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Age-specific bone tumour incidence rates are governed by stem cell exhaustion influencing the supply and demand of progenitor cells

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ABSTRACT

Knudson's carcinogenic model, which simulates incidence rates for retinoblastoma, provides compelling evidence for a two-stage mutational process. However, for more complex cancers, existing multistage models are less convincing. To fill this gap, I hypothesize that neoplasms preferentially arise when stem cell exhaustion creates a short supply of progenitor cells at ages of high proliferative demand. To test this hypothesis, published datasets were employed to model the age distribution of osteochondroma, a benign lesion, and osteosarcoma, a malignant one. The supply of chondrogenic stem-like cells in femur growth plates of children and adolescents was evaluated and compared with the progenitor cell demand of longitudinal bone growth. Similarly, the supply of osteoprogenitor cells from birth to old age was compared with the demands of bone formation. Results show that progenitor cell demand-to-supply ratios are a good risk indicator, exhibiting similar trends to the unimodal and bimodal age distributions of osteochondroma and osteosarcoma, respectively. The hypothesis also helps explain Peto's paradox and the finding that taller individuals are more prone to cancers and have shorter lifespans. The hypothesis was tested, in the manner of Knudson, by its ability to convincingly explain and demonstrate, for the first time, a bone tumour's bimodal age-incidence curve.

1. Introduction

A net increase in cells occurs during periods of normal growth or trauma and during homeostasis when damaged cells are replaced after apoptosis. Although proliferation is often associated with cancer, there is the apparent contradiction that cancer rates rise with ageing, yet the number, potential and differentiation of stem cells decline (Zhou et al., 2008) with replicative senescence, decreased self-renewal and quiescence, increased apoptosis, increased doubling time, degraded niches and impaired terminal differentiation. As a demonstration of a viable mechanism for neogenesis, I consider the induction of two bone tumours, osteosarcoma and osteochondroma, from aberrant mesenchymal stem cells (MSC) or their committed progenitors, a process also applicable to other tumours.

Osteochondroma is the most common benign bone tumour, occurring as an abnormal osteocartilaginous outgrowth of the epiphyseal growth plate with a low rate (≤2%) of malignant transformation to secondary chondrosarcoma (Mavrogenis et al., 2008). These tumours are usually solitary and non-hereditary and are often triggered by injury, including high-dose irradiation (Taitz et al., 2004). In this study, 'osteochondroma' generally refers to sporadic, solitary osteochondromas. The rarer, hereditary multiple osteochondromas usually occur by age 5 years, earlier than most solitary chondrosarcomas. The femur is the most common site for osteochondroma, although these tumours can be found in association with any of the many skeletal growth centers. Resting zone chondrocytes proliferate in the long-bone growth plates, with this cartilage later replaced by bone. In adolescents, growth plate senescence is followed by epiphyseal fusion when osteochondroma stop growing. This benign lesion, often asymptomatic, is usually discovered inadvertently, with diagnosis more common in adolescence and declining in adulthood (unimodal age distribution) (Unni, 1996).

Osteosarcoma is the most common primary bone malignancy (excluding multiple myeloma), originating from the transformation of aberrant bone-forming mesenchymal stem cells (MSC), also known as marrow stromal cells (Mohseny et al., 2009). Of the two forms, primary osteosarcoma mostly occurs before the age of 20 and is commonly found in the long bones near metaphyseal

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growth plates (Wagner et al., 2011). Whereas, secondary osteosarcoma occurs in older adults with Paget's disease of bone, a hyperproliferative lesion, and in those exposed to high-dose radiation (Richardson, 2011b). In rare cases, osteosarcomas arise from enchondromas, pre-malignant benign cartilaginous lesions of growth plates or cartilage rests in adults. Unlike osteochondroma, osteosarcoma has a bimodal age distribution (Mirabello et al., 2009). The first peak is generally recognized as being related to the adolescent growth spurt, whereas the second peak is associated with bone turnover and remodelling in the elderly.

Carcinogenesis is recognized as a multistage process, which has been elucidated by many analytical models that have been well reviewed (e.g., Little, 2010). In general, childhood cancers have fewer driver genes, typically two to nine, than adulthood cancers. Knudson (1971) presents a compelling model for retinoblastoma based on two mutational events (and one mutated gene, *RB1*) that simulated incidence rates in young children of the hereditary and non-hereditary forms of the disease. Osteochondroma and osteosarcoma have marked developmental differences from the Knudson-type model. Osteochondroma (especially the more common solitary form) and osteosarcoma do not generally arise from germline mutations (Kitsoulis et al., 2008; Mavrogenis et al., 2008; Mohseny et al., 2009). In addition, aneuploidy is rare in retinoblastoma, but fairly common in osteochondroma and extremely prevalent in osteosarcoma, which has about 100 driver genes and a high level of genetic instability (Bovee et al., 1999; Overholtzer et al., 2003; Mohseny et al., 2009; Kuijjer et al., 2012).

Compared with the modelling of cancers with just two mutational events, the age distribution characteristics of more complex genomic forms of neoplasm are less convincingly simulated and explained. For example, a multistage carcinogenesis model by Armitage and Doll (1954) proposed that the log–log rising slope of cancer incidence with age in adults (mostly between 0 and 6) represents the number of stages or mutations minus one. In a previous study, I noted that p53 gene mutations alone account for approximately one-quarter of the age-related rise in the worldwide incidence of all cancers, and that prostate cancer, a statistical outlier with a log–log slope of 11, is almost certainly not related to 10 stages or driver mutations, but is more likely linked to genomic instability and to prostatic hyperplasia (Richardson, 2013).

The p53 gene pathway regulates cell death and cellular senescence, both of which suppress benign and malignant tumours. They are also two important processes by which MSC are lost in bone and connective tissues (Zhou et al., 2008), and similarly, by which functional cell mass is lost in the skeleton and soft tissues. About half of osteosarcomas have genetic (and perhaps epigenetic) abnormalities of the p53 gene that advance replicative senescence, leading to genomic instability and aneuploidy, common chromosomal defects in osteochondroma and particularly osteosarcoma (Bovee et al., 1999; Overholtzer et al., 2003).

Defective osteogenic and chondrogenic differentiation has been implicated in osteochondroma and osteosarcoma, respectively. Differentiation is impaired by replicative senescence, although the exact biological process is unknown (Taitz et al., 2004; Wagner et al., 2011). For the growth and maintenance of the skeleton, differentiated progeny, including the osteoblastic, chondrogenic, and adipogenic cell lineages (producing bone, cartilage and fat, respectively), are produced by MSC (Wagner et al., 2011). In vitro, each single MSC cell can form colony forming unit-fibroblasts (CFU-Fs); those with alkaline phosphatase activity (CFU-F/ALP$^+$) are osteoprogenitors.

