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Lineage selection and the evolution of multistage carcinogenesis

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A wide array of proto-oncogenes and tumour suppressor genes are involved in the prevention of cancer. Each form of cancer requires mutations in a characteristic group of genes, but no single group controls all cancers. This lack of generality shows that the control of cancer is not an ancient, fixed property of cells. By contrast, it supports a dynamic evolutionary model, whereby genetic controls over unregulated cell growth are recruited independently through evolutionary time in different tissues within different taxa. The complexity of this genetic control can be predicted from a population genetic model of lineage selection driven by the detrimental fitness effects of cancer. Cancer occurs because the genetic control of cell growth is vulnerable to somatic mutations (or 'hits'), particularly in large, continuously dividing tissues. Thus, compared to small rodents, humans must have evolved more complex genetic controls over cell growth in at least some of their tissues because of their greater size and longevity; an expectation relevant to the application of mouse data to humans. Similarly, the 'two-hit' model so successfully applied to retinoblastoma, which originates in a small embryonic tissue, is unlikely to be generally applicable to other human cancers; instead, more complex scenarios are expected to dominate, with complexity depending upon a tissue's size and its pattern of proliferation.

Keywords: body size; cancer; retinoblastoma; somatic mutation; tumerigenesis; population genetics

1. INTRODUCTION

Non-familial cancer results from somatic mutations in critical proto-oncogenes and/or tumour suppressor genes within a particular cell lineage. Since the number of somatic mutations occurring in a cell lineage increases with the number of cell divisions, the much greater size and longevity of humans relative to mice should result in a vastly greater incidence of cancer in humans (Peto 1977). This vast difference is not observed and Peto's paradox is difficult to resolve if the cellular mechanisms preventing cancer are viewed as fixed properties of cells (see Loeb 1991; Harris 1995). However, an alternative view is that these cellular mechanisms evolve in response to selection resulting from the detrimental effects of cancer. Under this view the paradox disappears, since selection will act independently in both species to reduce the incidence of the cancers that lower Darwinian fitness. The data support the possibility of important differences in the genes involved in cancers in the two species (for example, see Goodrow 1996); differences that are superimposed upon their many similarities. Similarities between humans and rodents are expected under the evolutionary model because (i) many of the control systems preventing the unregulated cell division that leads to cancer must pre-date the split of rodents and primates; and (ii) any evolutionary change must exploit the available genetic variation and it is to be expected that, in general, a rather limited group of genes would create this variability.

Cancer is a by-product of one of the major evolutionary advances, the advent of multicellularity (Maynard Smith & Szathmáry 1995). The somatic cells of a multicellular animal are clonal and sacrifice their own reproductive potential for the common good of the germ line. The theory of kin selection (Hamilton 1964) allows us to view these somatic cells as kin-selected altruists, since cooperation is advantageous to the survival of the 'group' of related cells (the multicellular individual) over the long term. However, there still exists a potential conflict between the cellular level and the individual level: the short-term success of a cell derives from its proliferation within the individual, whereas its long-term success depends upon the survival and reproduction of the individual. The existence of multicellular organisms shows that this conflict is resolved in favour of the individual but, whenever such conflicts of short- and long-term benefit arise, we expect to see the occasional occurrence of selfish 'cheats' that exhibit antisocial characteristics (Maynard Smith 1964). In the case of multicellularity, these cheats are cancer cells.

2. LINEAGE SELECTION

The resolution of conflicts in favour of long-term selection benefiting the group, rather than in favour of shorter-term selection benefiting its selfish components, depends on the evolution of mechanisms that protect the group from the invasion of selfish cheats (Nunney 1985). Cheats may originate either from outside of the group, e.g. a foreign queen invading an established honeybee colony, or, as in the case of cancer cells, they may originate by mutation from within the group. Thus, to understand the suppression of cancer we need to understand

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the evolutionary dynamics of group protection against cheats that arise internally.

In the case of cancer, the dynamics of group protection derive from a conflict between the cellular and individual level, but analogous dynamics can arise in the conflict between the individual and species level. For example, I previously examined (Nunney 1989) the question whether sexual reproduction can be maintained by natural selection when it provides a long-term advantage (a low extinction rate), that is offset by a short-term disadvantage (generally referred to as the twofold cost of sex; Maynard Smith 1971). I showed that maintenance is possible because natural selection acts over the long term to decrease the frequency of asexual mutants arising within species, and consequently increase group protection against cheats. This occurs through a process of 'lineage selection' that acts on differences in the genetic architecture among the various species lineages to preserve those lineages that are least likely to give rise to asexual mutants.

