



## Review

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### Author for correspondence:

David Haig  
e-mail: [dhaig@oeb.harvard.edu](mailto:dhaig@oeb.harvard.edu)

# Maternal–fetal conflict, genomic imprinting and mammalian vulnerabilities to cancer

David Haig

Department of Organismic and Evolutionary Biology, Harvard University, Cambridge, MA 02138, USA

Antagonistic coevolution between maternal and fetal genes, and between maternally and paternally derived genes may have increased mammalian vulnerability to cancer. Placental trophoblast has evolved to invade maternal tissues and evade structural and immunological constraints on its invasion. These adaptations can be co-opted by cancer in intrasomatic selection. Imprinted genes of maternal and paternal origin favour different degrees of proliferation of particular cell types in which they reside. As a result, the set of genes favouring greater proliferation will be selected to evade controls on cell-cycle progression imposed by the set of genes favouring lesser proliferation. The dynamics of stem cell populations will be a particular focus of this intragenomic conflict. Gene networks that are battlegrounds of intragenomic conflict are expected to be less robust than networks that evolve in the absence of conflict. By these processes, maternal–fetal and intragenomic conflicts may undermine evolved defences against cancer.

## 1. Introduction

Cancer is an evolutionary problem. Natural selection within multicellular bodies favours somatic cell lineages that proliferate faster than their neighbours, even though rapid proliferation reduces organismal fitness. But, with a few notable exceptions, each cancer dies with its host's body. Intrasomatic selection must start anew each generation in a new body. Germ-cell lineages, by contrast, can survive the death of the bodies in which they reside and have been selected to produce new bodies each generation in service of the germ line. Premature death of bodies with less-effective defences results in preferential survival of genetic lineages descended from bodies that postponed cancer until later in life [1]. Present bodies are thus the current vehicles of genetic replicators that have resided in unbroken chains of past bodies that survived to reproduce before succumbing to cancer or other ailments. Intrasomatic selection has the advantage of numbers, many cells in one body, but intersomatic selection the advantage of experience. Anti-cancer mechanisms evolve over many generations but rogue cell lineages must start from scratch each generation with a genome already adapted for their control.

The incidence of cancer is predicted to increase with age because selection against cancer weakens as fewer individuals survive to older ages; because selection for early reproduction may have pleiotropic effects that promote cancer later in life; and because older bodies provide more time for intrasomatic selection. Selection to maintain bodily functions is stronger for longer lived organisms with larger bodies because such organisms delay reproduction to older ages. These arguments provide plausible reasons why cancer rates are independent of longevity and body size in interspecific, but not intraspecific, comparisons [2]. From this perspective, cancer deaths are subsumed under an evolutionary theory of aging that predicts all body parts will start to malfunction at roughly the same age within species but that senescence will occur at older ages in species that invest more in bodily maintenance and less in early reproduction [3,4].

A genetic change that increases susceptibility to cancer will sweep to fixation if it confers large benefits that more than compensate for the increased risk. Such

antagonistically pleiotropic effects could reflect a fundamental trade-off in which a benefit necessarily entails risk or could reflect recent selection for a benefit of which the predisposition was an 'incidental' companion carried along for the ride [5,6]. Given sufficient time, selection imposed by untimely deaths from cancer should decouple incidental predispositions from benefits, albeit with evolutionary delay. Evolutionary 'arms races' in which adaptations of one party select for counteradaptations of the other *ad infinitum* can function as engines of perpetual positive selection and thus provide a renewable source of incidental pleiotropy. Although each new predisposition should be temporary, the ground would shift constantly under the feet of anti-cancer mechanisms.

