grossman, M., and Henley, S.J. (2014). Age and cancer risk: a potentially modifiable relationship. Am. J. Prev. Med. *46*, S7–S15. https://doi.org/10.1016/j.amepre.2013.10.029.
75. Aizer, A.A., Chen, M.-H., McCarthy, E.P., Mendu, M.L., Koo, S., Wilhite, T.J., Graham, P.L., Choueiri, T.K., Hoffman, K.E., Martin, N.E., et al. (2013). Marital status and survival in patients with cancer. J. Clin. Oncol. *31*, 3869–3876. https://doi.org/10.1200/JCO.2013.49.6489.
76. Stordal, B. (2023). Breastfeeding reduces the risk of breast cancer: A call for action in high-income countries with low rates of breastfeeding. Cancer Med. *12*, 4616–4625. https://doi.org/10.1002/cam4.5288.
77. Rider, J.R., Wilson, K.M., Sinnott, J.A., Kelly, R.S., Mucci, L.A., and Giovannucci, E.L. (2016). Ejaculation frequency and risk of prostate cancer: updated results with an additional decade of follow-up. Eur. Urol. *70*, 974–982. https://doi.org/10.1016/j.eururo.2016.03.027.
78. Gupta, V., Giridhar, A., Sharma, R., Ahmed, S.M., Raju, K.V.V.N., and Rao, T.S. (2021). Malignancy in an undescended intra-abdominal testis: a single institution experience. Indian J. Surg. Oncol. *12*, 133–138. https://doi.org/10.1007/s13193-020-01262-9.
79. Larsen, S.B., Cowley, C.J., and Fuchs, E. (2020). Epithelial cells: liaisons of immunity. Curr. Opin. Immunol. *62*, 45–53. https://doi.org/10.1016/j.coi.2019.11.004.
80. George, K., and Kamath, M.S. (2010). Fertility and age. J. Hum. Reprod. Sci. *3*, 121–123. https://doi.org/10.4103/0974-1208.74152.
81. Kelsey, J.L., Gammon, M.D., and John, E.M. (1993). Reproductive factors and breast cancer. Epidemiol. Rev. *15*, 36–47. https://doi.org/10.1093/oxfordjournals.epirev.a036115.
82. Lambe, M., Hsieh, C.C., Chan, H.W., Ekbom, A., Trichopoulos, D., and Adami, H.O. (1996). Parity, age at first and last birth, and risk of breast cancer: a population-based study in Sweden. Breast Cancer Res. Treat. *38*, 305–311. https://doi.org/10.1007/bf01806150.
83. Domingue, G.J., Sr., and Hellstrom, W.J. (1998). Prostatitis. Clin. Microbiol. Rev. *11*, 604–613. https://doi.org/10.1128/cmr.11.4.604.
84. Amar, A.D., and Das, S. (1985). Vesicoureteral reflux in patients with obstructive prostatic disease. J. Urol. *133*, 194–197. https://doi.org/10.1016/s0022-5347(17)48878-1.
85. Johnstone, R.A., and Cant, M.A. (2019). Evolution of menopause. Curr. Biol. *29*, R112–R115. https://doi.org/10.1016/j.cub.2018.12.048.
86. Hinck, L., and Näthke, I. (2014). Changes in cell and tissue organization in cancer of the breast and colon. Curr. Opin. Cell Biol. *26*, 87–95. https://doi.org/10.1016/j.ceb.2013.11.003.
87. Sender, R., and Milo, R. (2021). The distribution of cellular turnover in the human body. Nat. Med. *27*, 45–48. https://doi.org/10.1038/s41591-020-01182-9.
88. Cleveland Clinic (2024). Blood cancer. https://my.clevelandclinic.org/health/diseases/22883-blood-cancer.
89. Doonan, J.H., and Sablowski, R. (2010). Walls around tumours — why plants do not develop cancer. Nat. Rev. Cancer *10*, 794–802. https://doi.org/10.1038/nrc2942.