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## Online links

**DATABASES**
**The following terms in this article are linked online to:**
**Cancer.gov:** http://www.cancer.gov/cancer_information/
cervical cancer
**GenBank:** http://www.ncbi.nih.gov/Genbank/
E6 | E7 | HPV16
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cyclin E | DNA polymerase-δ | DNA polymerase-ε | INK4A | Ki-67 | KIP1 | MCM2 | MCM3 | MCM4 | MCM5 | MCM6 | MCM7 | MN antigen | p107 | p130 | PCNA | RB | TERT | WAF1

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OPINION

# Cancer selection

*Armand M. Leroi, Vassiliki Koufopanou and Austin Burt*

Cancers are often thought to be selectively neutral. This is because most of the individuals that they kill are post-reproductive. Some cancers, however, kill the young and so select for anticancer adaptations that reduce the chance of death. These adaptations could reduce the somatic mutation rate or the selective value of a mutant clone of cells, or increase the number of stages required for neoplasia. New theory predicts that cancer selection — selection to prevent or postpone deaths due to cancer — should be especially important as animals evolve new morphologies or larger, longer-lived bodies, and might account for some of the differences in the causes of cancer between mice and men.

Cancers are selfish cell lineages: clones of cells that evolve high reproductive success relative to other clones, at the expense of the Darwinian fitness of their host. The process by which they arise and spread — several steps consisting of repeated bouts of mutation and selection — resembles the evolutionary dynamics of populations of single-celled organisms (for example, bacteria)[1–3]. As neoplastic cell lineages evolve, they slowly accumulate mutations that further their own survival and proliferation. These mutations might enable cells to produce their own mitogenic signals, suppress contact inhibition, evade apoptosis, metastasize, or even, in the case of advanced tumours, construct a vascular system of their own. The selfishness of neoplastic cells (for example, HeLa) is illustrated by their ability to live and spread in laboratory cultures. Canine transmissible venereal sarcoma (CTVS) is an even more vivid illustration of the same principle. Rather weirdly, this cancer — having arisen spontaneously in dogs — seems to be a single ultra-selfish cell lineage that is capable of moving from one host to another, so that it flourishes even after the death of the dog in which it originated (BOX 1). CTVS, however, is an exception. Outside the laboratory, all other cancerous clones remain confined to the body in which they originate.

Cancer is a hazard that few, if any, animals escape. Unambiguous neoplasias have been recorded from molluscs, arthropods, jawless fish, cartilaginous and bony fish, amphibia, reptiles and mammals[4–8], although whether they exist in cnidarians — simple animals that include jellyfish and anemones — is more debatable[9–11]. The antiquity and deleterious effects of cancers indicate that animals should have evolved devices against them. The cancers that are discovered can, indeed, be viewed as a failure of adaptation. Such failures of adaptation can occur when animals are exposed to unfamiliar pathogens, unfavourable environmental conditions or in old age. As animals age, selection for the maintenance of somatic integrity declines[12,13]. From this point of view, the cancers of old age can be explained in the same terms as senile osteoporosis, impotence and dementia.

All of these evolutionary explanations for the existence of cancers are familiar enough[14]. Here, however, we are concerned with yet another way in which a failure of natural selection can give rise to cancers. We argue that some cancers — especially those experienced by the young — might have their origins in recent evolutionary changes in morphology and life-history. We also indicate that such cancers might drive the evolution of many features of cellular behaviour and regulation.

### A by-product of novel adaptation

The idea that changes in morphology and life-history can expose animals to an increased risk of cancer has been argued most forcefully by James Graham in his 1992 book *Cancer Selection*[15]. As a businessman familiar with manufacturing, he notes that changes in the design of a product often result in a transient decline in its quality. Analogously, the evolution of a novel morphology might interfere with the quality control of development — a breakdown that manifests itself as an increased incidence of cancer. Indeed, Graham argues that the immense diversity in size, shape and life-history that is shown by animals today was bought at the expense of untold numbers of deaths due to cancer. But the process is self-correcting. Just as subsequent adjustments in a production line restore the product to its original high quality, so cancer deaths select for modifiers that make development more precise.