Antagonistic coevolution between hosts and pathogens is the classic example of an evolutionary arms race. The evolution of new host defences and new stratagems of pathogens to evade these defences could both have incidental pleiotropic effects that increased predisposition to cancer of hosts. However, pathogens, especially viruses, could also be directly selected to undermine anti-cancer adaptations of hosts. If host defences against cancer are also deployed against viruses, then viruses will be selected to circumvent these defences within infected host cells. If proliferation of infected cells increases viral titres and high titres increase new infections, then viruses will be selected to overcome host barriers to cell proliferation [7]. Such cancer-promoting adaptations can be fine-tuned over many viral generations as viral lineages move from cell to cell and body to body. These viral adaptations can confer proliferative advantages on host cells in intrasomatic selection even if the virus itself does not benefit.

Evolutionary conflicts associated with pregnancy provide another source of antagonistic coevolution that may increase vulnerability to cancer [6,8]. Mothers and fetuses 'disagree' over the depth of placental intrusion into maternal tissues, and fetal genes of maternal and paternal origin (matrigenes and patrigenes) 'disagree' over proliferation of particular cell types within growing bodies. Thus, a fifth column may exist within the genome that evolves to subvert controls on tissue invasion and cellular proliferation. Cancer progression involves evasion of extrinsic controls on metastasis and evasion of intrinsic controls on cellular proliferation [9]. The next section will consider evasion of extrinsic controls in the context of adaptations of trophoblast to circumvent maternal controls on its invasion of the uterus. The following section will consider evasion of intrinsic controls on proliferation in the context of conflicts between matrigenes and patrigenes over the expansion of particular cell populations.

## 2. Trophoblast and the subversion of extrinsic defences

'From a position of neglect and obscurity, placental tissue has rapidly passed into a place so important that it is likely to prove the point of departure for all future theories of tumour formation' [10, p. 592].

Similarities between trophoblast and malignant cells have been noted for more than a century [11–17]. Shared features include rapid proliferation, invasion of neighbouring tissues, deportation to distant sites, vasculogenic mimicry, induction of angiogenesis and modulation of immune responses [18–21]. Trophoblast and malignant cells both

use aerobic glycolysis [22,23] and many cancers express 'trophoblast-specific' genes [24–27].

The  $\beta$ -subunit of chorionic gonadotropin (CG $\beta$ ) is a quintessential product of trophoblast that is expressed by many trophoblastic and non-trophoblastic tumours [14,28] and has been considered a 'definitive cancer biomarker' [16]. Although CG $\beta$  possesses anti-apoptotic and invasion-promoting activities [29,30], any role in cancer progression must be primate-specific because the duplications that generated a cluster of CGB genes from an ancestral *LHB* gene are primate-specific [31]. Many similar examples could be given. Molecular similarities between trophoblast and cancer will be lineage-specific because placentas probably vary more among mammals than any other organ [32] and because trophoblast-specific genes are lineage-specific [33].

The earliest hypotheses of a special relation between placenta and cancer were inspired by two key discoveries of the 1890s [34]. The first was the recognition that the highly invasive and invariably fatal 'deciduoma malignum' had the same cellular composition as the sheathing layers of placental villi [35,36]. The second was the description of an early human embryo that had clearly penetrated into, and embedded itself within, maternal tissues [37]. As Adami wrote: the 'syncytial cells of the placenta...have, physiologically, well marked powers of eroding or breaking down the uterine tissue and through their agency it is that the villi penetrate into the maternal blood sinuses. Physiologically, that is, they possess what we regard as malignant properties. The highly malignant tumour, formed as a result of their overgrowth, the so-called deciduoma or syncytioma malignum, is thus clearly an example of cells which are the product of one individual invading the tissues of another individual' [38, p. 623]. Deciduoma (or syncytioma) malignum was renamed chorionepithelioma (now choriocarcinoma) to reflect the new understanding of its origin.