Post-natal stem cell replication leads to telomere shortening in somatic tissues, as telomerase activity in humans is not at sustaining levels. At the Hayflick limit of cell division, telomeres reach a critical length, triggering cells to become senescent or apoptotic. A recent publication provides quantitative evidence that soft tissue organ mass loss in humans aged 25–70 is significantly associated with the log of shorter cell turnover times, implicating stem cell exhaustion and replicative senescence in normal ageing (Richardson et al., 2014). Similar to soft tissues, the percentage accumulated mass loss in trabecular bone of the elderly is about twice that in cortical bone, and trabecular bone has a nearly six-fold faster turnover than cortical bone; this is significant because trabecular, rather than cortical, bone is more often associated with osteosarcoma (O'Flaherty, 2000; Richardson, 2011b). MSC, like other stem cells, have been observed to have a self-renewal and proliferative capacity that diminishes with age, and that is regulated by different pathways, such as antioxidant defence, DNA repair, and protein turnover, before entering a senescence-associated proliferation arrest (Simonsen et al., 2002; Zhou et al., 2008).

There are complex interactions between replicative senescence, ageing, mass loss and neoplasms (Krtolica et al., 2001; Jeyapalan and Sedivy, 2008). On the one hand, replicative senescence is a means to suppress neoplasms, as long as tumour suppressor genes, such as *TP53* and *RB*, are functional. On the other hand, replication senescence is a feature of many cancers, which exhibit shortened telomeres, yet employ antidotes, such as telomerase, against this shortening (Richardson et al., 2014). It is notable that, in individuals with osteosarcoma, especially females, short telomeres are found in telomere biology genes (Mirabello et al., 2011b).

There is a normal trade-off for a stem cell to self-renew or produce differentiated and differentiating progeny. High stem cell demand relative to supply appears to produce stem cell progeny with stopped differentiation but with self-renewal properties, perhaps triggered by senescent cell secretions (Krtolica et al., 2001). I therefore hypothesize that tumour incidence is related to stem cell supply-and-demand; if so, tumour incidence would be high at periods of high demand-to-supply ratios (DSRs).

Therefore, to better understand the conditions that lead to complex neoplasms, this paper investigates the hypothesis that age-related incidence rates of osteochondroma and osteosarcoma, common benign and malignant bone tumours, are related to stem cell senescence or, more aptly, exhaustion, creating an imbalance in the proliferative supply and demand of progenitor cells. Using previously published data sets, I evaluated DSRs for the progenitor cells of two stem-like cell populations: first, for chondrocytes in femur growth plates providing longitudinal growth in children and adolescents; and, second, for bone marrow clonal cells exhibiting osteoblastic features allied with bone formation from birth to old age. The validity of the supply-and-demand hypothesis was tested by evaluating DSR trends and comparing them with reported osteochondroma and osteosarcoma incidence rates across the whole lifespan, including the early elderly (65–74 years), the late elderly (75–84 years) and the oldest old (over 85 years).

2. Methods

2.1. Growth plates and osteochondroma

The sex-specific, age-related demand $D(sex,t)$ for progenitor cells is represented by the annual longitudinal growth rate (mm y^{-1}) in the distal femur of male (aged ≥1.5 years) and female (aged ≥3.0 years) children and adolescents (Kember and Sissons, 1976). The male and female growth rates under 3 years are assumed to be the same. The age of epiphyseal fusion was taken as the year after the last measurement of longitudinal growth in the growth plates.

The age-related rate of progenitor supply was assumed proportional to the residual percentage of stem-like cell pool. The size of the stem-like cell pool $S(sex,t)$ that supply chondrocytes to the human epiphyseal growth plates is unavailable for humans, and was therefore evaluated by the extending the ages of animal data to suit humans. Schrier et al. (2006) measured an exponential drop ($p < 0.001$) in the number of chondrocytes within the overall resting zone of femur and tibia growth plates in male rabbits from 100% at birth t_0, to around 10% levels at 17 weeks. Epiphyseal fusion was assumed to occur at 24 weeks. $S(sex,t)$ is represented by a

stem-like cell pool declining exponentially with complete exhaustion at epiphyseal fusion, occurring at 15 and 18 years for girls and boys, respectively.

The "cumulative demand" for progenitor cells for age period t_1 to t_2 (within period from birth t_0 to epiphyseal fusion t_{ef}) was calculated from longitudinal growth rates $D(sex, t)$, each age t representing an age range of Δt:

$$Cumulati\,D(sex, t_1, t_2) = \sum_{t_1}^{t_2} D(sex, t) \times \Delta t \quad (1)$$

$S(male,t)$ was modified for females by multiplying by the ratio of male to female *Cumulative D*:

$$S(female, t) = \frac{S(male, t) \times Cumulati\,D(male, t_0, t)}{Cumulati\,D(female, t_0, t)} \quad (2)$$

$DSR(sex,t)$ was calculated as the ratio of $D(sex,t)$, assessed by longitudinal growth rates, to $S(sex,t)$, measured as the residual percentage of resting zone cells normalized to unity at 6 months of age (at birth preferred, but data limited) in males, when the male and female stem-like cell pool size are assumed to be virtually the same.

The DSR-derived male-to-female ratio of osteochondroma was evaluated from birth to epiphyseal fusion ($t_1 - t_2$) as the accumulated product of $DSR(sex,t)$ and the population count (see Section 2.2) for each age t representing an one age range, Δt.

$$\frac{M}{F}(DSR) = \frac{\sum_{t_1}^{t_2}[DSR(male, t) \times Pop(male, \Delta t)]}{\sum_{t_1}^{t_2}[DSR(female, t) \times Pop(male, \Delta t)]} \quad (3)$$

2.2. Bone remodelling and osteosarcoma

Demand for progenitor cells is represented by bone formation, evaluated for young males and females from ages birth to 20 years from bone-specific alkaline phosphatase (BALP) data, based on protein mass ($\mu g\,L^{-1}$) or enzyme activity ($U\,L^{-1}$) (Rauchenzauner et al., 2007; Fischer et al., 2012). Similarly, BALP data for male and female adults aged 20–70 years were based on two studies (Romagnoli et al., 1998; Michelsen et al., 2013). These studies, with minor extrapolation, provided two BALP datasets for humans of ages birth to 70 years. Modifying factors were used to equalize their cumulative values and units. BALP values for the elderly up to 92 years were interpolated from a 20% reduction in the median value, observed in two groups composed of mainly females of mean ages 69 and 93 years (Mazziotti et al., 2006).