Lineage selection favours long-term fitness whenever there is a conflict between the short- and long-term effects of selection, provided that long-term lineages exist. The selection acts at the level of these lineages; hence, in the case of cancer prevention, it is a form of individual selection, whereas in the preceding example it is a form of group or species selection. Lineage selection affects genetic variation among lineages in two ways. First, it favours changes in genetic architecture that reduce the likelihood of a 'selfish' mutant phenotype arising, as described in the example of sexual reproduction. Second, it also favours variation that suppresses the detrimental effects of a selfish phenotype. This second effect promotes policing strategies (Frank 1995) and, in the specific context of cancer, favours individuals (lineages) with an immune system capable of recognizing and destroying cancer cells (cheats), supporting the view that this is an important evolved role of the immune system (McKean & Zuk 1995). Here, I focus on the first effect and, in particular, on qualitative variation in the mechanism of cellular growth control, variation that alters the likelihood of a cancer cell arising through somatic mutation.

3. A POPULATION GENETIC MODEL

There is now strong evidence that most cancers are indeed initiated as the result of a chain of mutational events, involving two (Knudson 1971) or more steps (reviewed by Loeb 1991; Knudson 1993). These steps generally involve dominant mutations in proto-oncogenes (Hunter 1991) and/or recessive mutations in tumour suppressor genes (Yokota 1994). After this initiation, pre-cancerous clones go through a continuing process of selection that favours cells more adapted to both growth and avoiding the body's defences (see Shackney & Shankey 1993). However, here I am concerned only with the initial chain of events that relaxes control over unregulated growth. This process is often assumed to be an intrinsic property of cells; however, viewed from an evolutionary perspective it can be seen that this is not possible. I will show that the levels of somatic mutation experienced by a small animal, such as the nematode *Caenorhabditis elegans*, and a large animal like us, are so different that no mechanism appropriate to the prevention of cancer in one would be evolutionarily stable in the other. Even within a species, variation across tissues is expected because lineage selection will act primarily to suppress the particular cancer causing the greatest loss of fitness. The response to such selection could be highly tissue specific, leading to more complex controls in cell types that divide the most and/or are subject to environmental mutagens, e.g. epithelial tissues (Frame *et al.* 1998).

To examine the evolution of cancer suppression, consider an organism that, when mature, has C cells of a particular tissue type that continue to proliferate after reaching full size, with each cell then undergoing a further K cycles of cell division. The tissue is vulnerable to a mutation-induced lethal cancer. The initiation of cancerous growth is prevented by some combination of proto-oncogenes that exert positive control over growth and the tumour suppressor genes that provide negative control. At each cell division the chance of somatic mutation in a copy of one of these genes is u per daughter cell.

The occurrence of cancer creates a selective differential (s) favouring any enhanced cellular control that reduces the incidence of the cancer. For a cancer that is lethal before reproductive age, s equals the probability (p) of cancer occurring. For a late-acting cancer, $s < p$. In either case, natural selection is effective only when s is large enough to overcome the random influence of genetic drift (Wright 1931). Selection can overcome drift provided that (approximately) $N_e s > 1$, where N_e is the effective size of the population. In a population with N adults, N_e is often expected to be around $N/2$ if N is constant, but is likely to be closer to $N/10$ if the population size fluctuates (Nunney & Campbell 1993). In the numerical examples that follow, I will use $N_e = 10^4$ to represent a fairly large population.