A possible example of this co-evolutionary process can be found in fish of the genus *Xiphophorus* that inhabit Mexican rivers. Certain populations of the platyfish, *X. maculatus*, are covered in dark spots that are composed of giant pigmented cells called macromelanophores[16]. The swordtail *X. helleri* — a close relative of *X. maculatus* — does not bear these spots, nor this specialized cell type. *X. maculatus's* spots are caused by dominant alleles of an X-linked locus, *Tu*, and when these species are hybridized in the laboratory — placing *X. maculatus* spot-causing chromosomes against an *X. helleri* genetic

Box 1 | **Dog venereal cancer: a highly degenerate mammal**

Mammals are continually sloughing off cells, but these cells usually die once they are separated from the organism. Even the most aggressive and invasive cancer cells usually die when their host dies. However, there is a fascinating exception: canine transmissible venereal sarcoma (CTVS) is an infectious disease of dogs that is caused by a pathogenic lineage of cancerous cells[70]. This cell lineage is transmitted from one dog to another, usually during coitus. Once on a new host, the cells reproduce to form a tumour-like growth, usually around the genitals, but occasionally on the skin and in and around the mouth. The figure shows a primary venereal cancer in the dog, involving the penis and surrounding tissue. The cell lineage can then be transmitted to another host. There are no obvious differences in susceptibility between breeds of dogs, and the cells can even be transmitted to foxes. It is this continuity of the cell lineage (as opposed to merely continuity of an infectious virus) that distinguishes CTVS from other transmissible cancers (for example, human cervical cancer). Even without treatment, tumours usually regress after 1–3 months, and if regression is complete, then the host is immune to subsequent re-infection. CTVS can be found in many parts of the world, and in some regions is the most common dog tumour. It is thought to have originated only once and spread worldwide, and a LINE retrotransposable element insertion upstream of the c-*MYC* oncogene[71] was presumably important in its genesis. This 'naturally occurring allograft' has become a true pathogen, even a highly degenerate mammal. Image courtesy of Wilfried T. Weber, Pennsylvania, USA.

background — some segregants are extremely susceptible to an aggressive melanoma that originates in the macromelanophores[16] (FIG. 1). So, an *X. maculatus* gene is oncogenic in a close relative. *Tu* turns out to be a gene complex, one locus of which encodes a receptor tyrosine kinase with homology to epidermal growth-factor receptor (EGFR), retroviral transforming protein ERBB2 and human RET, mutations in which are inherited in familial multiple endocrine neoplasia[17]. This locus seems to have arisen by recent duplication of a closely linked gene. The fact that wild *X. maculatus* are not riddled with cancers indicates that they also carry a tumour suppressor that *X. helleri* does not. This tumour suppressor — a single autosomal locus called *DIFF* — has not yet been formally cloned, but might be a *CDKN2*-like gene with high homology to the human tumour suppressor INK4A[18]. One scenario is that a weak form of *Tu* was selected because it conferred a novel and presumably adaptive morphology (spotting), despite occasionally causing cancer. This side effect was then eliminated by the evolution of *DIFF* — a protective tumour suppressor — which, in turn, allowed a stronger form of *Tu* to evolve that is almost certain to cause cancer in the absence of *DIFF*. *Tu* alleles that cause variable degrees of spotting and variable rates of cancer in the absence of *DIFF* have been observed[19].

If cancer arises as a side effect of evolutionary change, it should be particularly common after very rapid bouts of evolution, before protective devices have had a chance to evolve. Artificial selection might be one place to investigate this idea. Domestic chickens are notoriously prone to cancers of the reproductive tract: in one study, one-third of females developed ovarian and/or oviductal cancer by 4 years of age (H. J. Barnes, personal communication). A likely, if unproven, reason for these high rates is that chickens have long been selected for high rates of egg production. In addition, dog breeds such as Great Danes, Newfoundlands and St Bernards, which have been selected for very rapid growth and large body size, have a 180-fold greater risk of osteosarcoma than smaller breeds[20,21]. Breeds that are selected for small size do not show an increased incidence of cancers.

### Why children get cancer

About 3 in 1,000 people develop cancer during the first 20 years of life[22]. Without medical treatment, most of these cancers are fatal. In contrast to adult cancers — 83% of which occur in the perpetually self-renewing epithelia of various organs — paediatric cancers are of a much wider spectrum, with at least 50% in the immune system and central nervous system (CNS), and only 9% in epithelia[23]. From an evolutionary point of view, the existence of paediatric cancers is paradoxical. Natural selection should produce adaptations that eliminate them, so why hasn't it? One reason might be that these cancers occur in organs that have undergone recent and pronounced evolutionary change.