The skeletal supply of MSC progeny involved in bone turnover $S(female,t)$ was based on exponential best fit of the number of CFU-F/ALP$^+$ colonies from cultured bone marrow fluid (2 ml) aspirated from the anterior iliac crest of women 4–88 years of age (Nishida et al., 1999). The $S(female,t)$ residual pool size (%) was modified for males by multiplying by the ratio of female to male *Cumulative D* (similar to Eq. (2)). To explore the premise that the elderly have genetically superior maintenance genes, it was assumed that their supply of MSC progeny was stable from age 75 years onwards (see Sections 3 and 4).

$DSR(sex,t)$ was initially calculated as the ratio of the "localized" demand to supply, namely $D(sex,t)$ assessed as BALP concentration ($U\,L^{-1}$) to the residual percentage of stem-like cells in bone marrow normalized to unity at 6 months of age in females.

Osteosarcoma incidence data for US whites was obtained from nine registries of the Surveillance, Epidemiology and End Results (SEER) program during the period 1975–2005. The data was categorized by sex, age (0–4, 5–9, . . ., 80–84, ≥85 years) in the manner of Anfinsen et al. (2011). Age-specific rates per 1,000,000 person-years were evaluated employing the corresponding population data, also available from SEER (2008).

Male-to-female ratios of osteosarcoma were calculated for 3 age groups, 0–24, 25–59, and ≥60 years. For comparison, DSR-derived male-to-female ratios were calculated by Equation 3 for same 3 age groups ($t_1 - t_2$) from the accumulated product of $DSR(sex,t)$ and the population count for each median age t representing an age range of Δt (Eq. (3)).

As an alternative measure of the skeletal supply of osteoprogenitor cells and MSC provided by the exponential decline of CFU-F/ALP$^+$ colonies, the number of colonies for ages 30–72 was modified by the fractional decline in the osteoblast differentiation potential of bone-marrow-derived MSC from female and male adults aged 17–90 years obtained from Zhou et al. (2008). For females, the assessment was by ALP enzyme activity assays of MSC. For males (aged 42–75), the osteodifferentiation potential of STRO-1$^+$ mononuclear cells was taken as the ALP fluorescent immunoreactivity of cumulative cells, extrapolated from 40 back to 30 years.

DSR values were alternatively evaluated as the ratio of "whole body" demand, based on the product of BALP concentration and the whole body plasma volume, to "whole body" supply, based on the product of the number of CFU-F/ALP$^+$ colonies and skeletal active marrow mass. The age-dependent mass of the whole body and active marrow was interpolated from data for reference males and females, newborns to young adults, tabulated in ICRP (2002). The plasma volume concentration ($ml\,kg^{-1}$) was obtained using the algorithm, $45.02e^{(-0.0014 \times age\ in\ years)}$, extrapolating to 92 years (Altman and Dittmer, 1961). An annual loss of 0.45% of the skeletal active marrow mass of male and female young adults, from age 25–92, was assumed based on the study of haematopoietic tissue in the anterior iliac crest (Hartsock et al., 1965), with loss rates similar to other major sources of active marrow, e.g., vertebrae. The same annual reduction rate was assumed for the male and female whole body mass, from age 55–92, based on Japanese data, presuming no loss in the extra mass carried by ICRP reference individuals (Ogiu et al., 1997).

3. Results

3.1. Growth plates and osteochondroma

The demand for progenitor cells is represented in Fig. 1A by the longitudinal growth rate in distal femurs, which peaks at about

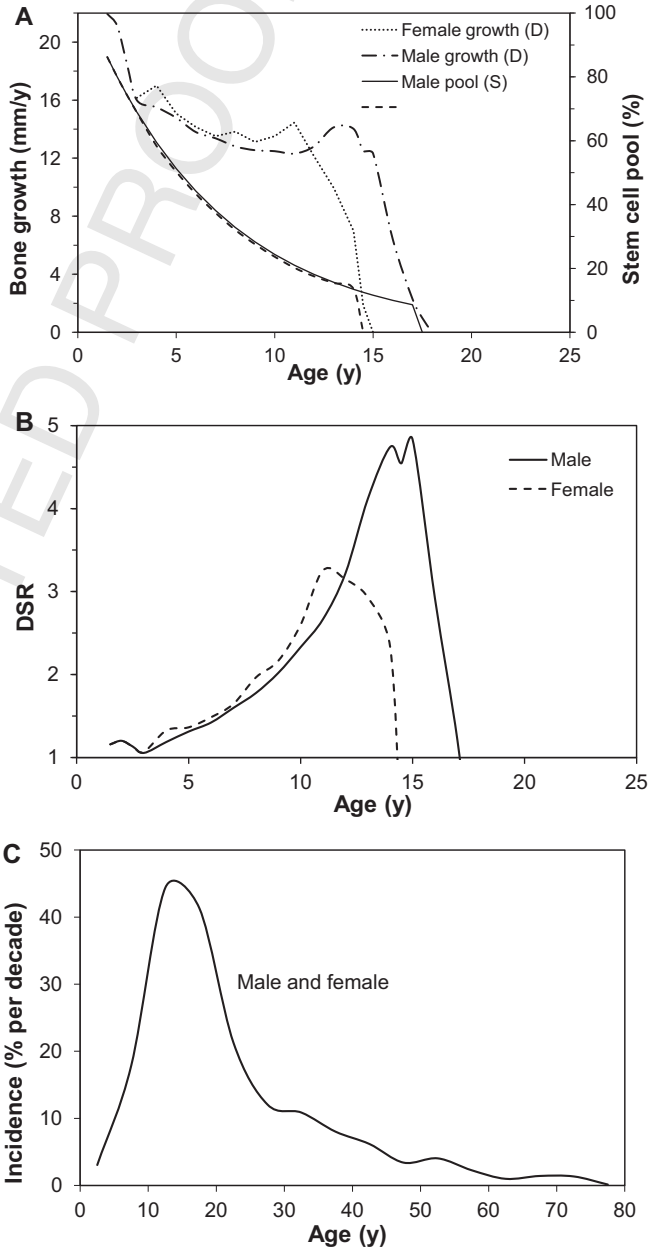

Fig. 1. Growth plates and osteochondroma: age-related progenitor cell demand by epiphyseal growth plates and supply by chondrogenic stem-like cells in males and females lead to a DSR similar to trends in the osteosarcoma incidence rate. (A) Demand is represented by annual longitudinal growth rate in the distal femur of male and female children and adolescents (Kember and Sissons, 1976). Supply of chondrogenic stem-like cells is modelled for humans on the resting zone cell pool in distal femur growth plates (Schrier et al., 2006). (B) DSR, normalized to unity at 0.5 years old, peaks in adolescence for females before males. (C) Osteochondroma incidence rates for males and females together peak in the second decade of life (Unni, 1996).

