CANCER IN RODENTS: DOES IT TELL US ABOUT CANCER IN HUMANS?

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Abstract | Information obtained from animal models (mostly mice and rats) has contributed substantially to the development of treatments for human cancers. However, important interspecies differences have to be taken into account when considering the mechanisms of cancer development and extrapolating the results from mice to humans. Comparative studies of cancer in humans and animal models mostly focus on genetic factors. This review discusses the bio-epidemiological aspects of cancer manifestation in humans and rodents that have been underrepresented in the literature.

The use of laboratory animals to identify the carcinogenic potential of chemicals, mixtures and other agents has a history in excess of 40 years. Much useful scientific and public health information has been extrapolated during this time. Some aspects of animal modelling are beneficial, whereas others still suffer from significant drawbacks that need to be carefully assessed[1,2]. Whereas laboratory animals are similar to humans in their response to hazardous exposures in some respects, there is a growing pool of experimental evidence indicating important differences (genetic, metabolic, ontogenetic and others) among mammalian species in the way that cancer develops[3–5]. This does not diminish the importance of animal modelling for studying cancer in humans; however, where studies disagree, the results require more careful interpretation before extrapolation of the data into the human situation[5]. Recently, Hahn and Weinberg[3] and Rangarajan and Weinberg[4] highlighted the differences between rodent and human carcinogenesis in two thorough reviews focusing on cellular and molecular–genetic events. However, many other aspects of comparative cancer development in humans and laboratory animals are currently not discussed adequately in the literature.

In this review, we focus on unusual aspects of comparing cancer manifestation in rodents and humans. We draw attention to hallmarks of cancer epidemiology and somatic ageing as a possible background for observed epidemiological patterns. We discuss cancer incidence and mortality rate curves in humans and laboratory animals and suggest links between the age-patterns of cancer appearance and fundamental ageing processes in the different mammalian species. We pay special attention to old-age deceleration/decline in overall cancer risk and factors of individual ageing and development that influence this decline in humans and rodents. Some other comparative aspects of cancer development in humans and laboratory animals are briefly discussed, including the spectrum of the most prevalent cancers and species-specific carcinogenic factors. We suggest possible explanations for the observed differences and similarities, as well as discuss (where possible) their implication for human cancer research. Overall, we address the general questions: to what extent can epidemiological and biological knowledge be incorporated as a useful tool for understanding the nature of cancer? And to what extent can one extrapolate the results from rodent experiments and apply them to humans to reliably predict the risks of developing, and the outcome of treating, human cancer?

Human cancers in laboratory rodents

In general, there is little similarity in the spectrum of spontaneous tumours that develop in humans

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Summary

- Whereas laboratory rodents (namely mice and rats) are similar to humans in some aspects, there are important differences among mammalian species that make valid interpretation and extrapolation of the results from rodent cancer experiments to humans problematic.
- The five most common human cancers are those of the breast (female), the prostate (male), and the lungs, colon, and stomach (both sexes). Mammary tumours are also common in rodents. However, there are no rat or mouse strains that exhibit a high incidence of spontaneous carcinomas of the stomach or colon.
- A decrease in the overall risk of cancer owing to old age has been recorded in both human and rodent studies. Three important factors could be responsible for this intriguing decline: detection bias, differential selection, and the effects of individual ageing. Studies in rodents argue against a diagnostic bias as a leading cause.
- The risk of cancer has increased over time in most human populations. Why this is remains unclear, but addressing this problem is crucial for understanding the nature of cancer.
- Some studies indicate that the differences in cancer incidence rates between males and females are similar in rodents and humans. This is a surprising finding that requires additional explanation.
- Whereas tumours often grow at a slower rate during old age, the chances for survival of a transplanted tumour in a recipient host often increases with rodent age. This is in agreement with human data indicating that ageing can both decelerate tumour growth and increase the chances of latent tumour survival in older organisms.
- The spontaneous regression of tumours is a rare phenomenon in adult humans, whereas it is common in mature laboratory rodents. This effect and its implications need further investigation.
- Few rodent carcinogens were established as clearly carcinogenic to humans. Similarly, some human carcinogens are not carcinogenic to rodents. This creates a significant problem for interpreting the results of animal experiments with carcinogens in relation to humans.
- These and other differences warn against the simple extrapolation of the results of rodent experiments to humans and call for further investigation of this important problem to reliably predict cancer risks, as well as foster success in treating human cancers based on data from laboratory animal studies.

compared with those of laboratory rodents (TABLE 1). Mice tend to develop sarcomas (tumours of mesodermal origin), whereas humans are more prone to carcinomas (epithelial tumours)[3,4]. It is important to stress, however, that the genetic background of a mouse strain is crucial in influencing the spectrum of tumours that the animals develop, as is the presence or absence of retroviruses. DePinho[6] noted that telomerase-deficient mice, heterozygous for mutant *Trp53*, showed a pronounced shift in their tumour susceptibility spectrum compared with mice in which telomerase function was intact. The ageing, telomerase-deficient *Trp53*-heterozygous mice developed mammary, colon and skin carcinomas as opposed to predominantly developing lymphomas and sarcomas. Interestingly, these mouse carcinomas had cytogenetic profiles typical of human carcinomas.

Some mouse strains are able to develop various tumours. For example, in C57BL/6 (B6) and B6F1, both sarcomas (particularly lymphomas) and mammary carcinomas are the most frequent tumour types[7]. CF-1 mice develop spontaneous hepatomas (the incidence varies from 21% to 39%), lung adenomas (the incidence varies from to 31% to 61%), and haematopoietic system tumours (occur in 13% to 36% of the animals)[8]. In outbred, Swiss-derived SHR mice, mammary carcinoma is observed in 26% of animals, lung adenocarcinoma and uterine adenocarcinoma in 2%, and leukaemia/lymphoma in 14% (REF. 9). Conversely, many mouse strains are prone to particular types of malignancy. In B6, 129SV $Trp53^{+/+}$ mice with intact telomere function, Artandi *et al.*[10] observed sarcomas in 50% of the animals, whereas epithelial tumours did not occur. In A-strain mice, the incidence of spontaneous lung adenomas approaches 90% when the animals reach 18 months of age. By 14 months of age 90% of C3H male mice develop spontaneous hepatomas, whereas 60–80% of virgin females of this strain manifest mammary adenocarcinomas by 18 months of age[11,12]. Such 'site-specific' strains are widely used as mouse models for studying particular human cancers. However, the fact that the majority of animals in these models develop a specific cancer type during their lifetime suggests that such models are genetically predisposed towards developing these tumours, a situation that is rare in humans.