Osteosarcoma is one of the more common paediatric cancers: an individual has a 1 in 10,000 chance of developing it in the first 20 years of life[22]. Primary tumours typically occur in the growth zones of the most rapidly growing bones in adolescents (distal femur, proximal tibia and proximal humerus)[24]. As in dogs, osteosarcoma seems to be associated with rapid growth in children: 50% of osteosarcomas occur in children in the top 75th percentile for height for their age group[25]. Indeed, children are at greatest risk from osteosarcomas during the pubertal growth spurt, which usually occurs between the ages of 13 and 15. Moreover, different bones undergo the growth spurt at slightly different ages, and the age at which each shows the greatest risk of osteosarcoma varies accordingly[26]. Juvenile osteosarcoma might, then, be a by-product of recent evolutionary changes in human growth. The pubertal growth spurt, in particular, seems to be an evolutionary novelty. It is absent in great apes and, some have argued, also in our predecessor *Homo erectus*[27].

The same logic might explain other paediatric cancers as well. The most common such cancers are of the immune system: the probability of developing leukaemia or lymphoma in the first 20 years of life is about 11 in 10,000 (REF. 22). As a general principle, the immune system is expected to be among the fastest evolving systems in any species, because it will be constantly selected in new directions by co-evolving pathogens and parasites. Many of the mutations that give rise to leukaemia and lymphoma are caused by misplaced activity of the enzymes involved in the programmed gene rearrangements and hypermutation on which the adaptive immune system depends[28]. We suspect that the selection imposed by perpetually changing parasites is constantly tinkering with this mechanism, and preventing it from becoming more perfect.

The second most common class of paediatric cancers are of the CNS (combined frequency of 5.5 in 10,000 over 20 years[22]). We attribute this high frequency to the fact that our brains have increased threefold in size compared to those of chimpanzees[29]. Unlike the immune system, which is expected to be under constant adjustment in all mammalian lineages, such marked changes in the CNS are found in only certain lineages.

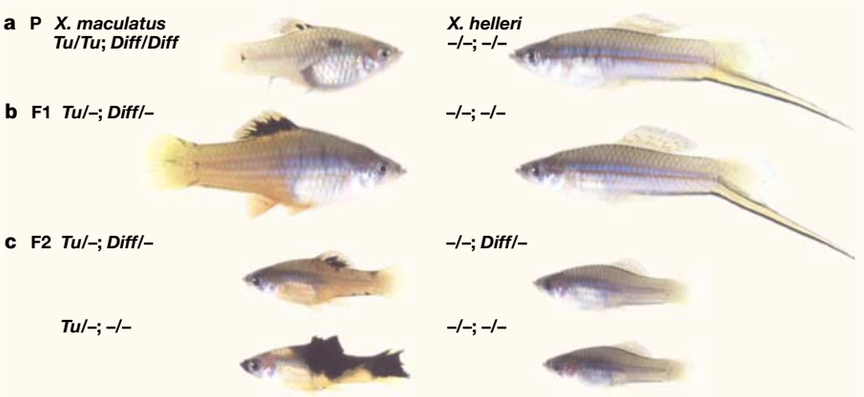


Figure 1 | **Hybrid fish with melanomas: the Gordon–Kosswig cross. a** | P, the parental generation: *Xiphophorus maculatus* female and *X. helleri* male. **b** | Hybrid (F1) female, which displays a benign nevus-like melanotic lesion, is backcrossed to an *X. helleri* male. **c** | F2, backcross progeny segregating the oncogenic *Tu* allele and the tumour suppressor *Diff* allele. Fish that carry one *Tu* allele but do not have any copies of *Diff* (bottom left) have malignant melanomas. Courtesy of Manfred Schartl, Wuerzburg.

Therefore, we predict that cancers of the immune system will be relatively common in all mammals, but not CNS cancers, for which high frequencies should only be found in specific lineages.