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ages 11.5 and 13.5 years in adolescent females and males, respectively (Kember and Sissons, 1976). Employing a combination of animal and human data, Fig. 1A shows that the supply of chondrocytes in the resting zone of growth plates declines exponentially from birth; in adolescence, the pool is abruptly exhausted, activating epiphyseal fusion. Based on the cumulative demands of femur growth (see Section 4), the ratios of female to male stem cell pool were close to unity (range 0.96–1.04, 0.5–14.5 years of age).

The DSR, evaluated as the ratio of longitudinal growth to the size of stem-like cell pool, peaks at the ages of 11–12 and 14–15 for girls and boys, respectively (Fig. 1B). These DSR trends are a good representation of trends in skeletal osteochondroma diagnosis (includes both sporadic and hereditary variants), which, similar to DSR, also peaks in the second decade of life (Unni, 1996).

The DSR peak is steep, but would be broader and more like the osteochondroma incidence trend from ages birth to 80 years (Unni, 1996; Mavrogenis et al., 2008), if allowance were made for multiple growth centers with variable fusion times, rather than the single growth plate site modelled. The DSR rates decrease abruptly after peaking. Given that this benign bone tumour is usually found incidentally, after the tumour has occurred, the true decline is more gradual than the abrupt decline of the DSR. Notwithstanding, the relative shapes of the DSR and osteochondroma incidence curves fit with observations of a short, but variable, mean latent period of ~5 years, which can range up to 27 years for radiation-induced tumours (Taitz et al., 2004). Both DSR and osteochondroma incidence rates exhibit no rise with old age.

Although sex-specific osteochondroma incidence rates are not available, these tumours are hormonally influenced and stop growing with skeletal maturity, which occurs earlier in girls than in boys. The DSR (from infancy to epiphyseal fusion), as a proposed measure of age-specific osteochondroma incidence, by Eq. (3), leads to a male-to-female ratio of 1.5:1, which is close to low end of the reported range 1.6–3.4:1 (Mavrogenis et al., 2008), but still significantly male-dominated.

3.2. Bone remodelling and osteosarcoma

The CFU-F/ALP$^+$ pool size as measured in human iliac crest bone marrow aspirates decreases rapidly (Fig. 2A) from birth to age 10, then depletes more slowly during adolescence and adulthood, according to the data of Nishida et al. (1999). This measure provides a good representation of the skeletal supply of osteoprogenitor cells and MSC, as the marrow cellularity of the iliac crest is similar to the mean skeletal cellularity.

A good marker of the skeletal demand for osteoprogenitors involved in bone formation (as opposed to osteoclast bone

