

OPINION

## Darwinian medicine: a case for cancer

Mel Greaves

Abstract | Epidemiological, genetic and molecular biological studies have collectively provided us with a rich source of data that underpins our current understanding of the aetiology and molecular pathogenesis of cancer. But this perspective focuses on proximate mechanisms, and does not provide an adequate explanation for the prevalence of tumours and cancer in animal species or what seems to be the striking vulnerability of *Homo sapiens*. The central precept of Darwinian medicine is that vulnerability to cancer, and other major diseases, arises at least in part as a consequence of the 'design' limitations, compromises and trade-offs that characterize evolutionary processes.

*No biological problem is solved until both the proximate and the evolutionary causation has been elucidated. Furthermore, the study of evolutionary causes is as legitimate a part of biology as is the study of the usually physico-chemical proximate causes.*

E. Mayr, 1982 (*The Growth of Biological Thought*)

A pragmatic focus on immediate, or proximate, causal mechanisms in cancer has been very productive. Epidemiologists identify cause as, for example, chronic exposure to cigarette tar, and molecular biologists indict gene mutations as mechanistic drivers. In turn, these insights provide genuine, practical advances in prevention, screening, differential diagnosis, prognosis and innovative treatments. We should all be happy. But there are two difficulties here, both related to our expectations of what the word 'cause' actually means and what level of understanding we aspire to. Environmental exposures and mutations are self-evidently not autonomous entities, but crucial components of a causal chain of events or components of a causal network. Second, even with a more realistic compound view of risk factors and molecular, biochemical mechanisms that produce cancer, we might still lack a coherent framework that can help us understand

vulnerability. Why should potentially lethal cancer be such a common biological phenomenon, and why do we, as a species, seem to be especially vulnerable? Why is the lifetime risk of breast cancer as high as one in ten? And, superimposed on what seems to be a species vulnerability, why are some individuals more at risk of particular cancers than others?

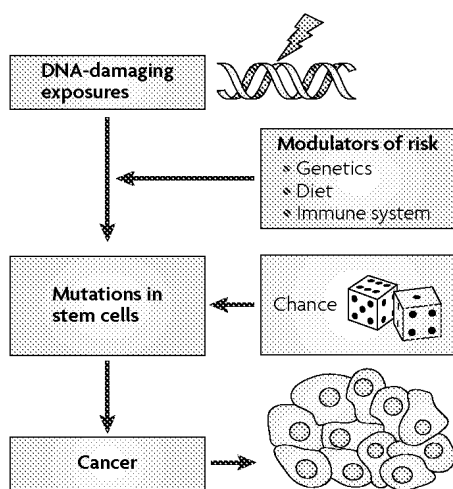
The lifetime risk of a clinical cancer diagnosis in humans is around one in three. Each year more than 10 million cases are diagnosed<sup>3</sup>. These are distributed roughly equally between the developed and less affluent societies, although with marked differences in cancer type; infection-related cases being considerably more common in the developing world<sup>4,5</sup>. Medical reports from antiquity and contemporary paleopathology studies do not provide cancer rates but they do tell us that cancer, for example of the bone, breast, cervix or uterus, certainly existed 2,000 or more years ago<sup>6–8</sup>. But the diagnosis of cancer, even with the battery of tests available today, underestimates its biological frequency. Autopsy histopathology on individuals dying of non-cancer causes have shown a strikingly high prevalence of covert malignant cancers or pre-malignant carcinomas *in situ* in the prostate, thyroid, kidney, breast and other

sites<sup>9–11</sup>. Oncogene-specific mutations within clonally expanded cell populations can now be detected by sensitive molecular methods that penetrate beyond the histopathological visualization of tumours. The application of such methods has shown that mutant clones are in all of us<sup>12–15</sup>, although clearly, and fortunately, most never see the light of day, clinically. The frequency of cryptic cancer clones increases with age, but even before birth paediatric cancers can be initiated at a much higher frequency (~100×) than is manifested in the overt disease rate<sup>16</sup>. The emergence of malignant or pre-malignant clones of cancer cells in humans seems to be ubiquitous. Which prompts the question: why is clinical cancer not even more common? Even so, why do we seem to be so extraordinarily vulnerable? A comparison with animal species is instructive.

Species in all vertebrate classes develop tumours and cancer<sup>17</sup>, and might always have done so, as suggested by evidence of tumours or metastatic cancer in fossils of dinosaurs from the Jurassic period<sup>18,19</sup>. Molluscs and other invertebrate species also harbour tumours<sup>20,21</sup>. Identified genes in *Drosophila* species and nematodes can control malignant cellular expansion<sup>22,23</sup>. Multicellularity requires the social cohesion of cells and the severe prohibition of clonal escape; in this context cancer seems to be a reversion to previous unicellular selfishness<sup>8</sup>. But what is its natural prevalence? Reliable population-based cancer incidence rate data on animal species is lacking. Limited data are available on wild animals where viral infections might have a prominent aetiological role<sup>24,25</sup>. More substantial data exist on captive or domesticated animals through veterinary pathology<sup>26–28</sup>, and indicate, overall, only a modest although significant rate of both benign and malignant cancers that increases with age<sup>29</sup>. Available data from zoos does not indicate a high rate of epithelial carcinomas in species with pronounced longevity, such as elephants and higher apes<sup>30,31</sup>. There have been few systematic autopsy-based histopathological screens to determine the prevalence of clinically covert cancers in animal species, as in humans, although abattoir records attest to the presence of

such cancers in horses at a rate considerably in excess of clinical diagnoses (~11% versus 2%)<sup>32</sup>. Autopsies on several thousand non-human primates suggest a low rate of cancers, ~1–2%, the frequency of which increases with age<sup>33</sup>.