In rats, epithelial tumours develop more frequently than mesodermal tumours[5,13,14]. In this respect, rats represent a more comparable model for human cancer than mice. However, even with rats, there is a problem with interpreting the animal data, as the spectrum of common cancers, including those characterized by a high incidence rate of spontaneous epithelial tumours, differs between humans and rats. The five most common spontaneous human cancers in developed countries are those of the breast (female), the prostate (male), and the lungs, colon and stomach (both sexes)[15]. In certain rat strains spontaneous female mammary carcinomas are also common (for example, in Sprague–Dawley and F344)[13,14]. Male Lobund–Wistar rats display a high incidence of metastasizing prostate adenocarcinomas[14]. Thyroid carcinomas are predominant in Han:SPRD rats[16]. Female BDII/Han rats are prone to endometrial carcinomas[17]. However, there are few strains of rats and mice that exhibit a high incidence of spontaneous

Table 1 | **Most common spontaneous cancers in humans and rodents**

Cancer	Mice	Rats	Humans
Breast carcinoma	+	+	+
Lung carcinoma	–	–	+
Prostate	–	+	+
Colon	–	–	+
Skin	–	–	+
Stomach	–	–	+
Liver	–	–	+
Endometrial carcinomas	–	+	+
Leukaemia/lymphoma	+	–	+
Thyroid	–	+	+
Bladder	–	–	+

+ indicates common spontaneous cancer, – indicates uncommon spontaneous cancer.

stomach, colon or bladder tumours, or bronchial tumours of the lung[5,18] (TABLE 1). This could reflect a difference in the spectrum of carcinogenic factors required for tumour development between these species. Indeed, 'normal' living conditions that are harmless for rodents could be carcinogenic to humans. For instance, crude (unprocessed) grain is a natural food for rodents, so chronic exposure to this food is unlikely to increase the risk of stomach cancer in these animals. By contrast, unprocessed grain might not be suitable for the human stomach; it might harm the stomach mucosa, leading to inflammation and increasing the risk of stomach cancer. Kagawa *et al.*[19] found that the high proportion of crude grain (barley) in the Japanese diet, which was common before the 1950s, was associated with an increased rate of stomach cancer.

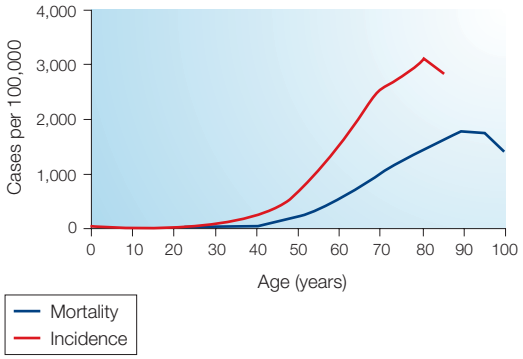

Figure 1 | **Typical age-patterns of overall cancer incidence and mortality rates in humans in the USA.** A figure showing both cancer incidence and mortality rates declining at the oldest old ages; mortality, however, decreases later in life (90 or more years of age). The decline in mortality can be attributed to a respective decrease in the incidence rate at earlier ages[25–27]. The deceleration or decline in cancer incidence rates at ages above 70 years can be attributed to a differential selection in the heterogeneous population[28] or to the ageing-associated changes in a human body that oppose cancer development[27]. Figure reproduced from REF. 27 © (2003) Max-Plank-Gessellschaft.

CANCER INCIDENCE RATE
A proportion of new cancer cases (registered for the first time) in a population of a given age.

PREVALENCE OF CANCER
A proportion of individuals with a diagnosed cancer (no matter when the diagnosis was made) in a population of a given age. The prevalence characterizes the cancer burden.

Age-associated decrease in cancer risk

The comparative analyses of data on cancer incidence published by the International Agency for Research on Cancer (IARC)[15,20,21], the National Cancer Institute (NCI)[22] and from other sources and epidemiological studies[23–33], indicate that after a steady increase during adult life, the CANCER INCIDENCE RATE decelerates or even declines at old age (above 70) for most sites of cancer development, as well as for all cancers combined (FIG. 1). Ageing is traditionally associated with an increasing risk of chronic disease; therefore a declining cancer incidence rate at old ages seems counterintuitive. Three major explanations for this phenomenon have been suggested: detection bias, differential selection, and the effects of individual ageing.

Detection bias. Many diagnostic procedures (for example, colonoscopy) might not be used in the later years of life because individuals are considered to be too frail. This might create a detection bias, as a number of cancers stay undetected in the oldest old, and so the decline might be spurious. This suggestion is, however, not supported by autopsy data. This data shows that the PREVALENCE OF CANCER declines in the oldest old[34,35] — tumours are approximately two times less frequent at age 90 years or above than they are in people in their seventies.

Data on cancer incidence in experimental animals support these observations. There is evidence of declining cancer risk in the later years of life in both mice and rats. Pompei *et al.*[36] have shown that the late decline in the incidence rate of spontaneous tumours is typical in laboratory mice. Published primary data from several studies[37,38] allow us to plot the typical age-patterns of the cancer incidence rate in experimental rodents (FIG. 2). Age-associated decline in cancer risk can be observed in both rats and mice that have spontaneous malignancy. Rodent data therefore indicates that the decline in cancer risk associated with increased age is not spurious. Indeed, in the case of experimental animals, such a decline cannot be because of a diagnostic bias.