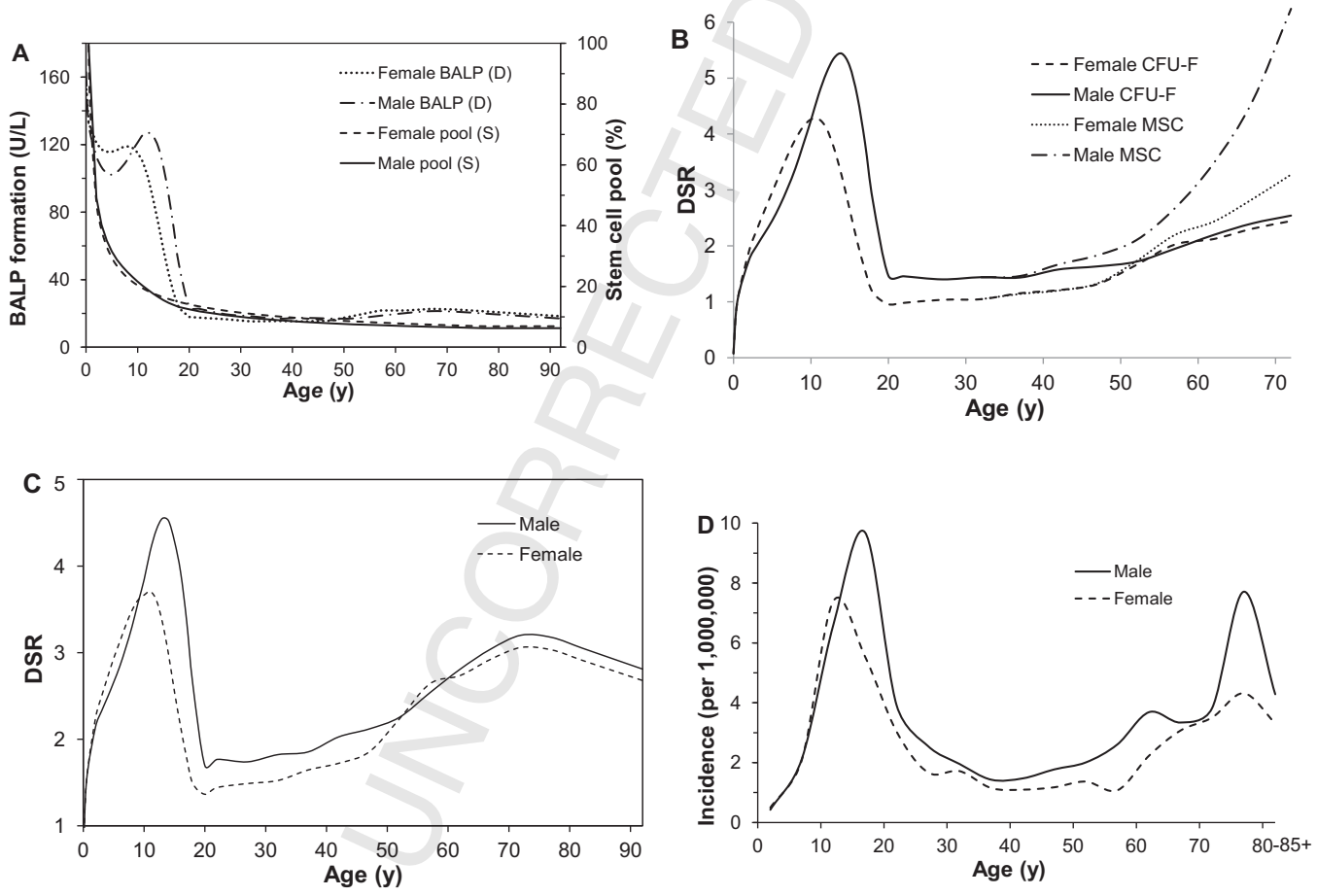

Fig. 2. Bone remodelling and osteosarcoma: age-related progenitor cell demand for bone remodelling and supply by stem-like cells in the bone marrow of males and females leads to a DSR trend similar to osteosarcoma incidence rates from birth to old age. (A) Demand is represented by the bone formation BALP activity (U L^{-1}). Supply of skeletal MSC-derived progeny is represented by CFU-F/ALP$^+$ colonies counted in bone marrow aspirates from the iliac crest (Nishida et al., 1999). (B) Employing the localized demand and supply data shown in Fig. 2A, the DSR, normalized to unity at 0.5 years old, peaks for females before males in adolescence, declines, and rises again in the elderly. In addition, an alternative evaluation of DSR is shown based on the decline in osteoprogenitor supply as represented by the osteoblast differentiation potential of MSC from female and male adults aged 30–72 years, employing the ALP activity data of (Zhou et al., 2008). (C) Employing whole body demand and supply data leads to a DSR peak at 72–77 years, assuming in the elderly and oldest old the supply of MSC-derived progeny is stable and BALP-derived demand slightly falls. (D) Osteosarcoma incidence rates for US whites are shown (SEER, 2008).

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resorption activity) is serum BALP activity (Fig. 2A). This marker is particularly sensitive to physiological changes such as adolescent growth spurt and menopause. The demand for progenitor cells participating in bone formation, as measured by BALP activity, is highest in newborns, slowly declines until early adolescence in girls and late adolescence in boys, then decreases rapidly to its lowest level in young adults (Rauchenzauner et al., 2007; Fischer et al., 2012), before increasing again in the latter half of adulthood (Romagnoli et al., 1998; Michelsen et al., 2013) to cope with the decline in osteocyte density and repair of accumulated damage related to ageing, e.g. bone microcracks (Vashishth et al., 2000). Based on the localized cumulative demands of bone formation (Eq. (1)), the ratios of female to male stem cell pool were 0.94 at 10 years, 1.13 at 20 years, 1.14 at 40 years and 1.10 at 70 years. When whole body demand is taken into account (see Section 2.2), the corresponding female to male stem cell ratios were 1.00, 1.07, 1.16 and 1.19: the higher ratios are partially due to the reference female 15 year old and adult having lower masses than their male counterparts. Therefore, on the basis of osteoprogenitor cell supply and demand, the MSC of adult females have a greater proliferative or regenerative potential capacity than those of males, as observed experimentally (Tan et al., 2013).

The DSR, evaluated as the ratio of BALP activity to the size of the stem-like cell pool, whether localized (Fig. 2B) or whole body (Fig. 2C) assessments, peaks at the ages of about 10–11 and 13–14 years for girls and boys, respectively. Sex-specific DSRs have similar trends to US (and world) osteosarcoma incidence rates for whites shown in Fig. 2D. In all international regions studied by Mirabello et al. (2009), the incidence peaks earlier in females, 10–14 years of age, than in males, 15–19 years. The DSR, like the osteosarcoma incidence rates, rises again in middle age. No quantitative estimate was made of the time delay between the rise in DSR and the increase in secondary osteosarcoma as the trend lines are complex: however the delay appears small.

As an alternative measure of the skeletal supply of osteoprogenitor cells and MSC provided by the exponential decline of CFU-F/ALP$^+$ during life measured by Nishida et al. (1999), ALP activity data for MSCs was obtained from Zhou et al. (2008) as a measure of osteoblast differentiation potential of bone-marrow-derived MSC from female and male adults 30–72 years. With the caveat that different methods were employed for the assessment ALP activity data (see Section 2.2), Fig. 2B shows a much greater rise in DSR in the elderly using this method.

Finally, as elucidated later, there is evidence that telomere length, and hence replicative senescence, stabilizes in the late elderly and very old, as seen in measurements in blood leukocytes of individuals aged 44–105 years (Atzmon et al., 2010), but particularly in the pituitary gland of those >75 years, in patients aged 0–100 years (Ishikawa et al., 2012) Although, comparable data are lacking for MSC, I assume the supply of MSC progeny and differentiation potential are stable age 75 years and older. In addition, a small decline in BALP demand, as observed in the early and late elderly (Mazziotti et al., 2006), is included in the model.

This results in a DSR peak at 72–77 years (Fig. 2C) and declining thereafter, similar to the osteosarcoma incidence peak seen in US whites aged 75–79 years (Fig. 2D) and in Europeans aged 70–74 years (Mirabello et al., 2009; Anfinsen et al., 2011). In Fig. 2C, DSR was evaluated from whole body demand and supply, although localized demand and supply results in a similar bimodal trend (not shown).

The reported overall world male-to-female ratio of osteosarcoma incidence in children, adolescents and young adults aged 0–24 years is 1.43:1; in adults, 25–59 years, 1.28:1; and in the elderly, ≥60 years, 1.01:1 (Mirabello et al., 2009). The ratio is lowest in the elderly age group as females tend to live longer than males. Similarly, male-to-female osteosarcoma incidence in the three age ranges is 1.29:1, 1.46:1 and 0.99:1 (Fig. 2D) and the product of DSR and the US white population by age result in male-to-female ratios of 1.34:1, 1.19:1 and 0.80:1 (Fig. 2C).

4. Discussion

4.1. Alternative model based on DNA mutation burden and progenitor demand

Before the attributes of the supply-and-demand hypothesis are discussed, an alternative model is considered based on accumulated somatic mutations, which are involved in both ageing and cancer (Kirkwood, 2005). Across the lifespan, there have been reports of linear and non-linear increases in nuclear DNA damage in both somatic and germ cells (e.g., translocations, γ-H2AX foci, and the DNA oxidative product 8-hydroxy-29-deoxyguanosine), accompanied by an exponential increase in cancer incidence (Tiemann-Boege et al., 2002; Richardson et al., 2014). For example, Vorobtsova et al. (2001) provide a mixed-gender dataset for the frequency of translocations in the lymphocytes of a control group, 3–72 years old: the best-fit age-response is a quadratic equation, $0.23 + 0.51 \times 10^{-3} \times t^2$, where t is age in years.