Beard extrapolated from chorionepitheliomas to all cancers: 'there is morphologically but one form of cancer, no matter how different it may appear to be in diverse localities'; all cancers develop from vagrant germ cells that differentiate aberrantly as chorionic tissue with unlimited growth [39, p. 1759]. A review of trophoblastic theories of cancer is beyond the scope of this paper but I will attempt to elucidate some features of Beard's thought that may be obscure to most modern readers. His hypothesis of vagrant germ cells was embedded within a broader theory of a fundamental unity between plant and animal life cycles [39–42]. Beard believed that the alternation of asexual (sporophyte) and sexual (gametophyte) generations of plants had its counterpart in an alternation of asexual (larval) and sexual (adult) stages in animals. Plant and animal life cycles differed in that the transition from asexual to sexual forms was accompanied by a halving of chromosome number in plants but occurred without chromosome reduction in animals (analogous to aposporous development in plants) [43]. The chorion was the 'larval' generation of mammals. Under abnormal conditions, this asexual generation could exhibit unrestricted growth and metastasis within its sexual host. Beard's hypothesis has had a chequered history: it has been promoted by advocates of controversial cancer therapies [44] and interpreted as prefiguring modern concepts of cancer stem cells [27].

Comparisons of trophoblast and cancer are usually qualified by a caveat that trophoblastic invasion is tightly regulated. Placentas are considered 'well-behaved tumours' [18]. But placentation is not a seamless collaboration between

the generations because mother and fetus are distinct genetic individuals with distinct genetic interests. The theory of maternal–fetal conflict accepts the existence of mutual interests but recognizes that cooperation to achieve common goals is not guaranteed. Mothers are selected to allow, but to limit, fetal access to nutrients and fetuses are selected to circumvent maternal controls [34,45,46]. Trophoblast, like the future child of which it is an agent, need not always be well behaved because mothers' capacities to control unruly placentas are constrained by placentas' abilities to evade restraint.

Gestational physiology is predicted to lack the exquisite homeostatic controls of evolved processes within genetically uniform bodies [47]. The high frequency of major health complications during the short nine months of pregnancy, compared with the reliable year-after-year function of other bodily systems, is a measure of this inherent instability. The classical distinction between physiology and pathology breaks down because what benefits one party may harm the other. Pre-eclamptic placentas release factors into maternal blood that cause endothelial damage (maternal pathology) possibly as an adaptation of insufficiently nourished fetuses to increase blood flow to the placenta (fetal physiology) [48]. But maternal feedback to limit damage cannot be 'trusted' because mothers and offspring have incentives to misrepresent their true state [47,49]. An embryo's ability to implant and develop to term at an extrauterine site provides some of the clearest evidence for the absence of intimate 'maternal–fetal dialogue' [50]. Neither mother nor embryo benefits from ectopic implantation but embryos have evolved to 'ignore' most maternal advice as potentially self-interested.

Trophoblast and maternal cells come into intimate contact during establishment of the uteroplacental circulation. Maternal arterioles are breached by trophoblast and converted into low resistance channels over which the mother has little vasomotor control. In this process of arterial remodelling, smooth muscle cells undergo apoptosis and elastic elements of the extracellular matrix are degraded and replaced by fibrioid [51]. Maternal blood is extravasated from the opened spiral arteries into the intervillous space of the placenta from where it returns to the maternal circulation via uterine veins. The capacity of the uteroplacental circulation to deliver nutrients near term is determined, in large part, by the extent of vascular remodelling in the first trimester, particularly the number of spiral arteries modified and how deeply their modification extends into the myometrium. Pregnancies in which remodelling is shallow, or affects few arteries, are associated with high resistance to flow in the placental bed and reduced perfusion of the intervillous space [52,53]. Although mothers and fetuses have a mutual interest in placental perfusion once a mother is 'committed' to carrying a fetus to term, fetuses favour the uterus receiving a larger share of maternal cardiac output, especially near term when fetal needs are greatest [48].

Maternal immune cells participate in the remodelling of the endometrial segments of spiral arteries [54,55]. Many researchers have succumbed to the temptation of conceptualizing vascular remodelling as an unproblematic collaboration of mother and fetus, but some maternal participation is what one might expect if the maternal purpose is to allow-but-to-limit arterial remodelling. Trophoblast does not need maternal cooperation to establish a placental blood supply when implantation occurs at ectopic sites [56]. No-one would suggest mothers have been selected to prepare the way for embryos outside the uterus.