Selection. Even if a declining cancer incidence rate in the elderly is a real phenomenon, this decline could happen for reasons other than a decrease in the susceptibility to cancer in the oldest old. Vaupel and Yashin[28] explained the decline in cancer rate in the oldest old in terms of differential selection in a heterogeneous population. Selection favours the survival of individuals who are less prone to cancer. As a result, the proportion of these individuals increases in the elderly population. Such a change in population structure produces the observed effect of deceleration or decrease in old-age cancer morbidity. This scenario is also plausible in the case of laboratory rodents. Even for animals of the same genotype (inbred strains), there is still a sufficient niche for phenotypic variability because of changes in their external and internal (for example, microbial) milieu. This creates a basis for differential selection. Therefore,

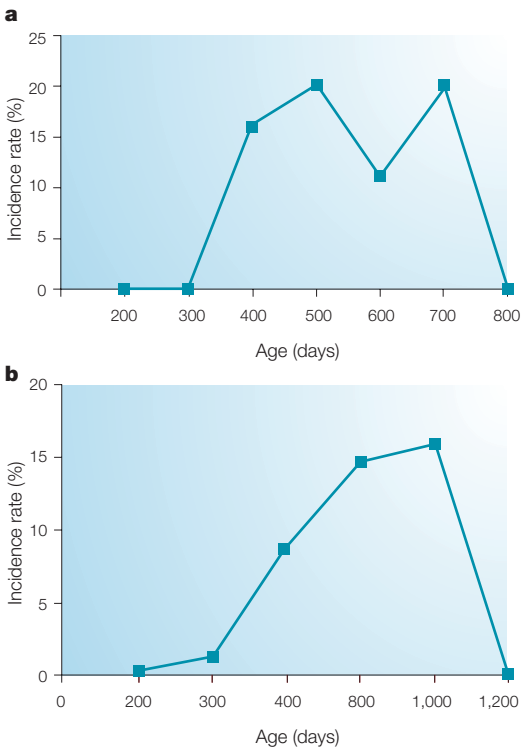

Figure 2 | **Age-patterns of cancer incidence rate in laboratory rodents of different strains. a** | Graph showing the rate of spontaneous malignant tumours in female C3H/Sn mice (30 animals) during the animals natural lifespan (REF. 38). **b** | Graph showing the rate of spontaneous tumours in female LIO rats (303 animals) during the animals natural lifespan[37]. Both of the graphs demonstrate a declining cancer incidence rate at old ages. The graphs were produced using data from REFS. 37,38.

data on rodents do not allow exclusion of the pivotal role of selection in declining cancer risk in the elderly. However, human populations are more heterogeneous than the groups of inbred animals in a laboratory as they exert a genetic heterogeneity in addition to an environmental one. This indicates that the effects of differential selection on cancer risk should be more pronounced in humans than in genetically identical rodents that have been exposed to a standardized environment. However, genetically homogeneous laboratory animals still show a decline in old age cancer risk similar to that seen in humans (FIG. 2). This indicates that differential selection might not be the only factor responsible for the decline in cancer risk at older ages.

Somatic ageing. Ukraintseva and Yashin[27,39] suggested that somatic ageing might create conditions that oppose cancer development in older patients. Several biological mechanisms have been suggested as explanations for such a contradictory influence.

First, the universal decline in the rates of basic biological processes in an ageing organism, such as the rates of metabolism, information processing and cell proliferation, might slow down the accumulation of some pathological changes in the human body. For example, an age-related decline in the rate of angiogenesis results in reduced blood supply to a latent tumour (if present). This process favours a decreased rate of tumour growth (that is, it increases the time between tumour cell doublings) that in turn contributes to a delay in the clinical manifestation of cancer and reduces the cancer incidence rate. An old-age decline in the tumour growth rate was recorded in numerous human and experimental-animal cancer studies[40–46]. However, there are studies demonstrating that some rodent tumours (such as hepatoma-22a and lung adenocarcinoma in mice) grow more rapidly in old rather than in young animals[47,48]. These data indicate that tumour-specific and host-specific factors such as tumour origin (histogenesis) can modify the effects of declining metabolism on the rate of tumour growth in an ageing body.

Second, the risk of cancer could diminish in the oldest old simply because the proportion of senescent cells (that is, non-proliferating cells in the state of irreversible growth arrest) increases in ageing organisms[27,49]. Such cells are less prone to malignant transformation[50,51].

Third, the physiological and metabolic changes that accompany ontogenetic transitions in an organism (for example, switching off reproductive function at the menopause) might change the spectrum of internal cancer-risk factors, resulting in decreasing vulnerability to some cancers later in life[27,39]. For example, at the menopause, ceasing internal exposure to oestrogens, which are a risk factor for endometrial cancer[52], could contribute to a decrease in the incidence rate later in life[39].

In summary, the decline in overall cancer risk during old age has been recorded both in humans and in rodents (FIGS 1,2). Rodent experiments have contributed significantly to the understanding of the causes of this decline, as they argue against a diagnostic bias as its main cause. At the same time, rodent experiments do not allow one to distinguish between the contributions of two other causes of this decline, namely differential selection in a heterogeneous population and individual age-associated changes, which might oppose cancer development in the old.

Patterns of cancer mortality

The age-associated pattern of overall CANCER MORTALITY RATE in humans resemble that of the incidence rate. However, the values of the mortality rate are lower than those of the incidence rate, for all ages. The cancer mortality curve is shifted to the right compared with the incidence rate curve (FIG. 1). It peaks at about 90 years and declines at greater ages[25–27]. Smith[25,26] attributed the decline in the cancer mortality rate to a decline in the cancer incidence rate at earlier ages.

Mortality from cancer also decreases with increasing age in some murine strains, resembling the pattern seen in humans[36,53]. However, incidence and mortality are almost the same among animals with an aggressive tumour, such as leukaemia, pituitary adenoma or carcinoma, or mammary carcinoma. This is because experimental animals are not treated for

CANCER MORTALITY RATE
A proportion of cancer deaths in a population of a given age.