The simplest growth-control model is one in which cell growth is regulated by a single proto-oncogene that, in its normal function, responds to a growth signal and initiates cellular proliferation. However, mutations can cause the gene product to respond to inappropriate signals and cause the cell to divide. Such mutations are dominant. Assuming geometric cell growth, the expected number of mutations in the gene across all cells of the tissue during its growth is $4(C-1)u$, i.e. two gene copies × two daughter cells × number ofdivisions × probability of mutation. Based on the Poisson distribution, the expected proportion of individuals lacking this mutation is $e^{-4u(C-1)}$. Thus, for an early-onset cancer, the selection against individuals with single proto-oncogene control, relative to those completely lacking cancers, is $s = p = 1 - e^{-4u(C-1)}$. Selection for increased growth regulation will be effective if $s > 1/N_e$. For even moderately sized animals, this inequality is almost always true. For example, if $u = 10^{-7}$ and $C = 10^3$, about the number of cells in *C. elegans*, the inequality is satisfied for $N_e > 2500$. However, for $C = 5 \times 10^6$, about the number of cells in *Drosophila melanogaster*, the inequality is satisfied for $N_e > 1$! Thus, early in the development of multicellularity, growth regulation involving more than a single oncogene would have evolved; otherwise almost all developing embryos with tissues of more than a few thousand cells would die of cancer.

When $N_e s < 1$, the evolutionary effect of a cancer is said to be effectively neutral, since it no longer has significant fitness consequences in the population. However,

Table 1. *The probability of a cancerous cell arising under various genetic models for the control of cellular growth*

(The tissue consists of C cells, with a somatic mutation rate of u per daughter cell ($u=4\times10^{-7}$ in the numerical examples). In the examples, a probability in bold indicates an evolutionary unstable condition, with cancer sufficiently common to drive selection for increased regulation; an underlined probability indicates no effective selection, assuming $N_e\leqslant10^4$. Under exponential growth, with k cycles of cell growth and negligible subsequent cell division, the two examples compare a hypothetical small tissue in a rat-sized mammal ($C=4.10^8=2^k$, $k=28.58$) to a roughly proportionate tissue in a human ($C=10^{11}$, $k=36.54$). Stem cell growth is modelled with K cycles of daughter cell production, assuming that only the persistent stem cells are capable of becoming cancerous. Two examples consider a human tissue of 10^{11} cells that divides every 90 days ($K=60$) or every six days ($K=900$) over a 15-year pre-reproductive period. The stem cell calculations are corrected for early mutations by using $K'=K+k/2$.)

	probability of cancer					
	exponential tissue growth			stem cell division ($C=10^{11}$ cells)		
genetic basis of growth control	generally[c]	$C=4.10^8$ small mammal	$C=10^{11}$ large mammal	generally	$K=60$ slow division	$K=900$ rapid division
two dominant genes	$8(2k-3)u^2C$	**0.0277**	**1.000**[a]	$(2K'u)^2C$	**1.000**[b]	**1.000**[b]
one recessive gene	$2(2k-3)u^2C$	**0.0069**	**1.000**[a]	$(K'u)^2C$	**1.000**[b]	**1.000**[b]
three dominant genes	$16(3k^2-9k+13)u^3C$	$\underline{9.7\times10^{-7}}$	4.0×10^{-4}	$(2K'u)^3C$	**0.0246**	**1.000**[b]
one recessive & one dominant gene	$4(3k^2-9k+13)u^3C$	$\underline{2.4\times10^{-7}}$	1.0×10^{-4}	$2(K'u)^3C$	**0.0061**	**1.000**[b]
four dominant genes	$64(2k^3-9k^2+50k-75)u^4C$	$\underline{2.7\times10^{-11}}$	$\underline{1.4\times10^{-8}}$	$(2K'u)^4C$	$\underline{1.5\times10^{-6}}$	**0.0291**
two recessive genes	$4(2k^3-9k^2+50k-75)u^4C$	$\underline{1.7\times10^{-12}}$	$\underline{8.8\times10^{-10}}$	$(K'u)^4C$	$\underline{9.6\times10^{-8}}$	**0.0018**

[a]The general exponential growth formula is not used since it is only accurate given $1\gg p$.
[b]When p is large, an accurate stem cell estimate is given using equation (2*a*) in place of (2*b*).
[c] More exact relationships than equation (1); see text.

when $N_e s>1$, lineage selection favours increased levels of cellular growth control. Growth control can be enhanced by combining the effects of proto-oncogenes and/or tumour suppressor genes. For each size of tissue, we can estimate minimum and maximum number of growth controls likely to be recruited by considering two extreme cases: the minimum number of controls is expected in a tissue that has minimal post-development division, i.e. the risk of cancer occurs early in development when the tissue is growing approximately exponentially; and the maximum number of controls is expected in a tissue where stem cells continue to divide throughout the life of the organism (table 1). This is in accord with the observation that embryonal cancers require the fewest mutations and those of renewal (stem cell) tissues the most (Knudson 1993).