Trophoblast is selected to evade maternal restraints on its invasion of maternal tissues, with each new maternal restraint undermined by new trophoblastic countermeasures. By this evolutionary process, trophoblast has evolved abilities to degrade extracellular matrix, penetrate basement membranes, induce apoptosis in maternal immune cells and ignore apoptotic signals [15,57–59]. All these attributes evolved because of the benefits they provided fetal genes in their struggle with maternal genes over the control of maternal physiology during pregnancy but all can be redeployed by tumour cells in intrasomatic selection to evade 'host' defences and facilitate malignant spread [8].

### 3. Genomic imprinting and the subversion of intrinsic defences

Chorionepitheliomas were often preceded by the abortion of a vesicular mole [60] (the noun refers to a mass rather than a burrowing creature). A vesicular, or hydatidiform, mole was a conceptus with abundant proliferation of trophoblast but usually without an associated embryo. The discovery that most 'complete' hydatidiform moles possess two haploid sets of paternally derived chromosomes without any maternally derived chromosomes [61,62] provided some of the first evidence that matrigenes and patrigenes had differential effects during human development and that patrigenes had a special role in trophoblast development.

A complete hydatidiform mole (CHM) is a conceptus composed of swollen placental villi without embryonic parts, whereas a partial hydatidiform mole (PHM) possesses both normal and swollen villi with an associated embryo [63]. Most CHMs are androgenetic diploids, whereas many PHMs are triploids [64] although not all triploids are PHMs because the phenotype of triploids depends on the parental origin of the constituent genomes. Diandric triploids develop as PHMs with placental hyperplasia, whereas digynic triploids exhibit placental hypoplasia [65,66]. Thus, proliferation of trophoblast depends on the ratio of maternal to paternal genomes of a conceptus ( $xm:yp$ ), with paternal genomes promoting trophoblastic hyperplasia and maternal genomes hypoplasia. Proliferation is greatest in CHMs ( $0m:2p$ ), less in PHMs ( $1m:2p$ ), less still in biparental diploids ( $1m:1p$ ) and least in digynic triploids ( $2m:1p$ ). Moreover, biparental diploids and digynic triploids develop as CHMs when maternal genomes acquire the epigenetic features of paternal genomes because of maternal mutations in *NLRP7* or *KHDC3L* [67–69]. Choriocarcinomas develop after one in 40 000 normal pregnancies, after one in 40 CHMs, but rarely after PHMs [70]. Thus, presence of a maternal genome dramatically reduces the risk of choriocarcinoma but absence of a maternal genome is insufficient for its development.

The kinship theory of genomic imprinting proposes that imprinted gene expression evolves because of conflicting selective forces acting on matrigenes and patrigenes [71,72]. In the context of pregnancy, fetal genes are selected to impose greater demands on mothers when a gene is a patrigenes than when the same gene is a matrigenes [45,73]. Thus, patrigenes promote (and matrigenes restrain) proliferation of trophoblast because this is the fetal tissue principally involved in resource acquisition from mothers. More generally, the theory predicts intragenomic conflict over cellular

proliferation whenever matrigenes and patrigenes favour different optimal sizes of a tissue.

Summers *et al.* [8] applied the kinship theory to cancer. Maternally expressed genes (MEGs) were predicted to restrain, and paternally expressed genes (PEGs) to enhance, cellular proliferation and invasion. Parent-specific monoallelic expression increased vulnerability to cancer because loss of function of MEGs and reactivation of the silent maternal copy of PEGs would promote cellular proliferation and metastasis. Consistent with these predictions, expression of a cyclin-dependent kinase inhibitor *CDKN1C* (a MEG) is frequently reduced in cancer [74,75], whereas expression of an insulin-like growth factor *IGF2* (a PEG) is frequently increased in cancer [76]. *CDKN1C* fits the initial predictions for a MEG closely, but not perfectly. Although, *CDKN1C* inhibits migration, invasion and cellular proliferation [77], no mutations have been observed in cancer [74,75]. A possible reason for the absence of oncogenic *CDKN1C* mutations is that p57, the *CDKN1C* protein, is required to prevent apoptosis [78,79] perhaps as a fail-safe control on proliferation.