These data suggest that a propensity to develop benign tumours and malignant cancer is a common feature of multicellular animals and that, although intrinsic risk or actual spontaneous rates might be expected to escalate with increasing complexity and longevity, these features alone do not adequately account for the vulnerability of *Homo sapiens*, which seems substantially greater than that seen in other mammals including the great apes. Some of the apparent difference in vulnerability between humans and great apes might be due to genetic and developmental



**Figure 1 | The cancer lottery.** The process of tumorigenesis is essentially a lottery. Epidemiologists might see this as less than 100% penetrance of disease in a group of highly exposed individuals; for example, only one in ten persistent high level smokers develop lung cancer. There is a biological rationale for this. Cancer can only emerge if a relevant gene is functionally mutated in a relevant cell. One per cent of our genes might be 'relevant' in this context, along with perhaps 0.1% of our cells. Exogenous or endogenous genotoxic exposures are almost entirely blind to gene or cellular functions, and are therefore indiscriminate with respect to these criteria. What we see in cancer clone mutants must be distilled or selected from a huge sea of noise — as in evolution (through germ-cell mutation) itself. Genetics: inherited allelic variation, for example, in genes and signal networks that underpin functions such as detoxification, DNA repair and immune recognition. Diet: the pattern of intake of total calories plus particular ingredients (for example, antioxidants and folates) coupled with energy usage through physical activity. Immune system: for example, surveillance against viruses.

differences<sup>34,35</sup>. However there are some striking and informative examples of animals with high rates of cancer, all related to human ingenuity: inbreeding and ageing in captivity (in ferrets)<sup>36</sup>, inbreeding and unnatural reproductive or growth histories (breast cancer and osteosarcoma in particular dog breeds)<sup>29,34</sup>, exposure to man-made carcinogens (beluga whales in the St Lawrence estuary)<sup>37</sup>, ovarian cancer in battery hens exposed to constant light<sup>8</sup> and mammary and uterine cancers in captive felines given contraceptives<sup>31</sup>.

Overall, these data suggest that cancer risk is underpinned by intrinsic fallibility, and that risk increases with increasing age and is greatly exacerbated by some aspects of human activity.

### Evolutionary medicine and cancer

Any engineer confronted with a recurring fault in a complex machine or plant would look not only at the immediate source and cause of the fault, but at system design, its compromises and limitations. The engineer will resort to a blueprint; we have evolutionary biology.

The essential tenet of the new discipline of evolutionary or Darwinian medicine is that susceptibility to malfunction and disease must in part reflect historical or evolutionary legacies<sup>38,39</sup>. The corollary is that we might then benefit from stepping back to take a broader look at human history and our protracted evolutionary trajectory. Even a cursory consideration of human anatomy reveals structural imperfections that are pregnant with potential for malfunction. For example, no intelligent designer would place the optic nerve and retina or prostate and urethra in the anatomical relationships in which we find them. The reality is of course that we have not been 'designed' or 'engineered' at all. The evolutionary processes involved in the diversification of molecules, cells, tissues and physiological processes rely on options generated randomly from previous templates. This is coupled with the selection of beneficial traits, by contingency or chance, or neutral drift. Evolutionary biologists continue to debate the relative importance of the mechanisms of selection, particularly as claims that traits were positively selected (the adaptationist argument) cannot always be substantiated. Irrespective of these uncertainties, the processes involved will inevitably result in 'designs' that have constraints or limitations on board, and trade-offs, collateral damage or negative impacts. Ultimately, inherent flaws are tolerated, at some level, as long as they do not impact deleteriously on reproductive fitness.

A systematic attempt to use the concepts of evolutionary biology to elucidate human vulnerability to disease has been long in coming. An important publication in this field was the 1991 review entitled 'The Dawn of Darwinian Medicine' by Randolph Nesse, an insightful physician, and George Williams, a distinguished evolutionary biologist<sup>38</sup>. In the years that followed its publication, evidence supporting the credibility of this perspective on health and illness has accumulated and the argument advanced that there are few areas of medical education, research or practice that cannot be enriched by such an evolutionary view, including the scourges of obesity, heart disease, diabetes, the enigma of female menopause, ageing and cancer<sup>8,40–44</sup>.

Inevitably, the strength of the argument for an evolutionary perspective varies from disease to disease. It is strongest for infectious diseases where there is compelling evidence that our confrontations with microbes over the past millennia have resulted in evolutionary arms races and the selection of both human and microbial genetic variants<sup>43</sup>. Similarly, the hugely problematic development of resistance to antibiotics — or cancer chemotherapeutics — is governed by Darwinian natural selection, an inevitable consequence of genetic diversity and selective pressure. Cancer biologists and most clinical oncologists are very familiar with the Darwinian picture of cancer clone evolution as introduced by Peter Nowell<sup>45</sup>. This has profound implications for the natural history of the disease, prognosis and drug resistance<sup>8,46,47</sup>. Here I advocate a broader evolutionary view of cancer, and explore the extent to which such a perspective might help explain why tumours are so widespread in animal species and, in particular, why human beings seem to be at such high risk.