### The paradox of the blue whale

Many types of evolutionary change could lead to increased risks of cancer. Changes in tissue architecture (for example, intestinal crypt structure) might influence the frequency and fate of neoplastic cells[30]. Novel cell types, such as the *Xiphophorus* macromelanophore, will be oncogenic if they lack appropriate proliferation controls. Rapid changes in the titres of growth-promoting hormones might be oncogenic as well. Humans with acromegaly — abnormal growth of the hands, feet and face, caused by overproduction of growth hormone from the pituitary gland — and giant mice with growth-hormone transgenes are unusually prone to various cancers[31]. The mechanism for this is unclear, although growth hormone is known to positively regulate serum insulin-like growth factor-1 (IGF1), which, in turn, is capable of suppressing genotoxic-dependent apoptosis[32]. Indeed, large, osteosarcoma-prone breeds of dogs are known to have much higher titres of serum IGFs than smaller breeds[33].

Perhaps the simplest way in which evolutionary change can cause an increased risk of cancer is by bringing about an increase in the number of stem cells and cell divisions, so increasing the opportunity for selfish lineages to arise. This would make larger bodies more oncogenic, so big dogs might be prone to osteosarcoma simply because they have more cells than smaller dogs. Long lifespans are also potentially oncogenic, particularly if they entail more proliferation of somatic tissues.

The protection from cancer that small bodies and short lives can provide is illustrated by recent results from knockout mice. Humans who are heterozygous for a null mutation at a tumour-suppressor locus are prone to cancer because the remaining wild-type allele is likely to suffer a somatic mutation that completely eliminates the product. Mice that are heterozygous for null mutations in such loci sometimes show similar pathologies; for example, *Pten*$^{+/-}$ mice develop many of the same tumours as *PTEN*$^{+/-}$ humans[34], and similarly for *Trp53*$^{+/-}$ mice[35–37]. In other cases, heterozygous mutant mice show little of the expected phenotype[38]. *NF1*$^{+/-}$ humans succumb to neurofibromatosis, but *Nf1*$^{+/-}$ heterozygous mice never do (although they do get other cancers)[39,40]. *BRCA1*$^{+/-}$ women have a 50% lifetime risk of developing breast cancer, but *Brca1*$^{+/-}$ mice do not seem unduly prone to any form of cancer, much less mammary-gland tumours[41,42]. However, in both cases, the lack of expected cancers in mouse heterozygotes is due to the absence of the second somatic mutation. If homozygous *Nf1*-null Schwann cells or *Brca1*-null mammary-gland cells are induced *in vivo* by *Cre*-mediated conditional deletion, the expected cancers do arise[43,44]. Apparently, the cancers do not develop in heterozygous mice because mutations are rare and the target population is small.

A medium-sized dog is about 1,000 times larger than a mouse, a human 3,000 times larger and a blue whale 6 million times larger. If the probability of a cell becoming cancerous was the same in all of these species, then, ignoring stem-cell dynamics and longevity differences, the larger species should have a proportionately higher cancer rate. Of course, this is not what happens. There are few data on lifetime cancer rates in (non-model) mammals, but cancer rates seem to vary by less than a factor of 2. In a population of wild *Mus musculus* raised in the laboratory, 46% had gross tumours at death[45]; about 20% of dogs die because of cancer[46]; and 22% of annual human deaths in the United States are directly caused by cancer[47]. And although cancers have been recorded in blue whales, their rarity indicates that most whales do not die from rampant malignancies[48]. The failure of whales and humans to be more cancer prone than mice has been called 'Peto's paradox' after Sir Richard Peto, who described it most lucidly in 1975 (REF. 1). Many evolutionary minded oncologists have noted the paradox and have usually resolved it by suggesting that the cells of large animals must be somehow more resistant to neoplastic transformation than those of small animals[1,15,30,49].

### Three ways to beat cancer

Because cancers develop through a multistep evolutionary process of somatic mutation and cell-lineage selection, anticancer adaptations must work in (at least) one of three ways. First, somatic mutation rates can be reduced. For example, at least some stem cells seem to arrange DNA replication and cell division such that they retain an 'immortal strand' of DNA, which should reduce the mutation rate[30,50]. Some stem cells also do not seem to repair certain forms of DNA damage, preferring instead to die, which could reduce the mutation rate[51]. In principle, therefore, one solution to Peto's paradox might be that large animals have lower somatic mutation rates than small animals. In practise, however, somatic mutation rates of mice and humans do not seem to be very different. The frequency of HPRT-null mutant cells in mouse kidney epithelia is 1–4 per 100,000 cells, and in humans it is 2–25 per 100,000, depending on age[52,53]. As human kidneys are made from more cell divisions than those of mice, these values indicate that mutation rates per cell division in the two species are broadly comparable, although further information would be useful here.