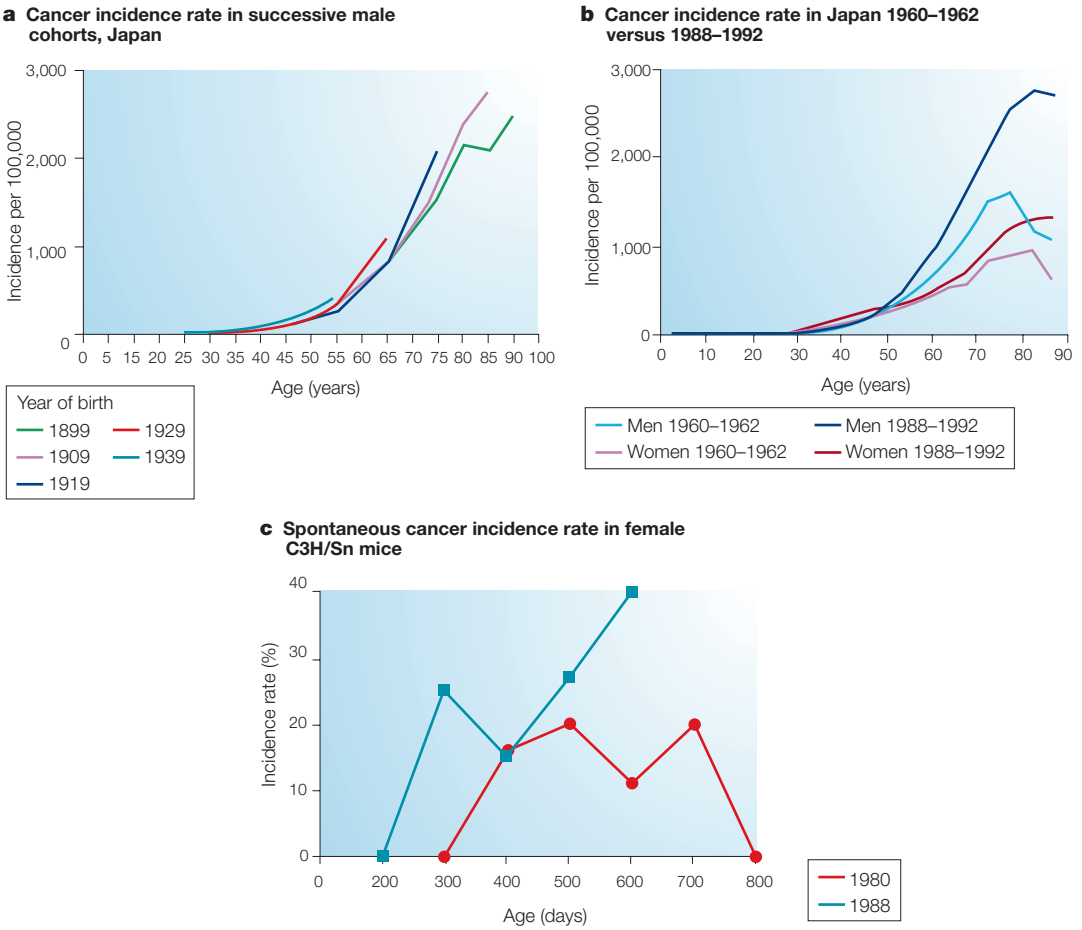

Figure 3 | **Time trends in overall cancer incidence rate. a** | Graph showing an increasing rate of cancer incidence in successive generations of Japanese men. **b** | Graph showing an increasing rate of cancer incidence over time for both sexes, drawn from cross-sectional data. Red line, data for women collated between 1988 and 1992; purple line, data for women collated between 1960 and 1962; blue line, data for men collated between 1988 and 1992; turquoise line, data for men collated between 1960 and 1962. **c** | The graph shows the spontaneous cancer incidence rate in C3H/Sn female mice in the same laboratory at different time periods. There were 30 mice in the group in 1980 (data taken from REF. 38) (red line) and 25 mice in 1988 (data taken from REF. 56) (blue line). The cancer incidence rate increased between 1980 and 1988. Figures **a** and **b** are reproduced from REF. 54 and were drawn using data from REF. 20.

cancer (except in studies of particular drugs), so they do not exhibit a significant time lag between clinical manifestation of cancer and death from the disease as seen in humans who undergo treatment.

Time trends and geographical differences

According to the IARC data (1965–2003)[20], overall human cancer risk is higher in developed regions of the world compared with developing regions. Until recently, the cancer incidence rate for all sites increased over time, along with economic progress[20,54,55]. This increase appeared in both period and cohort data (FIG. 3a,b). A direct comparison of changes over time or geographical differences in the cancer incidence rate between humans and rodents is difficult as laboratory animals live under more or less standard conditions in a vivarium, whereas humans live in heterogeneous environments. However, in particular strains of rats and mice that are kept in different vivaria there are some variations in spontaneous tumour incidence[13,14,56]. The incidence of phaeochromocytoma differed by two to three times in three colonies of Wistar rats kept at three animal facilities[57]. Wide variations in spontaneous tumour incidence were observed in six sources of Sprague–Dawley rats[58]. These variations might be related to differences in living conditions such as the number of animals per cage, the number of cages per room, the light regimen and brightness in the room, the electromagnetic environment, the quality and origin of laboratory rodent food (natural grain, meat, milk, vegetables or 'standard' rodent food), and so on.

Examples of increasing cancer risk in successive generations of rodents in the same laboratory are also of interest[38,59–61] (FIG. 3c). The overall cancer incidence rate has also increased over successive generations of people during the twentieth century[20–23,54,55] (FIG. 3a,b). Similar time trends in cancer incidence in humans and laboratory rodents, if confirmed, could indicate a 'carcinogenic' factor linked to economic progress that is common for these different species and might belong

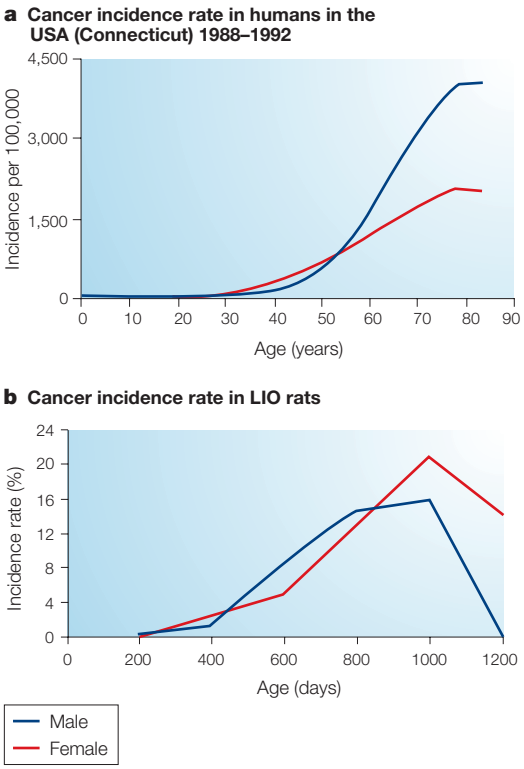

Figure 4 | **Patterns of sex difference in cancer incidence.** **a** | Graph showing a typical intersection between male and female cancer incidence rate curves in humans[20]. **b** | Graph showing incidence rates of spontaneous tumours for LIO rats (303 females and 349 males)[64]. The intersection between the male and female curves at ages around the switching off of female reproduction is typical of both species. Figure **a** is reproduced from REF. 54 using data from REF. 20 Figure **b** was produced using data from REF. 64.