### Evolutionary ground rules

I start with a perspective of the immediate or proximate mechanisms of cancer cause that acknowledges significantly more complexity and multi-functionality than mutation-driven clonal expansion (FIG. 1). The view is not dissimilar to the evolutionary emergence of new variants or species — a highly filtered outcome of a genetic lottery<sup>48</sup>. The question then becomes: what evolutionary logic might there be in 'winning', or rather losing, lottery numbers coming up so often?

There are many features or principles of evolution that can affect the risk of disease<sup>49,50</sup>. I have selected four for analysis in the context of cancer (TABLE 1).

### Lack of perfection in evolution

It is commonly assumed that evolution operates to increase efficiency, edging inevitably towards perfection. This is an optimistic and incorrect view; all natural selection can ever do is to select from the best or 'fittest' options available, and these are constrained by previous templates available for modification. A consequence is that emergent adaptations, or features that become prevalent through founder effects or neutral drift<sup>51</sup>, might be stable and relatively — or even very — effective, but with inherent 'design' limitations and potential flaws. Such flaws are tolerated and persist as long as they do not have a deleterious effect on reproductive fitness, but there might be circumstances in which inherent weaknesses are teased out.

Useful or crucial evolutionary adaptations that have 'design' constraints or pleiotypic effects that positively affect cancer risk are discussed below.

#### *The intrinsic mutability and recombination capacity of DNA, and the incomplete fidelity of repair.*

At least 1% of our coding genes, or more than 350 genes, can, as mutants, contribute to cancer clone evolution<sup>52,53</sup>. Mutations are accidents, but are they avoidable? The capacity for accidental or random changes in the information content of the genome, in germ cells, occurs or is 'set' at a variable but generally low level that might be a compromise between the generation of potentially adaptive variation and deleterious mutants<sup>54</sup>. No variation — no evolution. But the trade-off has to be occasional deleterious mutations that might include those that can initiate cancer through the germline transmission of non-lethal mutations, for example in suppressor genes<sup>55</sup>, or equivalent primer mutations in somatic stem cells. DNA damage occurs constantly, either spontaneously during DNA replication or in the face of endogenously- or exogenously-derived chemical insults. These are balanced with efficacious DNA-repair functions, but still result in a net vulnerability<sup>54</sup>. Every round of cell proliferation involves the serious challenge of faithfully copying the entire genome. Proof-reading DNA polymerases significantly limit errors in nucleotide incorporation, but they are not error free. The average net mutation rate for single base changes is about  $10^{-9}$  per replicative cycle of somatic cells in humans<sup>56</sup>. Double-strand DNA breaks (DSBs) are a rich source of transforming recombinants in cancer aetiology<sup>57</sup>. These can be induced by exogenous genotoxic insults such as ionizing

Table 1 | **Evolutionary constraints and risks**

Evolutionary feature	Potential or inevitable consequences
Lack of perfection in evolutionary engineering: just selects from the best available options	Deleterious trade-offs or malfunction under stress
Evolutionary adaptation has 'no eyes to the future' <sup>126</sup>	Rapidly changing circumstances result in genotype–environment mismatches
Natural selection will happen	Arms races work in favour of rapidly evolving 'parasitic' entities
The only fitness test of 'natural selectability' in evolution is survival and reproductive success	The post-reproductive affect of antagonistic pleiotropy, trade-offs and 'design' limitations

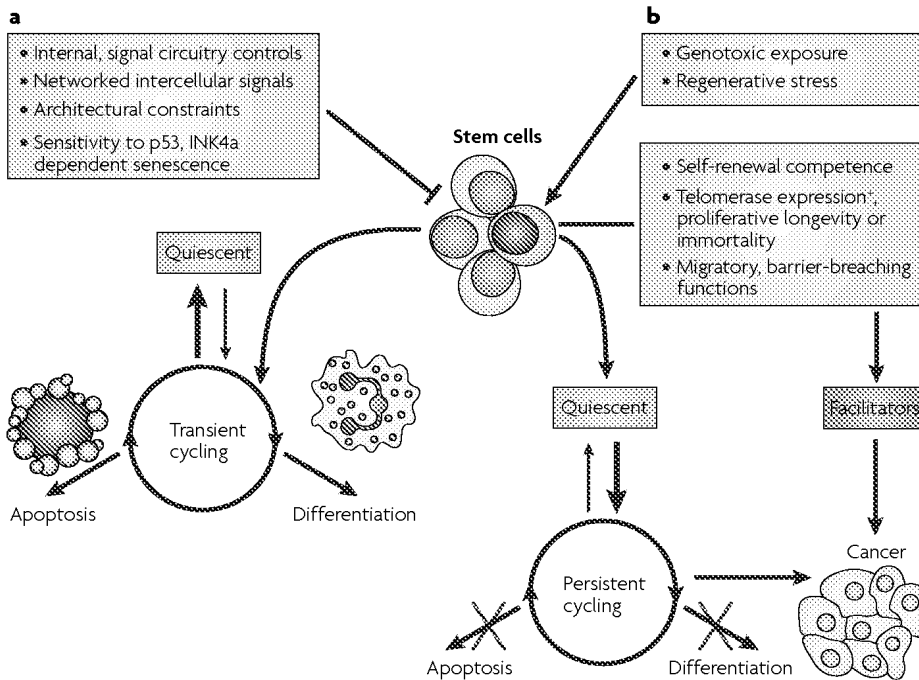
radiation and chemicals. What is perhaps more surprising is the rate at which these occur spontaneously — calculated to be 50 DSBs per cycle<sup>58</sup>. The capacity to repair DSBs is crucial, and occurs through homologous recombination or non-homologous end-joining (NHEJ) in mammalian cells<sup>57</sup>. The repair of double-strand DNA breaks by NHEJ is an efficient process but one that, in the absence of template use, is intrinsically error prone and can lead inadvertently to chromosome translocations, as in leukaemias and sarcomas<sup>59</sup>.