Second, the incidence of cancer can be decreased by reducing the selective advantage (at the level of competing cell lineages) of the contributing somatic mutations. For

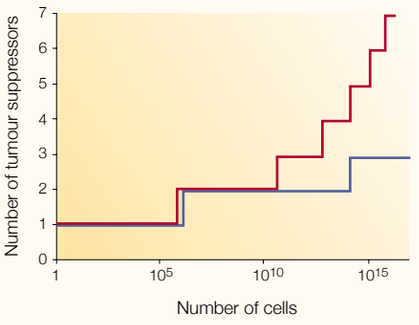


Figure 2 | **Number of tumour-suppressor loci required to keep the frequency of juvenile/pre-reproductive cancer below $10^{-4}$, as a function of the number of cells in the tissue or organism.** The blue line is for a tissue that grows exponentially during ontogeny and then stops; the red line is for a population of stem cells that goes through K divisions during adolescence, assuming $K=0.012C^{0.4}$, where C is the number of cells (for example, an 18-day cell cycle for 15 years in $10^{11}$ cells (=100g of tissue)). Calculated from Equations 1 and 2b in Nunney[55], assuming a mutation rate of $10^{-6}$ per somatic cell division. The number of tumour-suppressor loci required will increase if the somatic mutation rate increases (for example, due to a mutator phenotype), or if any of the mutations causes an increase in cell proliferation rate due to cell-lineage selection.

example, if a tumour-suppressor locus is incompletely recessive at the cellular level (that is, it is haploinsufficient), then a knockout of one allele could allow the cell to proliferate and thereby make the double mutant more likely to occur (or reduce the waiting time until it does). Selection at the individual level will therefore favour genotypes in which the selective advantage of the first mutation is reduced (or even turned into a disadvantage). In mice, the tumour suppressors *Cdkn1b* (which encodes Kip1) and *Pml* are incompletely recessive[54], and it would be interesting to know whether null mutations in human cells are more completely recessive.

The selective advantage of each intermediary step towards tumour formation can also be affected by stem-cell dynamics and tissue architecture. For example, Cairns[30] suggests that interposing a series of transiently amplifying cells between the stem cells and the terminally differentiated cells will reduce the number of stem cells required, and so also reduce the frequency of cancer (assuming that only stem cells can become neoplastic). Similarly, having separate patches of stem cells, between which migration is difficult or impossible (as is likely for those in the colonic crypts), also reduces the selective advantage of an oncogenic mutation.

Finally, extra redundancy can be added to the control of cellular proliferation, so that more mutations are needed to generate a cancerous cell. This is the scenario modelled by Nunney[55], who estimates the selective value of adding an extra tumour-suppressor locus as a function of the number of cells and the number of tumour suppressors that are already active (FIG. 2). A comparison of human tissues seems to be consistent with the idea that large tissues have more tumour suppressors than smaller tissues. Cells in the retina (a relatively small and non-proliferative tissue) can become cancerous by the inactivation of only one tumour-suppressor locus (*RB*), whereas cells in the lower gastrointestinal tract require knockouts of three loci, as well as the activation of an oncogene[3].

One obvious way to increase redundancy is by the duplication of tumour-suppressor loci. 'Super-p53' mice, engineered to have an extra copy of p53, are especially cancer resistant[56]. With genome sequences now available from mice and humans, it should be possible to test whether growth-suppressing loci have been more prone to duplication in the human lineage than growth-promoting loci, the opposite of what might be expected from simply comparing adult sizes. Another way to increase redundancy is for a gene to acquire tumour-suppressor function *de novo*. *Drosophila melanogaster* and *Caenorhabditis elegans* both have a single p53-like gene[57,58]. In both species, it seems to be involved in genotoxic-dependent apoptosis, but in neither is it a tumour suppressor. Indeed, the worm and fly p53 homologues are more similar to the other mammalian members of the family — p63 and p73 — which have a function in development, than to p53 itself. It seems, then, that p53 acquired its tumour-suppressor function only after the expansion of the family early in vertebrate evolution[58] — perhaps as vertebrate bodies started to grow.