An exploratory analysis was carried out to assess whether the age-related osteosarcoma incidence could be modelled by the product of progeny demand, represented by BALP concentrations, and the mutational burden (Fig. 3). The resulting curves have some characteristics similar to the osteosarcoma incidence (Fig. 2D). This is not surprising, considering the decline in DNA repair with ageing and the accompanying rise in telomere- and non-telomere-associated DNA damage, which are certainly factors affecting MSC pool size and function. However, the supply-and-demand hypothesis leads to DSR curves with a much closer fit to the incidence curves for osteosarcoma (compare Figs. 2C, D and 3); as well, the DSR model better demonstrates low cancer rates in infancy, adolescent cancers dominating those diagnosed in adulthood, and the declining rates in the late elderly.

Notwithstanding, the mutational burden has an influence on cancer incidence, as defects in the cellular response to DNA damage have been implicated in segmental premature ageing disorders such as Werner syndrome and Rothmund–Thomson syndrome, which predispose to osteosarcoma (Ferrarelli et al., 2013). However, these syndromes are caused by mutations in WRN and RECQL4 helicases, respectively, genes that promote telomeric maintenance. This further supports the supply-and-demand hypothesis.

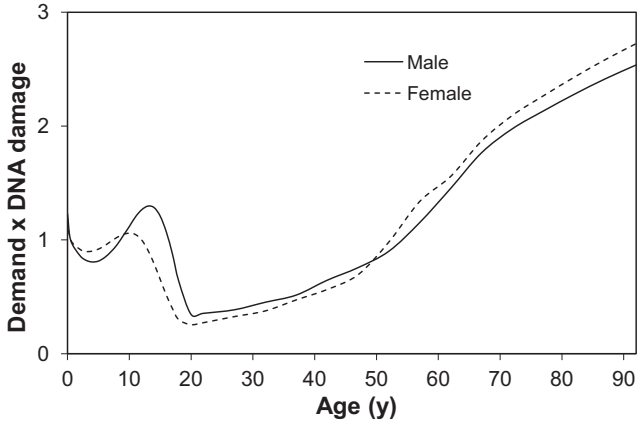

Fig. 3. Product of DNA mutational burden and progenitor demand: this model is the age-dependent product of the mixed-gender translocation frequency (Vorobtsova et al., 2001) and the gender-dependent, bone formation BALP concentration, the product normalized to unity at 0.5 years old.

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4.2. Implications of the stem cell supply-and-demand hypothesis

The multistage process of carcinogenesis can be separated into initiation, promotion and progression. Fig. 2B and D shows a remarkably short interval of about 2–4 years between the maximum DSR and the diagnostic peaks in childhood osteosarcoma. This indicates that a DSR crisis is a promotional/progressional event, rather than an initiation event, in the development of this cancer.

In the skeleton, DSR rises in adolescence, as the growth centers close, and again in old age, when demands for progenitor cells to replace apoptotic, necrotic or senescent (possibly with limited lifetime) cells outstrip the progenitor cells provided by exhausted stem cell pools, causing mass loss and frailty (Richardson et al., 2014). In particular, senescent cells can arise due to "epigenetic senescence" (initiated by histones altering activity of genes), stress-induced senescence or replicative senescence (von Zglinicki et al., 2005; Bork et al., 2010). In both periods of life, stem-like cells have limited proliferative potential, because of factors such as the finite telomere length of their chromosomes and niche degradation, driving the clonal evolution of premalignant stem cells.

This work demonstrates that cell proliferation is not in itself a risk factor for tumogenesis; instead, neoplastic promotion or progression occurs preferentially when, for example, stem cell exhaustion creates a short supply of progenitor cells at ages of high mitogenic demand. In childhood, growth is more than met by the progenitor supply from nascent stem cell pools at their maximum potential and DSR is low, i.e., low DSR = $D_{(\text{high growth})}/S_{(\text{maximum potential})}$. During the relatively homeostatic period of young adulthood, the proliferative demands of stable turnover are largely met by the supply of stem cell progenitors and DSR is moderate, i.e., moderate DSR = $D_{(\text{stable turnover})}/S_{(\text{moderate potential})}$. As mentioned above, high DSR arises when rapid growth or demand for replacements for apoptotic, necrotic or senescent cells exacerbate high demand for MSC progeny when stem cell pools are exhausted, i.e., high DSR = $D_{(\text{exacerbated cell growth})}/S_{(\text{exhausted potential})}$.

I first suggested that an imbalance in the demand and supply of progenitor cells is the main determinant of age-dependent cancer incidence rates in my study of precursor B-cells and acute lymphoblastic leukemia, which, similar to osteosarcoma, also has a bimodal age distribution (Richardson, 2011a). The incidence of acute lymphoblastic leukemia peaks from 2 to 5 years of age at a time of high demand for precursor B-cells during immune development. The infective lymphoid recovery hypothesis contended that a DSR crisis in lymphoid tissue is created by a low supply of precursor B-cells. This promotional advancement of the neoplastic process is brought about by infection-related glucocorticoid release soon after birth and subsequent transient involution of the thymus and other lymphoid organs, causing a decline in antitumour immunosurveillance and the maturation arrest of B-cells. These stressors increase both stress-induced (premature) and replicative senescence, prompt the demand for progenitor cells to outstrip supply, with pre-cancerous stem cells perversely filling a need by parasitizing normal niches of active stem cells (e.g., sites involved in bone remodelling), leading to overt cancer.

The supply-and-demand hypothesis is also supported by its ability to elucidate the neoplastic process for high-dose radiation (Fig. 4), a well-known cause of solitary osteochondroma and osteosarcoma. Radiation, similar to other stressors, including the greater vulnerability to infections and chronic inflammation associated with ageing, can increase the burden of reactive oxygen species and cumulative mutational load (Richardson, 2009). It can also decrease DNA repair, increase epigenetic gene silencing, induce hormonal changes, decrease stem cells' self-renewal capacity and advance their age-related apoptosis and senescence (Mauch et al., 1988; Martin et al., 1998). Ionizing radiation exposures produce free radicals and reactive oxygen species that excite a high proliferative demand on MSC involved in inflamma-