In other circumstances, physiological DNA breakage can contribute to cancer initiation. The recombination-driving enzymes RAG1 and RAG2 are an evolutionary innovation underpinning the extraordinary diversity and repertoire of immunological recognition<sup>60</sup>. But in the context of concurrent DNA breakage elsewhere in the genome of the same cell, and in concert with NHEJ, they help to generate oncogenic gene fusions<sup>60–62</sup>. Similarly, somatic hypermutation in B cells in germinal centres provides a valuable fine-tuning of antibody specificity but suffers from a lack of prohibition of collateral damage to other genes<sup>63</sup>.

The potentially oncogenic liability afforded by the intrinsic mutability of our genes might be reflected in the stark fact that we all accommodate mutations or rearrangements of cancer genes<sup>59,64–66</sup>. The reason we usually escape potentially lethal consequences is twofold. First, these mutations usually fail to be complemented with the necessary additional genetic changes required for the progressive evolution of a malignant clone. For example, crucial promotional factors or exposures might be absent<sup>67,68</sup>. Incipient cancer clones are therefore either stalled or they regress<sup>69</sup>. Second, these mutations only contribute functionally — to cancer clone emergence or evolution — if they arise in the appropriate cellular context. Usually

this will have to be in normal stem cells or progenitors, or in the stem-cell fraction of an already initiated pre-malignant clone.

**Complexities of embryogenesis and early development.** The stepwise process of sculpturing tissues correctly in time and space is very exacting and requires highly orchestrated cellular functions. It is perhaps not surprising that the error rate is substantial: most human embryos fail to implant or subsequently die<sup>70</sup>. Around 1% of us are born with recognized mutant phenotypes<sup>71</sup> and all of us are bequeathed about 100 new germline mutations<sup>72</sup>, of which a surprisingly high fraction might be potentially deleterious<sup>73</sup>. Unfortunately, many of the cellular attributes required for embryogenesis are, in effect, available for co-option or hijack by malignant cells, such as epithelial–mesenchymal transition, motility, chemotactic or signalling molecules, barrier-breaking migration and invasiveness<sup>74,75</sup>. Choriocarcinoma in adult females arises in part because of the naturally invasive and immunologically disguised fetal extra embryonic trophoblast<sup>76</sup>. These intrinsically risky activities, when coupled with the inherent fragility of DNA, or spontaneous mutation, might be sufficient to explain the initiation of some embryonic or paediatric cancers without the need for any external genotoxic exposures<sup>59,77</sup>. Additional risk of paediatric cancer might have been acquired in the relatively recent evolutionary past by rapid changes in growth patterns and morphology<sup>78</sup>, as suggested by long bone osteosarcoma in peri-pubertal adolescents<sup>34</sup>. Natural selection might be expected to weed out developmental errors that result in pre-reproductive deaths but there are limits to what is achievable, and an overt paediatric cancer risk of ~1 in 800, as recorded<sup>79</sup>, could be difficult to eliminate by natural selection, particularly over short time frames, and now in the face of curative therapies.



**Figure 2 | Programmed stem cell behaviour and cancer risk.** **a** | Normal stem cells, such as haematopoietic stem cells, are subject to many intrinsic regulatory signals, such as intracellular signalling networks, and are also regulated by the external environment, such as the size of the stem cell niche. All of these factors serve to restrict the proliferative capacity of stem cells, keeping them mostly in quiescent phase with periodic entry into the cell cycle when required. **b** | Stem cells might be transformed in response to various stimuli, such as exposure to genotoxic chemicals or signals that mediate persistent division. Self renewal, the expression of telomerase and migratory behaviour are essential tumour cell characteristics, which stem cells inherently possess (intrinsic fallibility). When coupled with a mutagenic environment, the risk of developing cancer is increased.

**Stem cells: a cellular source of all the trouble?** Stem cells were a profound evolutionary adaptation in metazoans, and are essential for both the resilience or renewal of tissue function and longevity in more complex animals, including ourselves. They retain intrinsic competence for transient, selfish replication under particular conditions of regenerative demand<sup>8</sup> and, as Cairns emphasized in the 1970s, reflect an evolutionary liability in terms of their vulnerability to natural selection as mutants<sup>80</sup>. Most malignant cancers probably originate in normal stem cell populations or in progenitors in which crucial stem cell properties, such as self-renewal, are reinstated by mutation<sup>8,81,82</sup>. To some extent, the risk of cancer must reflect the number of these inherently risky cells that are available for transformation in developing embryos and ageing adults<sup>80,83</sup>. Evolution has inevitably provided many adaptations to protect vital stem cells from DNA damage and loss, or selfish self-replication, particularly in rapidly repopulating tissues of larger, long-lived species<sup>80,84</sup>. Malignant cancer itself might have provided potent selective pressure for the evolutionary acquisition of restraining