## Searching for redundancy

One obvious place to search for differences in tumour-repressor redundancy — however it might be achieved — is to compare mice and humans. There are several possible ways of detecting such a difference. The first depends on estimates of age-dependent cancer rates. In simple mathematical models of tumour development, if *n* mutations are required, then the incidence of cancer is expected to increase in proportion to age raised to the power *n*-1 (REFS 59,60). Therefore, in a log–log plot of incidence against age, the slope of the regression line should be equal to *n*-1. If more mutations are required for humans than for mice, then this slope should be steeper. As it happens, the slopes for mice are between 5 and 6 (REF. 61; and F. Pompei, personal communication), indicating that six or seven mutations are required. This falls within the observed range for humans[60]. One weakness of this test is that it assumes an absence of cell-lineage selection — the extent of which could differ among species.

Second, if humans have more tumour suppressors than mice, then many loci that are tumour suppressors in humans should not have that function in mice. However, surveys of mouse tumour-suppressor knockouts indicate that this is not true[62]. The two species seem to have roughly equal numbers of tumour-suppressor loci. This test does not rule out the possibility that tumour suppressors in humans act in a greater diversity of tissues than those in mice, ensuring a greater number of active tumour suppressors in any given tissue.

Third, cultured mouse cells are more likely to spontaneously immortalize and are more susceptible to oncogenic transformation than are human cells, apparently due to the fact that more mutations are required for the latter[62]. At first glance, this difference seems to support the prediction, but a closer look raises some doubts. At the molecular level, the most obvious difference is that human cells require mutations that induce telomerase activity, whereas in mouse cells this enzyme is already constitutively active. However, suspicions that constitutive telomerase activity is a property of laboratory mice rather than the species as a whole are prompted by the observation that lab mice have much longer telomeres than their wild relatives — which are comparable to those of humans[63]. Another main difference, at least in fibroblast cultures, is that both the p53 and the RB pathways have to be inactivated for immortalization in human cells, whereas in mouse cells only the p53 pathway needs to be inactivated[62]. However, Rb is still a tumour suppressor in mice, in that $Rb^{+/-}$ heterozygotes have an increased frequency of cancers[38]. Again, perhaps the answer is that the *Rb* pathway is more widely active in human tissues than in mouse tissues.

Finally, we can compare the number of steps that are required for tumour formation in a given tissue in mice with the number in humans. To our knowledge, such data are available for only one tissue: the retina. Retinoblastoma requires deletion of one tumour-suppressor locus (*RB*) in

humans but two in mice (*Rb* and the related *p107*)[64,65]. So, the relative degree of protection against retinoblastoma in mice and humans is the opposite of what theory would predict. Given that retinoblastoma is rare even in humans (0.5 in 10,000; REF. 22), so is probably under little selection for a further reduction in incidence, the mouse retina seems decidedly overengineered.

Surveying these results, it is difficult to see much support for Nunney's extra-step hypothesis, at least as far as differences among species are concerned. Admittedly, the data are not strong, and we would like to have more direct comparisons of step number in homologous mouse and human tissues. Even so, these results lead us to suspect that evolved differences in cancer resistance in mammals depend less on the number and function of tumour suppressors than on adaptations that alter the selective value of tumorigenic mutations in the body. On the other hand, when the blue whale genome is eventually sequenced, we would not be surprised if it contains more copies of p53.

## The consequences of cancer selection

The idea that cancer selection is an inevitable consequence of morphological and life-history evolution has several consequences. First, it implies that anticancer adaptations are ubiquitous. Already many such putative adaptations have been identified. Some, such as dark skins in Africans, suntanning in hammerhead sharks and the deep location of epidermal stem cells in most mammals, are thought to reduce mutation rates[14,66,67]. Others, such as topology of stem-cell lineages and angiogenesis inhibitors, are thought to reduce the selective advantage of neoplastic lineages[30,68,69]. Many more traits like this will probably be identified; proving their adaptive value is another matter.

Second, cancer might be yet another selective influence on the evolution of body size and life-history in addition to the many others that are already well known: sexual selection, selection by predators, selection for high fecundity and so on.

Finally, the theory of cancer selection might have implications for the use of model organisms in the study of cancer. It implies that the very properties of model organisms — short life and small body size — that make them useful in the laboratory, also make them poor models for the study of human cancers. Whether this is true in practise is hard to say. Although mice might turn out to be poor models for a specific cancer, many anticancer adaptations are surely general to all animals that are larger than a worm.

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