to a non-specific home environment. Unfortunately, this issue is largely unexplored. However, there are few studies suggesting its potential importance. Baranova *et al.*[62] showed that the number of carcinogens (POLYCYCLIC AROMATIC HYDROCARBONS and NITROSO COMPOUNDS) in natural products used as food for laboratory animals changed significantly over time. The question of why the overall cancer risk has increased along with economic progress is important in human cancer epidemiology[54] and calls for a relevant animal study. However, there are limited observations suggesting that tumour incidence has not changed substantially in the past few decades for some rodent strains in the same laboratory[63].

Sex differences in the cancer incidence rate

According to the IARC data[20], overall cancer risk is higher in women compared with men before the female menopause and lower afterwards. Male and female rates therefore intersect around the age of the menopause (that is, roughly at ages 50–55) (FIG. 4a). This difference between the sexes shows surprising stability over time and is not substantially affected by the geographical location of the population[20].

A similar pattern of sex differences has been recorded in some rodent species[37,64]. In adult outbred, female LIO rats, the overall incidence rate of spontaneous tumours is at first higher and then lower than that observed in male rats[64] (FIG. 4b). Similar to humans, male and female incidence rate curves intersect at the end of the female reproductive period in rats. The sex differences in the behaviour of incidence rate curves both in humans and in rodents could be attributed to the sex differences in hormonal status. Unfortunately, relevant studies of differential age-patterns of cancer incidence rates in male and female rodents are limited and does not allow us to draw any general conclusions as yet.

Tumour survival in the ageing organism

Whereas existing tumours often grow at a slower rate in older individuals, the chances of survival of a transplanted tumour or grafted neoplastic cells in a recipient host often increase with age in rodent experiments[47,65]. No such experiments, of course, can be done in humans. However, human autopsy studies indicate that host factors, which increase the probability of survival of latent tumours in a human body, contribute to an increased overall cancer risk in old compared with young people[66,67]. Surprisingly, these can be the same factors that favour a decelerating cancer risk in later years of life both in humans and in rodents[27].

Cellular senescence. One such factor is cellular replicative senescence. As discussed above, the state of irreversible growth arrest (which is characteristic of cellular senescence) can reduce the risk of malignant transformation of human and animal cells[50,51]. At the level of tissue or organ, however, senescence might favour the survival of transplanted or latent tumours. At least two mechanisms might account for this.

First, the competition between tumour and host cells is probably altered in older people. Cancer cell growth can be suppressed by young, rapidly proliferating host cells — for example, through direct competition for growth factors and nutrients in the surrounding microenvironment[68–71]. However, cancer cells can outgrow ageing host cells as cancer cells are more resistant to apoptosis and can proliferate to an unlimited extent, whereas ageing host cells cannot[27,72,73]. McCullough *et al.*[65] have developed an experimental system that enables the assessment of the effects of cellular phenotype and tissue microenvironment, as well as the effect of age, on tumour development. This experimental system employs the intrahepatic transplantation of aneuploid BAG2-GN6TF liver epithelial cells. The authors have shown that intrahepatic transplants of hepatoma cells rapidly produce small tumours at the site of inoculation in young hosts. However, these tumours regress within 1 month of their formation[74]. By contrast, when hepatoma BAG2-GN6TF cells are inoculated intrahepatically into old rats, they quickly produce expanding, undifferentiated liver tumours, causing death[65,74]. Remarkably, when the tumour

POLYCYCLIC AROMATIC HYDROCARBONS
Their metabolites (diol epoxides) bind DNA and induce point-mutations in oncogenes (for example, *HRAS*).

NITROSO COMPOUNDS
Potent alkylating mutagens and carcinogens. The most important target in DNA is guanine at the O^6 position.

cells were transplanted into the spleen of young rats, individual transplanted cells were distributed throughout the liver and underwent hepatocytic differentiation, which suppressed their tumorigenicity. However, following splenic inoculation in old rats or when young hepatic-transplant recipients are allowed to age, the hepatocytic progeny of BAG2-GN6TF cells proliferate to form foci, suggesting that the liver microenvironment of old rats incompletely regulates the proliferation and differentiation of tumour cell-derived hepatocytes[74].

Second, as was suggested by Krtolica and Campisi[75], age-related accumulation of the senescent cells in the organism might create a pro-oncogenic tissue environment owing to factors secreted by these cells. Krtolica *et al.*[76] previously showed that the proliferation of human pre-neoplastic epithelial cells *in vitro* is better in an environment consisting of senescent cells rather than pre-senescent cells, a finding that is in agreement with both competition and pro-oncogenic stimulation.

Decline in the rate of physiological processes. As discussed above, another factor, the age-related decline in the rates of basic physiological processes in an ageing organism, might simultaneously contribute to a deceleration in tumour growth, an increase in tumour transplantability, and a poorer prognosis in the later years of life. A decline in the proliferation rate of immune cells might also improve the chances of tumour survival with advancing age. This is because the decline results in a diminished host immune response[77], reducing the organism's capacity to respond to antigen. This makes it more difficult to completely suppress an infection, so that inflammation can persist in the elderly[27,77,78]. Available data strongly indicate that chronic inflammation favours cancer development. Chronic inflammation is accompanied by the chronic proliferation of many cells, accumulation of connective elements in tissues, increased levels of active metalloproteinases, and other factors that promote cancer[79]. These factors might also favour the survival of transplanted tumours.

The decline in the rates of physiological processes probably contributes to a decline in stress resistance that is typical of old age — slower physiological processes increase cellular recovery time[27]. The decline in stress resistance in turn increases individual vulnerability to death at old ages and could therefore decrease the survival of cancer patients. Similar effects are seen with the relationship between stress, lifespan and cancer in rodents[80,81]. Further examples on tumour transplantability (the probability of tumour survival in a host) and the rate of tumour growth in humans and rodents are given in TABLE 2.