adaptations<sup>34,84-86</sup>. These controls include limiting the number of stem cells and using transitory precursor cells for gross amplification of cell numbers by proliferation. DNA damage is limited by architectural constraints such as residence at the base of intestinal epithelial crypts. Microenvironmental signals and niche or stromal matrix contacts ensure steady-state cell-cycle quiescence, the tight regulation of transient self-renewal<sup>87,88</sup> and the imposition of differentiation on proliferating stem cell progeny (FIG. 2). And, when potentially oncogenic DNA damage does occur, the tumour suppressors p53 (REF. 89), INK4a<sup>90</sup> and other key regulatory molecules signal cellular senescence or apoptosis<sup>91</sup>. But these controls must be relaxed on regenerative demand, and regulatory stringency is not infallible, particularly over long periods of time. Moreover, the persistent evocation of DNA stress responses provides potent selective pressure for escape mutants in the protective signalling pathways<sup>87,88,91,92</sup>. Normal stem cell division can also limit the risk of cancerous transformation by asymmetric division; that is, one daughter cell differentiates, one self-renews as a stem

cell<sup>80,93</sup>. Mutations arising as errors in DNA replication can then be selectively segregated to differentiating progeny, with stem cells retaining the unmutated, immortal parental strand<sup>80,94</sup>. However, this can only provide limited protection, as unrepaired (or misrepaired) double-strand breaks will persist in stem cells, and mutations that promote or bias self-renewal will tend to be selected<sup>93</sup>. A recent report that some normal stem and progenitor cells might be intrinsically deficient for the cell-cycle G2 decatenation checkpoint raises the possibility that these cells have additional cancer-prone features<sup>95</sup>. These and other observations (BOX 1) endorse the contention that inherent constraints on the expression of many adaptive or beneficial biological processes contribute positively to the risk of cancer clone escape.

**‘No eyes to the future’**

Darwinian natural selection operates on a ‘what works best today’ basis<sup>49</sup>. In other words, it selects genetic variants from the limited options available that best fit the prevailing conditions. It follows from this that winners today can become losers tomorrow if circumstances change, for example, through climatic shifts or the invasion of new competitors. An important consequence of the short-term nature of adaptation by natural selection, other than begetting further selection, is that what emerges from time to time are flagrant mismatches between genotype and environment or genotype and ‘lifestyle’<sup>28,40,44</sup>. For many species, this will be a wake-up call or farewell. For *Homo sapiens* as a species, this can also have profound consequences. Over the past 200,000 years or so, humans have intermittently been selected as genetic variants by the selective forces of lethal epidemics or massive environmental challenges<sup>96</sup>. Additionally, mutations become prevalent, over centuries, through founder effects, as is likely to be the case for common breast cancer susceptibility mutations in *BRCA1* in Ashkenazi Jews<sup>97</sup>. But humans are especially unique in their rapid social and cultural evolution, largely divorced from fitness tests for competitive adaptability or genetic selection<sup>8,40,41,44,98</sup>. As a result, most contemporary populations of humans are, in effect, genetically primed for ‘Stone Age’ challenges that no longer exist, or for which we take leave of through our modern lifestyles<sup>98</sup>.

**Skin cancer.** Perhaps the most obvious case of inherent cancer risk increasing as a result of current mismatches is the high cancer risk in people with pale skin and

a limited melanin-filtering capacity to counter the DNA-damaging impact of the UV component of the solar spectrum. Pale skin is thought to be a positive adaptation to cloudy northern climes, resulting in increased UV-dependent vitamin D synthesis<sup>99</sup>, although this explanation is contested<sup>8</sup>. Regardless of its evolutionary origin, it is a longstanding genetic feature of certain populations living in higher, northern latitudes<sup>100</sup>. The mismatch comes when these individuals intermittently or permanently migrate to sunnier latitudes and fail to protect themselves from excess exposure and sunburn. The high rate of skin cancers in black African albinos<sup>101</sup> shows that the same mismatch can arise by mutation rather than migration. Few, if any, other species undergo such gross changes of habitat without resultant genetic selection.

**Breast and prostate cancer.** Non-seasonal oestrus with cyclical mammary gland priming is a uniquely human attribute. Its origins are unknown but it might have arisen as a strategy to increase reproductive capacity facilitated by protection from the vagaries of climate. The physiological cycle presumably operates under the normal constraint of early and spaced but repetitive pregnancy, and in the context of protracted breastfeeding and of particular dietary circumstances. The mismatch that increases the risk of breast (and ovarian) cancer risk falls on women in modern or affluent societies who do not conform to hunter-gatherer lifestyles with respect to reproductive patterns, including breastfeeding<sup>8,102,103</sup>. This risk, through persistent, cyclical stress to mammary (or ovarian) stem cells might be exacerbated by common dietary and/or exercise habits that fuel cell proliferation through excess calories or increases in circulating oestrogen levels<sup>104</sup>.

There are many parallels between the hormonally-driven cancers of women and prostate cancer in men<sup>105</sup>. Could there be an evolutionary component to vulnerability to prostate cancer? The increasing and ultimately very high incidence of covert prostate cancer with age begins in the third or fourth decade of life<sup>106</sup> and is globally widespread, including populations in which progression to lethal malignancy is relatively rare<sup>106</sup>. This suggests an inherent fragility of control. It might not be coincidental in this context that the only other mammal intrinsically (that is, genetically) endowed with a large prostate — the dog — is also the only other mammal to have a high rate of spontaneous prostate cancer. One line of evolutionary speculation is that, for human males, large but ultimately

error-prone prostates might have been co-selected with female non-seasonal oestrus<sup>8</sup>. With no malignant trade-off until older age, there would be little or no counter-selection. Coffey has argued that the unique vulnerability of humans and dogs to prostate cancer might reflect the relatively recent (within the past 10,000–15,000 years) acquisition of dietary habits that fuel androgen-driven proliferation<sup>105</sup>.