This evolutionary model can be used to support Knudson's (1971) 'two-hit' model for retinoblastoma, a tumour of the retina that is generally inherited. He proposed that individuals with the inherited form of the disease carry a recessive mutation in the *RB1* tumour suppressor gene, and that somatic mutation of the second copy initiated tumours. Hethcote & Knudson (1978) modelled this process and estimated a somatic mutation rate in *RB1* of 4×10^{-7} per daughter cell ($=u$) in the pair of retinoblasts that reach a combined size of approximately 4×10^6 cells ($=C=2^k$; $k=21.93$). The probability of both copies of *RB1* mutating to yield a cancerous cell is $p=2(2k-3)u^2C$ (see table 1), giving $p=0.00005$, i.e. 1/20 000, which is in good agreement with the observed rate of non-familial cases. On the other hand, for those carrying the recessive mutation, the probability of the second mutation is given by $1-\exp(-2uC)=0.96$, with a mean number of mutations of 3.2. Thus, as originally noted by Knudson (1971), the effect of somatic mutation is so strong that almost every individual (96%) carrying the recessive mutation will develop the disease. However, we can take this logic one step further. The selection to recruit further protection against this disease is very weak, since the maximum selection (assuming the disease is always lethal) is $s=0.000\,05$.

The source tissue for retinoblastoma is unusual in that (i) it is extremely small, and (ii) it does not continue to divide throughout life. What if the tissue is larger? Formulae defining the incidence of cancer (p) allow us to determine when selection is too weak to recruit additional safeguards. In a growing tissue that exhibits minimal post-development growth, the incidence of cancer, when rare, is approximated by the formula

$$p=2\,MC(k-1)^{M-1}\prod_{i=1\ldots M}(2^{D_i}u_i), \qquad (1)$$

where M is the number of mutations needed for cancer initiation and u_i is the per locus rate for each mutation, with $D_i=1$ if the mutation is dominant, or else $D_i=0$. Precise formulae for $p\ll1$ and $C\gg1$ are given table 1. These are calculated by summing the probability of all possible mutational orderings within the expanding population of cells, e.g. for the two-hit model, sum the probability of both mutations in the same daughter cell over all cells, and add to that the probability, summed over all daughter cells, of the first mutation occurring in a given cell with the second mutation occurring later in the same cell lineage.

If the tissue continues to divide as a stem cell population then

$$p = 1 - \left[1 - \prod_{i=1\ldots M} (1 - \exp(-(1 + D_i)u_i K))\right]^C, \qquad (2a)$$

noting that the term raised to the power C is the probability that, in a given cell line, all M mutations do not occur; hence p is the probability that at least one cell has all M mutations. For small p, equation (2*a*) can be simplified:

$$p = C \prod_{i=1\ldots M} (2^{D_i} K u_i). \qquad (2b)$$

Replacing K, the number of post-growth divisions, by $K' = K + k/2$ provides an approximate correction for mutations accumulated during the growth phase, since k is the number of divisions required for tissue growth.

Armitage & Doll (1954) modelled the effect of stem cell proliferation in essentially the same fashion (although they assumed that a specific ordering of the mutations was necessary). They were particularly interested in age-specific incidence of cancers. However, since K, the number of cell divisions, is proportional to t, the age of an individual, the results are related. By differentiating (equation (2*b*)), then we can derive their result that the age-specific incidence of cancer is proportional to t^{M-1}.

4. DISCUSSION

The equations (1) and (2) predict the expected incidence of cancer under specified conditions, with equation (1) being relevant for early onset cancers, where mutations accumulate through the growth phase, whereas equations (2) assumes later onset, with most mutational events occurring during the stem cell divisions of later life. However this division is a mathematical convenience and the general principles are applicable to any form of cancer. For a given level of cellular control, the likelihood of cancer is dependent upon the number of long-lived dividing cells, since it is assumed that only dividing cells can mutate. It also depends upon the somatic mutation rate. The estimated rate from the retinoblastoma data (Hethcote & Knudson 1978) is 4×10^{-7} per daughter cell, and I will use this value as the reference rate for the purposes of discussion. However, before applying this somatic rate, it is important to note that, in the case of a stable population of dividing stem cells, described by equations (2), the apparent mutation rate could be considerably higher.