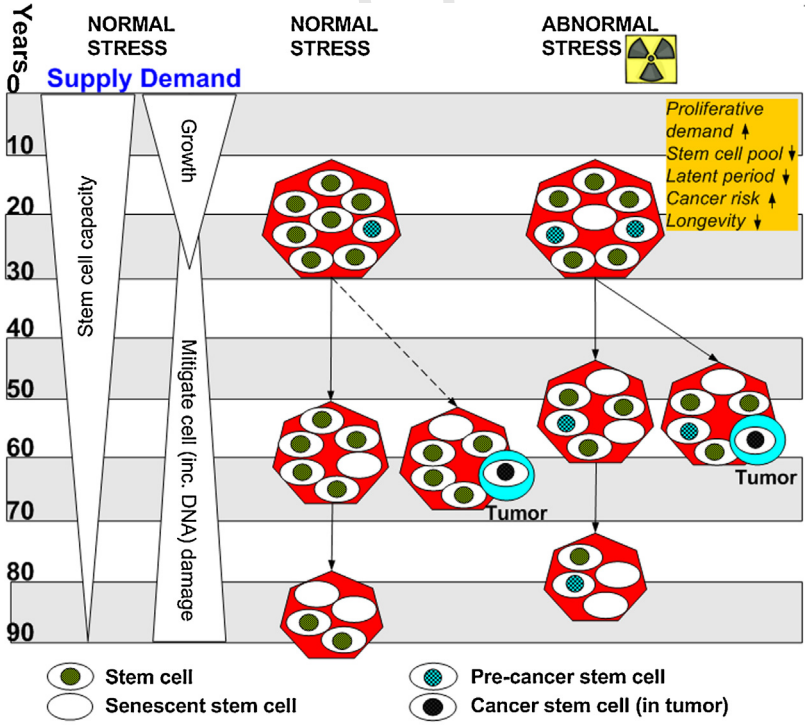

Fig. 4. Spontaneous and radiation-induced tumours initiated in young adults: organs undergoing normal and abnormal radiation-induced proliferative demands and stem cell supplies. Under normal conditions, ageing decreases the supply of progenitors from stem cells, resulting in skeletal and organ involution and the suppression of cancer in the majority of a population. For a minority of those under normal stress and a larger fraction of those exposed to radiation, especially high dose, higher proliferative demands and/or greater stem cell exhaustion elevates DSR, leading to a shorter latent period and a higher risk of cancer. The schematic figure does not account for telomeric homeostasis in the late elderly and very old.

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tion and subsequent fibrosis. When bone marrow is subjected to a high dose, there is an increase in expression of the ageing and senescent cell biomarker $p16^{INK4a}$ (Le et al., 2010; Bork et al., 2010) reducing the capacity for stem cell renewal and, consequently, causing a decline in cellularity commensurate with premature ageing (Barranco et al., 1969). Radiation-induced high DSR puts proliferative pressure on aberrant MSC and their progenitor cells, increasing the risk of osteochondroma and osteosarcoma (Taitz et al., 2004; Richardson, 2011b). Therefore, radiation exposure is an example of a stressor that advances replicative senescence, and particularly stress-induced senescence of stem cells (Richardson et al., 2014), and prematurely elevates the ageing-related rise in DSR, shortening the latency period leading to cancer.

4.3. Explanation: males more prone to tumours

The supply-and-demand hypothesis provides explanations for five well-known observations concerning humans' and other species' propensity for tumours and physiological conditions that shorten lifespan. The first observation is, that compared with males, in females tumour rates in general, and osteochondroma and osteosarcoma rates in particular, are lower. Among humans and many other mammals, females live longer than males. These differences have been credited to differences in lifestyle, antioxidants, oestrogenic compounds and immune system, but these explanations have not been definitive (Vina et al., 2005). Here I explore the potential involvement of a mechanistic difference affecting replicative senescence; namely, the longer telomeres of adult females than of males, evident in humans and some other mammals (Daniali et al., 2013). For example, both Mirabello et al. (2011b) and Nordfjäll et al. (2008) report ~9% significantly longer telomeres in the peripheral blood of young and middle-aged adult females. Smaller differences were found in leukocytes and three somatic tissues from individuals of mean age 44 years (Daniali et al., 2013). Oestrogen may extend the potential for cell proliferation by stimulating human telomerase reverse transcriptase (hTERT) activity, leading to increased telomerase, longer telomeres and, presumably, delayed replicative senescence in females compared with males (Terry et al., 2008).

As well, this analysis found less exhaustion of MSC in female than in male adults (Fig. 2A), supporting the same observation made experimentally for MSC (Tan et al., 2013). This sexual dimorphism can be attributed to hormonal, genetic, or epigenetic factors that can have a differential effect on the stem cell pools of males and females. Conservatively, the age-related rate of progenitor cell supply was assumed to be proportional to the residual percentage of the chondrocyte- and osteoblast-like stem cell pools. The difference of 10 or 19% in the stem cell pool of adult males and females aged 70 years was evaluated on the basis that, in males, the localized or whole body cumulative demand for osteoprogenitor cells is greater than in females, although, as indicated, other factors may enlarge this difference.

Richardson et al. (2014) reported an unexplained observation that human males in general exhibit greater acceleration of mass loss in some major soft tissue organs and body cell mass than females, yet males have comparatively higher tumour rates in general, and are more prone to osteochondroma and osteosarcoma in particular. For soft tissues, this finding, at least in part, can now be explained in terms of the supply-and-demand hypothesis: the greater senile mass loss in males is due to replicative senescence, elevating their DSR ratios and tumour risk. Yet, the situation is more complex for bone, where oestrogen levels play an important role. Although peri- and post-menopausal women experience greater bone resorption than men the same age, nevertheless the cumulative demand on their osteoprogenitor cells is lower, their replicative senescence less advanced, and consequently their bone tumour risk reduced compared to men.

4.4. Explanation: tall individuals more prone to cancers and a shorter lifespan

The second observation is the unexplained yet consistently found link between high birth weight or adult height in humans, as well as full-grown size in dogs, and risk of cancer, including osteosarcoma (Green et al., 2011; Mirabello et al., 2011a; Renehan, 2011; Kraus et al., 2013). One suggested explanation is that height predicts cancer risk because taller people have more cells and thus a greater opportunity for mutations or epigenetic silencing, leading to malignant transformation (Albanes and Winick, 1988). The weakness in this argument is that the number of cells is not as relevant as the number of pre-malignant cells or cancer stem cells – and there is no evidence that there is a greater number of these in the larger individuals of a species. However, a supply-and-demand crisis provides a solution, with supportive evidence that, first, cancer risk is elevated by replicative senescence, e.g. short telomeres is a characteristic of most cancer cells, linked to the cumulative demand for progenitor cells (Richardson et al., 2014), and, second, that the initial size and replicative senescence characteristics of the stem cell pool may depend more on the species (e.g., mouse to human MSC telomere length is ~5:1) than on the individual's birth weight or height.