**Childhood leukaemia.** From an evolutionary perspective, the immune system has been 'engineered' through adaptation to lethal infectious challenges<sup>107</sup>. One crucial design feature seems to be that frequent infection early in life is not only anticipated but required to modulate or balance the immunological network<sup>107</sup>. But lifestyles in affluent societies tend to insulate infants from common infections before their inevitable exposure through social mixing. The consequences of this mismatch are thought to include the epidemic of allergies in modern, sanitized societies<sup>108</sup>, and the relatively high levels of several autoimmune diseases<sup>107,109</sup>, including juvenile or type 1 diabetes<sup>110</sup>. The most prevalent cancer in children — acute lymphoblastic leukaemia — might have an equivalent origin as an evolutionary mismatch between immunological programming and patterns of infection early in life<sup>68,111</sup>. Epidemiological evidence in support of this view was reviewed recently in this journal<sup>68</sup>.

Susceptibility to leukaemia, allergies or type I diabetes in childhood seems to be underpinned by the inheritance of alleles of immune response and/or cytokine genes that have increased functionality<sup>68</sup>. This raises the possibility that such alleles were subjected to positive, adaptive selection, possibly in the context of epidemics of

parasitic or microbial infection in relatively recent human history<sup>68,112</sup>.

Other pertinent examples of genetic–lifestyle mismatches that relate to the risk of cancer and other chronic diseases include those linked to diet<sup>44,98</sup>. Epidemiological studies can successfully identify statistically significant associations of lifestyle factors or exposure with cancer risk. The contention here is that this only makes sense in the context of contemporary mismatches.

### The inevitability of natural selection

Natural selection is the inevitable consequence of unstable conditions or competition. Given heritable genetic variation within species and limited resources or other environmental challenges, tests of fitness are automatically imposed and best adapted survivors emerge. This fundamental principle has huge consequences for human society in terms of the emergence of virulent species of microbes such as HIV and H5N1 influenza, MRSA in hospitals, and insecticide and pesticide resistance. In cancer, as has long been recognized, this natural biological law makes an indelible imprint on the emergence and progressive evolution of cancer clones through the acquisition of mutations that corrupt distinctive but complementary signal pathways in cells in the context of microenvironmental selective pressures<sup>8,45,46,55,80</sup>. This then provides an appropriate framework for understanding both the diverse natural histories of cancers and the 'unnatural' history of drug resistance that follows therapeutic intervention. Modelling the stepwise clonal evolution of cancer cells now incorporates more complex dynamics than simple linear succession<sup>46,113</sup>, and has been subjected to mathematical or computational modelling using concepts derived from evolutionary

#### Box 1 | Other examples of evolutionary adaptations and cancer risks

- \* **Telomerase.** This enzyme was no doubt a clever evolutionary trick to protect the integrity of chromosomes in germ cells and in many long-lived stem cells and T cells. The benefit is again, as with stem cells, resilience (or health) and reproductive longevity; highly selectable adaptations. Telomere maintenance might also restrain chromosomal instability that can contribute to cancer clone development<sup>134,147</sup>. Unfortunately, the natural engagement of telomerase in stem cells is a trade-off that automatically endows immortality to emergent cancer clones<sup>146</sup> that have acquired mutations other than through the erosion of telomeres and consequent instability.
- \* **Inflammatory lesions and oxidative metabolism.** These physiological processes are essential functions but they are crucially dependent on constraints in time and space; lax regulation leads to collateral damage in the form of mutagenesis and/or cancer promotion through reactive oxygen (or nitrogen) species or the increased production of cytokines and/or chemokines<sup>149,150</sup>. A substantive fraction of human cancers, particularly of the gastrointestinal tract, involves promotion through chronic inflammatory lesions<sup>149</sup>.
- \* **Angiogenesis.** The capacity for neo-vascularization is an essential ingredient of normal wound repair<sup>151</sup>. But it is highly vulnerable to hijack by stress responses and anoxia in tumours. It provides not only cellular sustenance to cancer cells, but escape routes for metastasis<sup>152</sup>.

**Box 2 | Implications of the Darwinian development of cancer clones****Selected not dictated**

Genotoxic damage that initiates cancer is largely blind to cell type or gene function.

- Specific genetic associations seen in cancer (for example, specific chromosome translocations in subtypes of leukaemia) are distilled from a sea of noise or chance; the result of intense selection pressure and low probability (hence clonality).

**Uncertain futures**

Most tumours never emerge through all the bottlenecks: cancer is commonly or ubiquitously initiated but promotion to full malignancy is rare.

- Promotional factors and/or exposures are crucial in aetiology.
- Prognostic uncertainty.

**Moving targets**

The progeny of neoplastic cells emerging through bottlenecks are more likely to be robust (that is, resistant to stress or apoptosis), and are often genetically unstable.

- Increases the likelihood of drug resistance.
- Genotoxic therapy might exacerbate mutation load in cells resistant to cell death.
- Early intervention should be beneficial.
- Tackling the microenvironment is important (Darwinian bypass): angiogenesis and chronic inflammation.
- Target the inherent genetic instability<sup>1</sup> or oncogene addiction<sup>2</sup> of cancer cells.

**Stem cells**

Cancer populations evolve and are sustained by mutations in rare 'stem cells' — which have a germ-cell-like function.

- Therapies might be directed at the wrong cells.

**Clonal individuality**

Each cancer clone has a unique evolutionary trajectory and genetic profile.

- How should treatments be tailored to individual cases?