The result (equations (2)) is conservative with respect to the number of mutations expected under specified conditions if there is a tendency for a mutated cell to form a stem-cell clone when only part of its division control system has been destroyed. Cairns (1975) emphasized the potentially important role of an early selective advantage to pre-malignant cells, a theme further developed by Tomlinson *et al*. (1996). Cairns (1975) noted that the physical arrangement of cells may inhibit such early clonal expansion and that in some cases, e.g. intestinal stem cells, particular structures may have been favoured by natural selection for this reason. Recently, Brash (1997) has pointed out that under some conditions early clonal expansion could occur without any selective advantage. He noted that local exposure of the skin to UV is likely to have two important consequences. First, the mutation rate will be elevated and most of the damaged stem cells will ultimately die; second, neighbouring cells with sublethal exposure (but still elevated mutation rate) expand to fill the void. This process provides the opportunity for the early clonal expansion of mutated cells. The effect of such clonal expansion would be to increase the number of cell divisions following a mutation, but in practice the effect could be viewed as an increase in the mutation rate. For example, if a cell proliferates to 1000 cells following a particular mutation, then the next mutation is 1000 times more likely. This kind of process may be relevant to the discussion over whether or not pre-malignant cells typically have elevated mutation rates (Loeb 1991; Strauss 1998).

Using equations (1) and (2), the success of any given model of cellular control can be evaluated under various conditions. Each model is defined by some combination of proto-oncogenes (which are vulnerable to dominant mutation) and tumour suppressor genes (which can only be disabled by two recessive mutations). As an example, consider the generality of the two-hit model defined by a single tumour suppressor gene. A tissue that is 100 times larger than the retinoblasts ($C = 4 \times 10^8$; see table 1) is still small (less than half a gram). Considering only cell division occurring during tissue growth, the two-hit model of regulation predicts a frequency of cancer ($p = 0.0069 = 1/144$) high enough to promote lineage selection for additional cell regulation. If this selection recruits an additional regulatory gene then the residual effect of selection is trivial and no further change would be expected. Since controls can only be added in integer steps, the three-step control that would protect such a tissue would also provide fairly good protection for a tissue some 250 times larger ($C = 10^{11}$; see table 1). Knudson (1993) suggested that Wilms' tumour, another childhood cancer, may arise following the breakdown of a three-hit control system.

Selection for additional controls becomes stronger when cells divide throughout life. For example, in a human tissue of $C = 10^{11}$ cells that divide about once every 90 days over a period of 15 years, a three-hit model is inadequate ($K = 60$; see table 1); and in a tissue that divides every six days ($K = 900$), even a four-hit model fails to effectively control cancer. Turnover rates of six days or less are found in a number of tissues (Cameron 1971). This raises the interesting question of why childhood cancers of proliferating tissues (such as chronic myeloid leukaemia, CML) do not continue to occur with increasing frequency in adulthood. One hypothesis is that regulation of future cell proliferation is different during development. It has been suggested in the case of CML that the primitive progenitors of the stem cells are susceptible to a relatively simple set of 'false' signals at some critical stage, yet these signals may have no effect later (Clarkson *et al*. 1997).

If the somatic mutation rate (u) is close to that estimated for the *RB1* gene, then in humans, the two-hit model will be restricted to small tissues that exhibit minimal post-development division, while control mechanisms resistant to more than four mutational hits may evolve in fairly large tissues that proliferate throughout life (table 1). These