A cluster of imprinted loci at human chromosome 11p15.5 includes *CDKN1C* and *IGF2* and is implicated in the regulation of fetal growth and its perturbation in Beckwith–Wiedemann syndrome (BWS), Silver–Russell syndrome (SRS) and IMAGE syndrome [80–82]. Fetal overgrowth is a feature of BWS, whereas intrauterine growth retardation characterizes SRS and IMAGE syndrome. *CDKN1C* mutations, when inherited from mothers, cause familial BWS when the mutation inactivates the encoded protein but SRS or IMAGE syndrome when the mutation enhances protein stability [81,83–87]. Reactivation of *IGF2*'s maternally silent allele, or duplication of its paternally active allele, is associated with BWS, whereas silencing of the paternally active allele is associated with SRS [88–90].

Normal intrauterine growth thus depends on 'balanced' expression of *IGF2* and *CDKN1C* with imbalance in favour of the PEG associated with overgrowth and in favour of the MEG with undergrowth. IGF-II and p57 act, respectively, as an accelerator and brake on the G<sub>1</sub>-to-S phase transition of the cell cycle and this may explain why over-expression of *IGF2* and under-expression of *CDKN1C* result in similar clinical phenotypes [91]. BWS is associated with disproportionate overgrowth of tongue, liver, kidney, pancreatic islets and adrenal cortex [92] and high risk of embryonal tumours of childhood, including nephroblastoma, hepatoblastoma, adrenocortical carcinoma, rhabdomyosarcoma, pancreatoblastoma and neuroblastoma [93,94]. The tissues subject to overgrowth and embryonal tumours can be conjectured to be those in which patrigenes favour greater size than matrigenes. As an exemplar, I will consider one of these tissues, the adrenal cortex.

The highly developed adrenals of human fetuses at term undergo dramatic postnatal involution. The major activity of the fetal adrenal cortex is the production of large quantities of androgens that are converted to oestrogens by the placenta before being released into the maternal circulation [95]. Adrenal androgen production is a distinctive feature of primate fetuses, although the function of the placental oestrogens is unknown [96]. Whatever their precise function, placental oestrogens are predicted to manipulate maternal physiology for fetal benefit [49]. Therefore, patrigenes are predicted to favour production of greater amounts of adrenal androgens than are matrigenes and to favour larger size of the fetal adrenal cortex. Both *IGF2* and *CDKN1C* have substantially higher

expression in fetal than adult adrenal, but *IGF2* expression is increased and *CDKN1C* expression reduced in adrenocortical tumours [97–99]. Enhanced function of *CDKN1C* in IMAGE syndrome is associated with adrenal hypoplasia [86,100].

Decisions of stem cells—to divide, differentiate or die—determine organ size and are thus predicted to be foci of contention between MEGs and PEGs. *IGF2* has been implicated in self-renewal and *CDKN1C* in quiescence of stem cells [101–104]. *H19* (a MEG) counters the efforts of *IGF2* to activate stem cells by release of a microRNA that suppresses the receptor through which IGF-II signals [104]. The multiple roles of imprinted genes in the dynamics of stem cell populations have been characterized as an Imprinted Gene Network (IGN) [105–107]. These genes are expressed predominantly at the transition from proliferation to exit from the cell cycle [108]. The kinship theory predicts that this network's interactions have evolved in the context of evolutionary conflict over aspects of network performance. As a result, the IGN is predicted to exhibit less-effective homeostatic feedbacks than networks that evolve in the absence of conflict. Increased vulnerability to cancer may be one of the costs.