With most common cancers, there is a striking and well-recognized general relationship between clinical incidence and age incidence, which rises linearly when plotted on a log–log scale<sup>127–131</sup>. Ageing alone is unlikely to be a sufficient explanation for the big increase in cancer risk in older age. If this were to be the case, then age-specific rates for particular subtypes of epithelial cancers would not be subject to such striking time trends or geographical variation (up to 500-fold)<sup>132,133</sup>, and other species with marked longevity (such as elephants, tortoises and cetaceans) might be expected to be equally vulnerable, which they do not seem to be.

Age might be such a powerful correlate of cancer risk in humans for at least two different reasons. First, cancer might arise as part of an ageing phenotype, with increased vulnerability to cancer-initiating or cancer-promoting genotoxic insults at the cellular and DNA level. This might occur because of diminished, post-reproductive capacity for anti-cancer 'caretaker' functions, particularly for DNA or chromosomal damage limitation, through detoxification, antioxidation, repair or telomere maintenance<sup>129,134</sup>. However, current direct evidence for this view is limited or inconsistent<sup>129</sup>. Moreover, epidemiological and experimental observations argue strongly that age itself is less important in governing risk than the duration of genotoxic exposures<sup>132,133</sup>. Variations on this theme are that age-associated decline in the integrity of the stromal, tissue microenvironment<sup>135</sup> or in immunosurveillance<sup>136</sup> might be permissive for cancer clone emergence<sup>135</sup>.

A different view is that continued tissue turnover or stem cell proliferation over decades, coupled with lifestyle-associated chronic, low-level mutagenic exposure, simply provides the sustained window of opportunity, or chance, for the winning (or losing) lottery numbers to come up. Or, in other words, if you wait long enough, the inherent 'design' constraints bequeathed by evolution plus persistent mismatches engendered by lifestyle will inevitably promote the emergence of cancer, probably from the base of pre-malignant clones generated much earlier. This explanation accords with the predictions of multi-step pathogenesis over time identified epidemiologically<sup>128</sup>, by histopathology<sup>137</sup> or as driven by sequential independent mutations<sup>138</sup>. In reality, both mechanisms are probably relevant, and in combination they could explain much of our vulnerability to cancer.

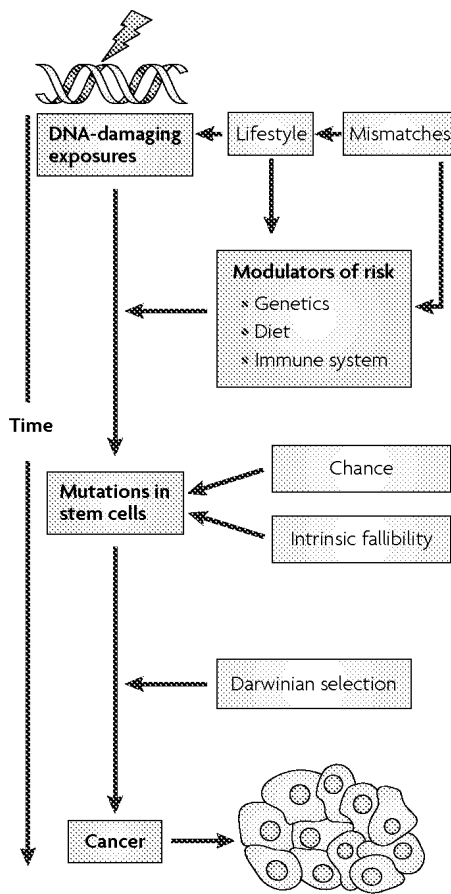
or population biology, including the importance of reciprocal interactions with the environmental landscape in which cells reside and move<sup>47,114,117</sup>. These aspects of cancer cell evolution are discussed in detail in a recent review in this journal by Merlo and colleagues<sup>47</sup>. Darwinian models of cancer now need to adopt the concept of cancer stem cells; that small population of self-renewing cells that maintain most of the cancer cell population and, in self-replicating, provide the essential reservoir for further genetic variability and selection<sup>118–121</sup>, equivalent in evolutionary terms to germ cells.

The epidemiological and clinical consequences of this Darwinian perspective are substantial<sup>1,116</sup> (BOX 2), and highlight several practical problems. For example, and as is exemplified by systematic screening for breast and prostate cancer, if most incipient cancers are evolutionarily aborted or stalled, the issue of whether or when to therapeutically intervene faces an inevitable tension: intervene too soon and pay the price of side effects for what most likely would have remained an innocuous cancer, or wait until clinical symptoms appear or escalate, in which case it might be too late. The high degree of genetic complexity of cancers, even within a histopathological subtype, creates another tension that needs

resolution: is the answer to individualize patient treatment (with significant cost implications), or should we strive to target more generic features of cancer clones?

**The only evolutionary currency**

Natural selection has a harsh reality that worried Charles Darwin: ultimately all that seems to matter is reproductive success. But what happens when it stops for us? Human post-reproductive longevity and ageing or senescence have provided rich pickings for evolutionary speculation<sup>122,123</sup>. As Peter Medawar suggested many years ago<sup>124</sup>, degenerative health problems that accrue after reproductive life have finished are inevitable, and are in themselves evolutionarily neutral; they cannot be selected against by natural selection, accepting the counter-argument that nurturing (kin-selecting) grandmothers could in theory be positively selected<sup>125</sup>. Indeed, in some respects degenerative health problems might be a negative trade-off of positive adaptations that improve reproductive fitness (a concept known as antagonistic pleiotropy)<sup>126</sup>. Therefore, it is to be expected that as the clock ticks on, the intrinsic 'design' limitations or trade-offs of our bodies eventually come into play.