Spontaneous regression of tumours

The spontaneous regression of human cancers can occur during childhood — for example, in infant neuroblastoma[22,82]. In adults, this phenomenon is rare. In rodents, however, regression of both spontaneous and induced tumours has often been documented — for example, carcinogen-induced skin papillomas in mice[83]. Generally, cancer in rodents is easier to induce than it is in humans[3] and, at the same time, it is easier to reverse the process in rodents[84]. Although this has not been studied in all rodent strains, this effect (when confirmed) possibly reflects the increased metabolic rate in rodents compared with humans that allows rodents to recover faster. The tendency of mice and rats for spontaneous tumour regression might have applications in studies of new anticancer therapeutics tested in experimental animals. As adult rodents show an increased propensity for recovery, it is possible that they might require lower doses of an anticancer drug to be cured when compared with humans.

Carcinogens in humans and rodents

The IARC monograph series on the evaluation of carcinogenic risks to humans, published between 1972 and 2001, describes the results of studies of 869 agents and mixtures found in the modern environment[85]. Among these, only 10% (n = 87) were established as clearly carcinogenic to humans. This means that for the majority of substances there is not sufficient evidence to determine their carcinogenic risk to humans. By contrast, many of these substances were shown to be carcinogenic in rodents. Widely prescribed human medicines — acetaminophen, chloramphenicol, and metronidazole — are examples. Acetaminophen (paracetamol in the UK), an antipyretic that has been used extensively in developed countries since 1946, is not classifiable by the IARC by its carcinogenic effects on humans. However, animal experiments have shown that it increases the incidence of induced renal adenomas in rodents[85]. These agents are only carcinogenic in high doses, sometimes only at the maximum tolerated dose. Chloramphenicol, an antibiotic, increased the incidence of induced lymphomas in mice, but the drug did not show a carcinogenic effect in humans[85]. Metronidazole, an antibiotic that can destroy *Helicobacter pylori* and, therefore, probably decrease the risk of stomach cancer in humans, increased the incidence of induced colon cancer in rats[85,86].

Similarly, some human carcinogens do not affect rodents. For example, the anticonvulsant diphenylhydantoin (phenytoin) is classified as carcinogenic to humans, but showed no carcinogenic effect in experimental mice and rats[14,18,38]. These and other data reveal a serious problem in interpreting the results of animal carcinogen experiments in relation to humans. Nevertheless, there are examples of similarity in target-tissue susceptibility to carcinogenesis induced by exposure to some agents[87].

There might be several reasons for the substantial divergence between humans and rodents in the spectrum of carcinogens. One reason could be species-specific differences in microbial flora. Most cancer-promoting substances are not directly carcinogenic — they need to be metabolically transformed in an organism before they become harmful. Bacteria have a crucial

Table 2 | **The similarities between selected cancer characteristics in humans and rodents**

Characteristic	Humans	Rodents
Age-pattern of overall cancer incidence rate (spontaneous)	Typical features: low rate in youth; increase until old age; deceleration/decline at older ages	Typical features: low rate in youth; increase until old age; deceleration/decline at older ages
Cancer mortality at old ages	Cancer mortality decelerates or declines at oldest old ages	Cancer mortality decelerates or declines at old ages in some strains
Time trends in the cancer incidence rate	The overall cancer risk increased during the twentieth century	A tendency towards increases in the spontaneous tumour incidence in successive generations of some rodent strains
Place differences in the cancer incidence rate	The overall cancer risk is higher in the more developed countries	For the same rodent strain, spontaneous incidence of separate cancers varies among laboratories
Sex differences in the cancer incidence rate	Male and female cancer incidence rates intersect around the age of the female climacteric	Male and female cancer incidence rates intersect around the age of the oestrous cycle termination in female rodents
Rate of tumour growth	Commonly declines with age	Commonly declines with age; some tumours double faster in older animals
Tumour transplantability in rodents or survival chances for latent tumour in humans	Commonly increases with age; some tumours (non-Hodgkin and Hodgkin lymphomas) are more common in younger humans	Commonly increases with age; some transplanted tumours (melanoma B16, rhabdomyosarcoma RA-2) grow more readily in younger recipient animals
Identified carcinogenic factors	Nearly 90 factors, including ionizing radiation and industrial occupations, are carcinogenic in humans	Many agents are carcinogenic in rodents; some of them (but not all) are also carcinogenic in humans
Infection and cancer	Hepatitis B, *S. haematobium*, and *H. pylori* are carcinogenic in humans	Hepatitis B, *H. pylori* and *H. hepaticus* are carcinogenic in rodents
Oestrogens	Hormonal replacement therapy increases risks of ovarian and endometrial cancers, but reduces the risks of colon and cervical cancers in postmenopausal women	Oestrogens are commonly carcinogenic in rodents, particularly when administered at old ages (20 months and older)
Physical activity	Heavy exercise increases the risk of cancer; moderate exercise might decrease it	Heavy physical exercise might promote cancer
Light-at-night exposure	Increases the risk of breast and colorectal cancer in female night workers	Constant light regimen promotes spontaneous and induced carcinogenesis in rodents
Proto-oncogenes and tumour suppressors	*TP53* and *RB1* are key tumour suppressors in humans. Major proto-oncogenes are *MYC*, *RAS* and RTK genes	*Trp53* and *Rb1* are key tumour suppressors in rodents. There are homologues of some human proto-oncogenes
Parameters of individual ageing and development	Late menopause and tallness increase the risks of some cancers	The age of maturation correlates with the susceptibility to carcinogens

H. hepaticus, *Helicobacter hepaticus*; *H. pylori*, *Helicobacter pylori*; *RB1*, the retinoblastoma tumour-suppressor gene; RTK, receptor tyrosine kinase; *S. haematobium*, *Schistosoma haematobium*.

role in this process. For example, *Escherichia coli* in the gut can transform normal metabolic products, such as bile acids, into internal carcinogens, thereby increasing the risk of colon cancer[88]. Carcinogenic production depends on a dynamic balance between populations of bacteria — for example, *E.coli* versus bifido-bacteria in the intestine[89]. Interspecies differences in microflora are therefore likely to effect differences in the spectrum of carcinogens between humans and rodents.

