Quantitative implications of the approximate irrelevance of mammalian body size and lifespan to lifelong cancer risk

Richard Peto

Nuffield Department of Population Health, Oxford University, Oxford, UK

The probability of cancer developing within the normal lifespan of a species seems to be of comparable magnitude for small, short-lived mammals such as laboratory mice and for large, long-lived mammals such as humans, or even whales. From an evolutionary point of view, of course, this observation makes good sense; evolutionary pressure will tend to ensure that cancer incidence rates are relatively low up to the reproductive and child-caring years, but not beyond (as avoiding cancer in old age by excessive checks on cell division at earlier ages could retard growth, delaying reproduction).

Turning, however, from evolutionary perspectives to biochemical mechanisms, there are two reasons why this superficially unremarkable comparability of lifelong cancer risks demands some extremely remarkable mechanistic explanation(s) [1,2]. The first reason is obviously the 10-million-fold difference in body mass between a 20 g mouse and a 200-ton blue whale (so each mouse-sized piece of blue whale tissue must in some sense be about ten million times more cancer-proof than a mouse-sized piece of mouse tissue).

The second and somewhat less obvious reason is that the lifespan of a laboratory mouse is only about 2.5 years while that of a human or whale is about 80 years, which represents five doublings of the mouse lifespan. At first sight this 32-fold difference in lifespan may seem less important than the 3000-fold difference in body mass between mouse and human or the 3000-fold difference in body mass between human and blue whale, but in some ways it is numerically even more important.

This is because for many types of cancer (particularly carcinomas of epithelial cells in organs such as the stomach or intestine that are common to both sexes, and are therefore little affected by age-related changes in sex hormone levels), the risk of developing the disease before a given age increases steeply with age, and for some common types of cancer it is proportional to the sixth power of age. Thus, it is given approximately by the formula $Ct^6$, in which a constant of proportionality $C$ that determines susceptibility to cancer induction is multiplied by the sixth power of the age in years, $t$. (N.B. By differentiating this formula, it can be seen that the incidence rate is approximately proportional to the fifth power of age.) This sixth-power formula for risk means that doubling the time available for such a cancer to arise produces not just a twofold difference in risk but about six twofold differences in risk, i.e. about a 64-fold difference in risk. As the 80-year lifespan of long-lived animals such as blue whales or humans differs by five doublings from the 2.5-year lifespan of a laboratory mouse, the constant $C$ relating risk to the sixth power of time has to be about a billion-fold smaller ($5/C^6 = 30$ powers of $2$) in humans than in mice for the two species to have comparable lifelong risks of developing cancer.

Combining this approximately billion-fold factor reflecting the effects of differences in lifespan between humans and mice, and the approximately 3000-fold factor reflecting differences in body size, if the risk per gram of tissue is written as $k$ times $t^6$ for humans and $K$ times $t^6$ for mice, then $k$ is about 3 trillion times smaller than $K$. These constants of proportionality are

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directly proportional to cancer incidence rates, so, gram for gram, human tissue is in some real sense about 3 trillion times less susceptible to cancer induction than mouse tissue.

To illustrate that these constants of proportionality do directly determine real cancer incidence rates, consider a 60 kg person with risk $k^t$ per gram of tissue by age $t$ years, and consider the effects of twofold variation in $k$. If $k = 10^{-17}$, then the risk by age 80 would be 1 in 6, if $k = 2 \times 10^{-17}$ then this risk would be 1 in 3, and if $k = 0.5 \times 10^{-17}$ then this risk would be 1 in 12. Thus, twofold differences in $k$ really matter; doubling $k$ doubles the risk of getting cancer, and halving $k$ halves it. Yet, $k$ for human tissue differs from $K$ for mouse tissue not by a factor of 2, but by a factor of about a trillion. By what biological mechanisms does evolution produce trillion-fold differences between species in this constant of proportionality, which are essential for large body size and long lifespan to exist? Do those mechanisms operate within the cell, within the local stem cell architecture or in the whole animal?

It has long been recognized that a power-law relationship between risk and age could be produced by a multi-stage model in which the process of changing a normal epithelial stem cell into the seed of a growing cancer involves several consecutive changes in the genetic material of that cell, with the rate-constants governing progression of a partially altered cell from one stage to the next being largely unaffected by age [3,4].

If there are six stages that are rate-limiting (i.e. improbable in the time available), then the risk of developing cancer before a certain age would be expected to be approximately proportional to the sixth power of age [1,3], which is consistent with what is observed for some types of cancer. (Note that if six cellular changes all have to happen to get cancer by a certain age, then by half that age each of those six changes would have had only half as long to happen, and the probability of all of them happening would be halved six times.) It was soon recognized, however, that roughly the same sixth-power relation with age would be predicted by many different hypothetical models [1], some having fewer stages but some selective advantage of partially altered cells over their unaltered neighbours [4], and some having more stages but susceptibility to neoplastic change varying substantially between individuals [2]. Hence, these early multi-stage models could not even predict the number of rate-limiting steps needed to go from a normal to a fully neoplastic cell, let alone what heritable cellular changes those steps actually involved. They did, however, suffice to show that the 1000-fold differences in cancer rates between old and young adults that had already been noted did not necessarily imply any effect of ageing itself on the separate cellular processes leading to cancer. This conclusion has been confirmed by animal experiments in which carcinogenic treatments were started at different ages. In some (despite a power-law relation of risk to the duration of regular treatment), age was of no independent relevance to the production of cancer [1,2,5], and in others carcinogenic treatments actually elicited cancer somewhat less rapidly in older than in younger animals [1,2,6,7].

Ever since multi-stage models for the process of changing a normal cell into the seed of a growing cancer were proposed in the 1950s [3,4,8], this trillion-fold difference, or something roughly equivalent to it, has puzzled many scientists (R. Doll, personal communication). I came across it in the late 1960s when Doll, investigating the age distribution of human cancer, was arguing that age itself did not materially affect the processes of carcinogenesis [9,10], a null result that we confirmed for mouse skin carcinogenesis [5] and for smoking and lung cancer [11,12]. The lack of any direct effect of ageing, whatever that might mean, on the mechanisms of production of the common carcinomas served, however, to sharpen discussion of what did cause the trillion-fold species differences in cancer susceptibility. As my name began with P, the problem of the approximate irrelevance of mammalian body size and lifespan to cancer risk happened to become known alliteratively as Peto’s paradox, but could more appropriately have become known as Doll’s dilemma [10] or Cairns’ conundrum [13], as both of them had emphasized how important it was to understand this properly.

Although the issue has been discussed for decades, it could not previously be investigated properly because far too little was known about normal cell biology, cancer cell genetics, mammalian stem cell kinetics and the many mechanisms for avoiding accumulation of permanently fixed mutations in stem cells. Now, however, as the papers in this theme issue show, the question is starting to be addressed successfully by observation and experiment, informed by increasingly detailed species-specific knowledge of genotypes, DNA repair mechanisms and stem cell biology. But, although the papers in the present issue go some way towards explaining the enormous differences between species in the susceptibility of their tissues to carcinogenesis, there is still far to go if the numerical effects of both body size and lifespan on cancer incidence rates are to be fully accounted for.

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