**Figure 3 | The cancer lottery: an evolutionary heritage.** The cancer lottery, as outlined in FIG. 1, is influenced by causal mechanisms involving evolutionary mismatches (lifestyle, diet and environment) and intrinsic fallibility (for example, the biologically required characteristics of stem cells). Once mutations are in place that enable increased cell survival or proliferation, Darwinian selection will then select for these 'positive attributes'.

But there is also evidence that the interplay between ageing and cancer might well be more complex, with evolutionary adaptations that restrain the emergence of mutant cancer clones having opposing effects on ageing phenotypes<sup>139</sup>. Some so-called caretaker functions, mostly of very ancient evolutionary origin, seem to protect against both cancer and ageing phenotypes through, for example, the maintenance of DNA integrity by repair. Others — 'gatekeeper' tumour suppressors including p53 (REF. 140) and INK4a<sup>90</sup> — might eliminate or restrain damaged or mutated stem cells through apoptosis or senescence, but at a cost of increasing ageing phenotypes through diminished stem cell capacity<sup>141,142</sup>. Telomerase attrition has a similar affect<sup>139</sup>. This further exemplifies the principle of antagonistic pleiotropy or

delayed (post-reproductive) trade-off<sup>126</sup>, and suggests that evolutionary selection results in a balance between cancer suppression, tissue resilience and ageing<sup>139</sup>.

### Implications

Intrinsic vulnerability to cancer (or other chronic diseases) must be counterintuitive to anyone who views our bodies as the product of purposeful design or engineering. Evolutionary or Darwinian medicine provides the opposite view: the blind process through which we and other species have emerged carries with it inevitable limitations, compromises and trade-offs. The reality is that for accidental or biologically sound, adaptive reasons, we have historically programmed fallibility. Covert tumours arise constantly, reflecting our intrinsic vulnerability, and each and every one of us harbours mutant clones with malignant potential. Clinical cancer rates would be even worse if it were not for the fact that cancer clone emergence is a relatively inefficient evolutionary process, subject to many constraints or bottlenecks. Most potentially oncogenic mutations occur in irrelevant cells and at a low frequency. Perhaps only 1% of covert pre-malignant clones ever acquire the necessary additional or complementary mutations required for graduation to malignancy. However, humans are especially or uniquely vulnerable to clinical, malignant cancer compared with other similar complex and long-lived species. This unforeseen penalty arises because of the coupling between extended post-reproductive life spans and mismatches between our pedestrian genetics and rapidly changing lifestyles teasing out inherent flaws or trade-offs. Some of this discord is intrinsic to *Homo sapiens* (for example, cyclical non-seasonal fertility in females). Occasionally, and particularly with human intervention, a similar vulnerability is seen in other mammalian species. Other examples of particular cancer types in humans are more recent genetic legacies that affect particular 'at risk' individuals (for example, variation in melanin or immune responses). These might come to be seen as increasingly important once large-scale studies with global genome screens (for example, single nucleotide polymorphism (SNP) arrays) have identified precisely which genetically programmed functions place individuals at an increased risk of common cancers. It is likely that at least some genetic variation linked to increased cancer risk will have an evolutionary, adaptive rationale. For example, could it be that women endowed with genotypes selected for

increased fertility are at greater risk of breast and ovarian cancer<sup>143</sup>?

This evolutionary perspective does not conflict with more conventional views of cancer causation derived from molecular biology or epidemiology. These approaches to aetiology and pathogenesis have been enormously insightful and important. But, they provide a proximate and somewhat myopic view of cause. Underlying the prevalence of cancer in human societies, there is an inherent vulnerability acquired as a legacy of our evolutionary history (FIG. 3).

The cancer specialist or pragmatist will still query whether such a view, even if basically sound, contributes anything other than a biological perspective of the origins of vulnerability to cancer. I suggest that it does. First, there can be little doubt that the Darwinian evolution of cancer clones has huge implications for screening, prognosis and therapy (BOX 2). This has been argued previously<sup>8,45–47</sup>, but has only just begun to be taken on board by those involved directly in cancer drug development and treatment. Attributing the special vulnerability of humans to the lethal combination of intrinsic fallibility, chronic mismatches and age is less obviously of practical value, although it does offer a plausible explanation of a medical conundrum to which a solution is not obvious or perhaps not even possible without the evolutionary perspective. No formal test of the proposition might even be required; we already have adequate evidence from the high cancer rates, in particular those that result from migration or are imposed on other mammalian species by human intervention. At a practical level, this analysis suggests that, for evolutionary reasons, as a species we are inherently more likely to develop cancer than we might like to admit. We cannot reverse our genetic legacies and propensity to cancer, but emphasizing intrinsic vulnerability in this way provides a very strong endorsement of current attempts to combat cancer. These effectively seek to neuter mismatches and minimize the impact of intrinsic risk — even if the practitioners involved do not realize it. For example, there is a recognized urgent need to educate on lifestyle choices or, where these are unlikely to be fully effective, as perhaps with breast or cervical cancer, to focus efforts on prophylactic hormonal<sup>144,145</sup> or immunological<sup>146</sup> intervention.

Mel Greaves is at the Section of Haemato-Oncology, The Institute of Cancer Research, London, UK.  
e-mail: mel.greaves@icr.ac.uk

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#### Competing interests statement

The author declares no competing financial interests.

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