Another reason could be interspecies differences in the host enzymatic systems that metabolize the carcinogens. For example, epidemiological studies have shown that occupational exposure to 2-NAPHTHYLAMINE is strongly associated with the occurrence of bladder cancer in humans. Given orally, it has also produced bladder carcinomas in the dog and monkey, and hepatomas in the mouse. But in the rat and rabbit, it has little carcinogenic effect because of species-specific differences in the metabolism of aromatic amines[90].

2-NAPHTHYLAMINE
The oxidation of 2-naphthylamine at the amine group leads to the formation of hydroxylamine, which binds DNA in the target tissue.

Finally, differences in age-specific susceptibility to carcinogens might have a role. For instance, several prevalent medicines (for example, phenobarbital, clofibrate, nafenopin and reserpine) induce tumours when given to old, but not young, rodents[14,48]. This important observation allows us to hypothesize that, with the currently prevailing practice of rodent experiments, some substances that are thought to be harmless based on studies in young rodents might actually be carcinogenic in elderly humans. According to regulations in many countries, each new medicine is subjected to a long-term test for carcinogenicity. However, today's rules do not support life-long experiments[18]. Experiments are usually limited to 2 years duration[91,92]. This can lead to the underestimation of potential carcinogenic effects in elderly subjects.

Light-at-night exposure

Davis *et al.*[93] and Schernhammer *et al.*[94,95] showed that there is a significant increase in the risk of breast and colorectal cancers among women who are frequently awake at about 1:30 am — when melatonin levels are typically at their highest. Melatonin levels quickly drop after exposure to artificial light during the night. The 'melatonin hypothesis' suggests that reduced pineal melatonin production increases human breast cancer risk because lower melatonin output leads to an increase in the level of female sex hormones and stimulates the proliferation of breast tissue[96].

Mice and rats are nocturnal. Nevertheless, like humans, rodents have a night peak of serum melatonin[97], indicating that the release of melatonin is linked to a light–darkness regimen rather than sleep patterns. Exposure to constant illumination increases the incidence of spontaneous and induced tumours in both rats and mice[98–101]. Therefore, rodents seem to be an adequate model for studying the carcinogenic effects of light-at-night exposure in humans.

Parameters of individual ageing

ONTOGENY-related factors (linked to individual ageing and development) such as the age of menarche and menopause, the weight and height at maturation, the age at growth cessation and parental age, can influence cancer risk in both humans and rodents, as the following examples show.

Reproductive age. In a study of 3,993 breast cancer cases and 11,783 controls, the age at menarche was found to be a risk factor for cancer among both pre-menopausal and post-menopausal women. A delay in menarche of 2 years corresponded to a 10% reduction in breast cancer risk (confidence interval (CI) 6–15%). That is, a later menarche reduced the risk of developing breast cancer[102]. As for rodents, the susceptibility of the mammary gland to chemical carcinogens is dependent on the age at which rats reach the reproductive stage[103]. Sprague–Dawley rats are more susceptible to polycyclic aromatic hydrocarbons than Long–Evans rats if they are exposed to carcinogens between 50 and 55 days of life. However, the maturation time in Long–Evans rats is much longer than that in Sprague–Dawley rats, and treatment of Long–Evans rats with carcinogens just after maturation gives the same rate of cancer incidence as in Sprague–Dawley rats[14,18,104].

Age at menopause. In humans, a late menopause is associated with an increased risk of developing ovarian and endometrial cancer[105,106]. Similarly, a higher age at the switching off of the oestrus cycle correlates with an increased incidence of several tumours in rats. The induction of anovulation (persistent oestrus syndrome) correlates with an increased risk of mammary, ovarian and uterine tumours in rodents[14,18]. The cancer-promoting effects of decreasing the age of menarche as well as increasing the age of menopause can be explained in terms of prolonged exposure to internal oestrogens. Indeed, a prolonged reproductive period is associated with protracted exposure to internal growth factors and oestrogens, which could contribute to increased vulnerability to certain hormone-related cancers, as discussed above.

Body size. Tallness and large body size are both associated with an increased risk of breast cancer in postmenopausal women[107]. Taller people also face an increased risk of colon cancer[107,108]. The carcinogenic effect of height in humans is possibly related to an increased exposure of tall individuals to growth factors, an excess of which is considered to have a role in cancer development[109]. In accordance with this view, dwarf mice were shown to be less prone to the development of spontaneous tumours[18,110]. Ikeno *et al.*[111] have found that long-living Ames dwarf mice have a significantly lower incidence of fatal lung adenocarcinomas and show less severe lesions (both neoplastic and non-neoplastic) compared with a control mouse of average size at the time of death. Importantly, the Ames dwarf mice also showed a delayed occurrence of fatal neoplastic disease. The deficiency of growth hormone(s) and resulting suppression of peripheral insulin-like growth factor-1 (IGF1) levels are assumed to have key functions in the delayed ageing of Ames dwarf mice[111]. The striking similarities between insulin–IGF1 signalling pathways in yeast, worms, flies and mammals have been described[112]. Many characteristics of mice that are long lived because of genetic modifications resemble the effects of calorie restriction in wild-type animals[110,113].

Body weight. There are reports on the correlation between greater body weight and tumour incidence in rodents[114–116]. Our findings have shown that heavier body weight at the ages of 3 months and 1 year is a predictor of increased tumour incidence both in female and male rats[115,116].

In humans, however, the relationship between weight (or the more popular body mass index, BMI, which incorporates information about the weight and

ONTOGENY
The total of the stages of an organism's life history.

Box 1 | **Essential differences in cancer development between humans and rodents**

- **Tumour origin — commonly mesodermal sarcomas in mice compared with epithelial carcinomas in humans.**
- **Carcinogenic risk factors — many rodent carcinogens are non-carcinogenic in humans and vice versa; some popular human medicines (for example, acetaminophen, chloramphenicol and metronidazole) are carcinogenic in rodents.**
- **The spectrum of common spontaneous tumours — there are no rodent strains with a high incidence of spontaneous stomach, colon or bladder tumours that, by contrast, are common in humans.**
- **The number of genetic events necessary to induce malignant transformation — fewer genetic events are required in rodents.**
- **Spontaneous regression of tumours — occurs in infants but is rare in adult humans, whereas it is common in adult mice.**
- **Excess weight — in humans, extreme obesity, as well as low weight, can increase the overall risk of cancer, whereas moderate excess weight might decrease this risk. In rodents, obesity and overfeeding were shown to increase cancer risk, whereas calorie restriction decreased it.**

height) and overall cancer risk is not so straightforward and seems to be 'U'-shaped. That is, too high or too low BMI both increase the overall cancer risk in humans, whereas moderately increased weight might decrease this risk[117]. As for separate cancer sites, the data indicate a complex relationship. For instance, higher BMI has opposing effects on the two most common histological types of oesophageal cancer in 23-year follow-up study of 2 million Norwegian men and women[118]. A positive association between BMI and cancer risk is most frequently recorded for prostate and colon cancers[119].