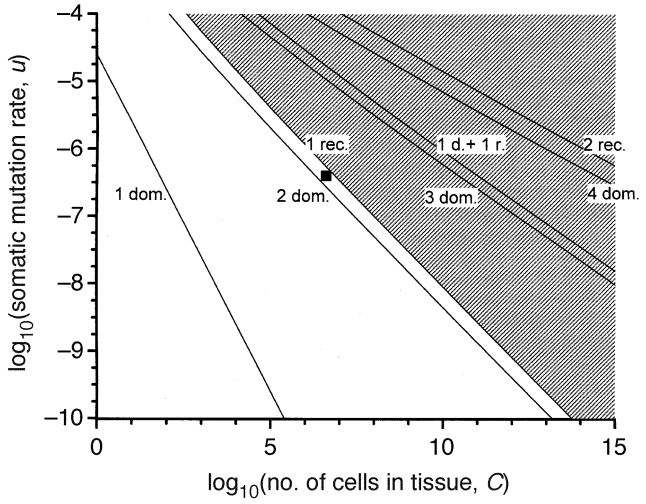

Figure 1. The effect of lineage selection due to cancers arising during exponential tissue growth. The line defining effective neutrality ($N_e s = 1$ for $N_e = 10^4$) is shown in terms of somatic mutation rate and tissue size for seven models of cellular growth regulation. Lineage selection promotes additional regulation above and to the right of each line. The shaded area defines this region for the two-hit model and the square shows the estimated position of retinoblast tissue. The models shown are one-hit (one dominant (1 dom.) gene), two-hit (2 dom. or one recessive (1 rec.) gene), three-hit (3 dom., or one dom. plus one rec. (1d. + 1r.)) and four-hit (4 dom. or 2 rec.).

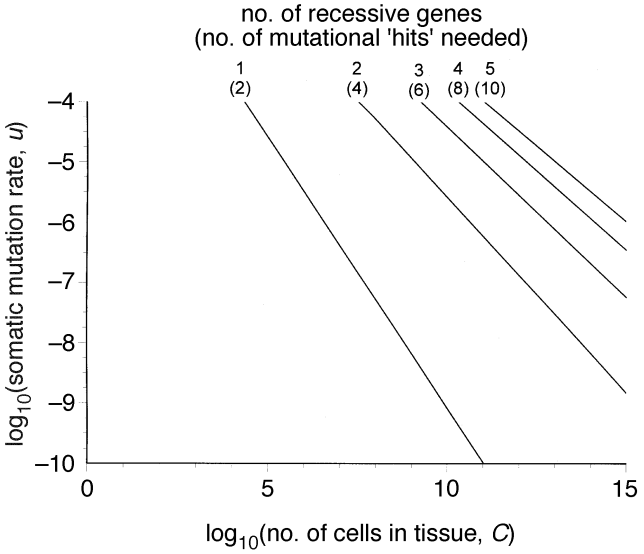

Figure 2. Lineage selection due to cancers arising from stem-cell proliferation. The line defining effective neutrality ($N_e s = 1$ for $N_e = 10^4$) is shown in terms of somatic mutation rate and tissue size for models with from one to five recessive tumour suppressor genes (i.e. two to ten mutational steps) controlling unregulated cell growth. The number of cell divisions (K) is scaled by $C^{0.4}$, relative to a reference of 300 divisions in a tissue of 10^{11} cells.

conclusions assume $u = 4 \times 10^{-7}$, but the general relationship between somatic mutation rate and tissue size in non-proliferating tissues is summarized in figure 1: the two-hit model is adequate only within the unshaded region. The parameters from retinoblastoma estimated by Hethcote & Knudson (1978) place the tissue at its expected location, just within this region.

Increased longevity (increased K) and increased mutation rate (increased u) both affect the likelihood of cancer in the same way ($(Ku)^M$; see equations (2)), so that an increase in either is amplified by the number of mutations (M) necessary to destroy cellular control. This predicts that cancers of large tissues of proliferating cells (which have the largest M) are much more susceptible to non-specific changes in mutation rate than are cancers of smaller or less rapidly dividing tissues. Consistent with this is the observation that inherited DNA repair abnormalities increase the incidence of such cancers: lymphoma, leukaemia, skin cancer and colon cancer (Hall *et al.* 1995). Longevity is expected to have the same effect; however, this is a much weaker effect: mutation rates increased by a factor of 5 would have a 625-fold effect on the baseline frequency of a four-hit cancer, but longevity is more realistically increased by a factor like 30%, which has only a threefold effect.

Increases in size (C) increase the likelihood of rare cancers in an approximately linear fashion (see equations (1) and (2)). This is a weak effect, only promoting genetic change close to the boundaries shown in figure 1. However, over evolutionary time, increases in size are usually associated with an increase in longevity, which generates much stronger selection for new cellular control mechanisms. On average, generation time increases with body size approximately as $(\text{size})^{0.4}$ (Fenchel 1974). As a result, the prevention of cancer in rapidly proliferating tissues becomes increasingly difficult as the size of an animal increases (figure 2), requiring the accelerating recruitment of additional controls. This pattern may represent a real barrier to the evolution of large, long-lived animals and predicts that those that do evolve (e.g. whales) have recruited additional controls to prevent cancer.

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