Addressing the second condition, Dingli and Pacheco (2007) make the case for mass-dependence of the hematopoietic stem cell pool in mammals, conforming to a 3/4 power scaling law. Assuming that this allometric law applies to both interspecies and intraspecies stem cells, the interspecies mass range is ~27 orders of magnitude, whereas a human's (intraspecies) postnatal mass range is less than two orders of magnitude. However, further evidence that interspecies variability dominates over intraspecies variation is that the haematopoietic stem cell (vascular, rather than quiescent) population in cord blood differ with birth weight in humans (Capittini et al., 2011); however, the contribution of birth weight to adult weight is significant but very small, with R^2 of <0.1% (Eide et al., 2005). Therefore, in terms of the hypothesis, taller individuals of a species require greater proliferative growth; consequently, the increased cumulative demand depletes their species-allocated stem cell pools more rapidly than in shorter individuals, hence increasing DSR and their propensity for cancer.

4.5. Explanation: larger, taller individuals live shorter lives

The third observation is that an individual's size or height is a lifespan modifier. The majority of cell divisions in a lifetime occur during developmental growth and sexual maturation; therefore, this period has a major influence on the overall rapidity of stem cell senescence (Fig. 2A). Kraus et al. (2013) reported data and analysis of the well-known shorter lifespans of larger breeds of dogs. In addition to having a lower cancer risk (see previous section), tall humans (when comparing genders, different populations or those within a population) also die earlier on average than short ones (Samaras, 2007). In terms of the supply-and-demand hypothesis, taller individuals place a greater cumulative demand for progenitor cells on their species-dependent stem cell pools (Dingli and Pacheco, 2007), which would not be affected by human population or by dog breed (as all humans are the same species, as are all dogs). This results in quickened replicative senescence of stem cells, increasing DSR and cancer rates, increasing premature ageing and reducing the lifespan of taller individuals. Although stem cells have been implicated in ageing (Smith and Daniel, 2012), this extension of the hypothesis, and its ability to explain published

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observations, provides strong evidence implicating stem cell exhaustion in ageing.

4.6. Explanation: Peto's paradox

The fourth observation is Peto's paradox (Peto et al., 1975), which states that the incidence of cancer does not appear to increase in larger mammals; for example, comparing humans with blue whales. This is surprising, considering large organisms are associated with long lives and a greater number of cells and cell divisions. It has been suggested, although not shown by experimental evidence, that larger animals have more common but less lethal malignant tumours (Nagy et al., 2007), or have more cancer suppressor genes than smaller creatures (Roche et al., 2012). An alternative explanation is simply that the DSR of progenitor cells has similar values for corresponding developmental stages, regardless of the size of the organism.

4.7. Explanation: cancer rates decline in the very old

The fifth observation is that the incidence rate of almost all cancers, including osteosarcoma (Fig. 2D), peaks at about 75 years of age and begins to fall, with other diseases becoming more important causes of morbidity and mortality (Harding et al., 2008). Ageing and cancer are inextricably intertwined and involve multifaceted mechanisms. These include stem cell exhaustion, in which replicative senescence and epigenetic senescence play important roles, which are generally considered to be genetically programmed. Recently, Richardson et al. (2014) reported a strongly significant association between cell proliferation and functional mass loss, a form of disposable soma affecting fitness and ageing (Kirkwood, 1977). We found that two-thirds of the human variability in mass loss can be assigned to the log of tissue turnover times and made a case that this observation is characteristic of replicative senescence and stem cell exhaustion. Furthermore, we suggested that replicative senescence and stem cell exhaustion are not biological necessities, but evolutionary adaptations in humans, suppressing cancer, as long as proliferative/apoptotic genes are functional.

Studies of monozygotic and dizygotic twin pairs reveal that ~20–30% of the overall variation in adult lifespan is accounted for by genetic factors. The genetic effect on lifespan is minimal before age 60, yet substantial (30–40%) for those surviving beyond this age (Hjelmborg et al., 2006). Moreover, telomere length has a higher heritability than longevity, strengthening the case for mass loss associated with replicative senescence being an evolutionary adaptation. Telomere length heritability is about 80% in young and middle-aged adults and estimated at about half that value in twin pairs aged 73–95 years (Bischoff et al., 2005).

Although telomeric length measurements in MSCs throughout the lifespan are not available, telomeric studies of other cell types are relevant here, as replicative senescence at the level of the organism is similar within any species (Dingli and Pacheco, 2007). A lack of association is generally reported between telomere length and longevity, with telomere length more related to a body's capacity to absorb damage (somatic redundancy) due to lifestyle, chronic disease and social weathering (Terry et al., 2008; Boonekamp et al., 2013). Indeed, telomere lengths have been shown to stabilize or even increase slightly in advanced age groups (Atzmon et al., 2010; Ishikawa et al., 2012). The oldest old may be genetically different from those dying younger, with progenitor supply enhanced by greater telomere maintenance gene activity; for example, FOXO3a gene activity is frequent in centenarians (Terry et al., 2008; Flachsbart et al., 2009).

In addition, demand for progenitors in the elderly is reduced because of accelerating actual or functional mass loss in organs, estimated at up to 35% between ages 25 and 70 years old (Richardson et al., 2014). Taken together, telomeric homeostatis and accelerating mass loss, especially in males, may lead to future models of DSR trends that better follow the trend, and difference, in elderly male and female osteosarcoma rates in particular, and cancer rates in general.

4.8. Limitations of supply and demand data

Our analysis is limited by the uncertainty arising from the lack of published data on MSC pool size in the late elderly and oldest old. As well, it is limited by the use of data from femur and tibia growth plates in rabbits, rather than humans. In addition, there is a lack of continuous age-based whole body mass, active marrow mass, and BALP data to cover the entire age range of this analysis, availability being particularly sparse and having limited reference values for the early and late elderly and oldest old. Concerning the exploration of declining cancer rates in the late elderly and oldest old, the data employed are solid; however, the extrapolations, inferences and trends assumed need further experimental confirmation. In particular, Zhou et al. (2008) have shown the great potential of age-related changes in osteoblastic differentiation, ALP activity, senescent cells and apoptotic cells associated with MSCs, but their study was based on bone marrow analysis of a small sample and narrow age range.

5. Conclusion

In the manner of Knudson, the stem cell supply-and-demand hypothesis was tested and proved valid by showing that DSR trends provide an explanation for the unimodal age distribution of osteochondroma and bimodal age distribution of osteosarcoma. Stem cell functional exhaustion – replicative senescence alone is too simplistic – has been quantitatively and inextricably implicated in both human tumours and ageing. This analysis has employed the hypothesis to explain five well-known published observations concerning neoplasms and ageing, implying a major role for stem cell exhaustion. Future work will evaluate DSR from infancy to old age to understand the promotion and age distribution of acute lymphoblastic leukeumia and acute myeloid leukemia.

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