The association between BMI and cancer mortality seems to depend on sex. In a study of cancer and all-cause mortality among 47,212 middle-aged Finnish men and women, BMI has shown an inverse association with cancer mortality among men and non-significant direct association among women[120]. However, there are studies, such as the 17-year follow-up of the Basel cohort (Switzerland) of 2,974 men, which demonstrate that with increasing BMI, overall cancer mortality does not change[121].

A protective effect (if any) of increased weight/BMI on cancer risk in humans might be (hypothetically) related to a higher production of reactive oxygen species (ROS) in obese people. ROS are necessary for apoptosis (cell suicide) and apoptosis is important for cancer suppression. This consideration, however, is hard to apply to rodents as they do not clearly demonstrate a reduced cancer risk if they are overweight. The promoting effect of extreme obesity on cancer risk might be in part related to HYPERINSULINAEMIA in both humans and rodents. Increased insulin levels are an important factor in the development of both diabetes and cancer[122–126]. Antidiabetic drugs are efficacious in the prevention of age-related deteriorations in glucose metabolism and also in resistance to carcinogenesis[110,127]. A study addressing a new scheme of metabolic rehabilitation in cancer patients — which includes a restricted intake of fat and carbohydrate, and treatment with biguanides (ANTIDIABETIC MEDICINES) — has shown a significant increase in the survival of breast and colorectal cancer patients after treatment for 5 and 10 years. An increase in the length of the cancer-free period and a decrease in the incidence of metastasis compared with control patients was also reported[128].

Parental age. A late age at childbirth is associated with an increased risk of cancer both in mothers and in offspring. In particular, older mothers have an increased risk of breast cancer and their offspring have an increased risk of developing childhood leukaemia and brain tumours[129–132]. This is an important finding as increased parental age is common in developed countries. Rodent studies confirm the positive association between parental age and cancer risk in progeny. The offspring of old (25-month-old) male and young (3-month-old) female LIO rats[64] are more susceptible to the carcinogenic effects of *N*-nitrosomethylurea (NMU) than the offspring of young (3-month-old) males and young (3-month-old) females[133]. Mesenchymal kidney tumours developed in 2 out of 11 male and in 3 out of 17 female progeny of 25-month-old male rats exposed to a single intravenous dose of NMU (20 mg kg^{-1}) and no kidney tumours were found in 24 male and 33 female progeny of 3-month-old male rats exposed to NMU. The mean survival time of the female tumour-bearing progeny of old rats was significantly shorter than that in the progeny of young males (354 ± 30.8 days and 480 ± 14.4 days, respectively; $p<0.05$). For male tumour-bearing progeny, the relevant survival time was 430 ± 39.2 days and 559 ± 20.4 days, respectively; $p<0.02$.

Genes involved in cancer development

Genetic mutations, epigenetic modifications or deregulated gene expression have an important role in cancer development. Hanahan and Weinberg[72] listed several capabilities that a cancer cell must have. These include growth signal autonomy, evasion of apoptosis and growth arrest, insensitivity to outside growth limiting signals, sustained angiogenesis, an unlimited replicative potential, the capacity to invade other tissues and growth at metastatic sites. A number of mutations or epigenetic modifications are required to acquire these characteristics. This number is flexible

HYPERINSULINAEMIA
An increased level of insulin in the serum.

ANTIDIABETIC MEDICINES
Antidiabetic drugs, phenformin (1-phenylethylbiguanide), buformin (1-butylbiguanide hydrochloride) and metformin (N,N-dimethylbiguanide) decrease the blood glucose level and increase the susceptibility of tissues to insulin.

and might differ between cancers, as well as between humans and rodents[3,4,134,135].

Available data indicates that there are similarities in the genes involved in carcinogenesis in humans and rodents. For instance, many proto-oncogenes and tumour suppressors are the same or homologous in humans and rodents. Examples include the p53 and retinoblastoma (RB) tumour suppressors, as well as *MYC*, *RAS* and tyrosine-kinase-receptor proto-oncogenes. However, important differences between humans and rodents are evident in the number of genetic events involved in cancer development. Fewer genetic, epigenetic or gene-expression-altering events are required to induce a malignant transformation in murine cells compared with human cells. Hahn and Weinberg[3] and Rangarajan and Weinberg[4] reviewed this divergence in depth. In brief, the authors showed that at least four to six mutations are required in humans to reach this state, whereas fewer are required in mice. Human cells must break several genetic barriers to achieve immortalization, including telomere shortening and subversion of the RB and p53 tumour-suppressor pathways. By contrast, ablation of the ARF–p53 pathway alone is often sufficient to immortalize murine cells[3]. The exact reasons for these and other differences in human and murine carcinogenesis are not clear and need further investigation.

Concluding remarks

TABLE 2 summarizes the available data on similarities of selected cancer characteristics and risk factors in humans and laboratory rodents. There is a significant resemblance in many of these characteristics between the mammalian species. The age-patterns of overall cancer incidence and mortality rates (in particular, old age decline in cancer risk) show remarkable similarity between humans and rodents. This fact might reflect important coincidences in the basic mechanisms of age-specific predisposition to cancer between the different mammalian species. It might indicate that ageing, as a fundamental process, affects susceptibility to cancer in humans and rodents alike. Rodent experiments have contributed substantially to understanding the causes of the old age deceleration/decline in cancer risk and have narrowed the list of its possible causes to differential selection and somatic ageing.

There are still significant differences between humans and rodents in the ways in which cancer develops (BOX 1). However, these differences do not diminish the importance of animal modelling. Rather, they warn against simplified extrapolation of the results of rodent experiments to humans and call for further investigation of this problem to reliably predict cancer risks, as well as foster success in treating human cancers based on data from laboratory animal studies.

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