A precursor of the IGN can be conjectured to have existed before the evolution of genomic imprinting and to have efficiently regulated stem cells. But, 'political' considerations intruded into the evolutionary engineering of the network with the origin of imprinted expression and the network was reshaped by the conflicting agendas of MEGs, PEGs and BEGs (bially expressed genes) [109]. Political processes are notoriously inefficient. Not all decisions implemented by the IGN need be ones over which MEGs and PEGs disagree but areas of agreement may be difficult to isolate evolutionarily from points of contention. Channels of communication that once existed may have been severed as 'collateral damage' of conflict. All parties might benefit if areas of consensus could be implemented by robust processes but, to extend the political metaphor, compromise may founder on the unwillingness of mutually suspicious parties to abandon entrenched positions.

*CDKN1B* and *IGF1* are paralogues of *CDKN1C* and *IGF2*. The kinship theory predicts that interactions involving unimprinted *CDKN1B* and *IGF1* will be more stable, evolutionarily and physiologically, than interactions involving oppositely imprinted *CDKN1C* and *IGF2* but that this contrast should be absent in taxa in which all four genes are unimprinted. The IGNs of mammals (with their mixture of MEGs, PEGs and BEGs) are predicted to be less robust than corresponding networks of organisms in which all genes are BEGs.

## 4. Cancers of childhood

Some cancers affect mostly young animals and thus challenge a simplistic view of cancer as just another expression of general senescence. Leroi *et al.* [5] proposed that early-life cancers are side effects of recent positive selection. Childhood cancers are dominated by tumours of the immune and central nervous systems. These authors proposed that early deaths from leukemias and lymphomas were side effects of coevolution between pathogens and immune systems of hosts. Comparable tumours should therefore occur in young animals of most species. Brain tumours, by contrast, were proposed to be side effects of the recent expansion of the human brain and should therefore be less frequent in species that have not undergone recent increase of brain size [5].



Intragenomic conflicts between MEGs and PEGs over tissue size are likely to be most intense during the prenatal and postnatal period of maternal care and therefore could contribute to a proportion of childhood cancers. Children with BWS have elevated risk of rare embryonal tumours but not of leukemias, lymphomas or brain tumours that are numerically the most important childhood cancers. The reasons for this pattern deserve study. Children with SRS are relatively macrocephalic [110] and one of the few tumours reported from these children was a brain tumour [111,112]. *Igf2* appears to act as a MEG rather than a PEG in parts of the mouse brain [113]. Perhaps matrigenes, rather than patrigenes, favour greater expansion of some cell types within the brain [114].

Evolutionary hypotheses complement developmental explanations of age-specific cancer incidence. Non-epithelial tumours predominate in the first decade of life, whereas epithelial tumours dominate at older ages [115]. Epithelia are constantly renewed and thus maintain relatively large populations of dividing stem cells at all ages. By contrast, many childhood cancers affect tissues for which most stem cell divisions occur early in life. Osteosarcomas and testicular germ cell tumours have peak incidences around the onset of puberty when previously quiescent stem cells undergo rapid expansion [5,116]. The age-specific incidence of pediatric cancers parallels changes in human growth velocity [117].

## 5. Towards a truly comparative oncology

Comparisons of cancer rates between human populations require careful epidemiological studies and the difficulties are accentuated for interspecific comparisons. Nevertheless, good comparative data would be invaluable for understanding human vulnerabilities to cancer because similarities point towards processes that are shared, whereas differences suggest species-specific factors.

In this paper, genetic conflicts associated with mammalian pregnancy are proposed to have been associated with increased vulnerability to cancer. A straightforward prediction is that mammals should experience higher rates of cancer than oviparous vertebrates (*ceteris paribus*). Two long-term series of necropsies from the San Diego and Philadelphia zoos suggest that tumours are indeed less common in birds than in mammals but the series combine very heterogeneous data and the evidence should be considered suggestive rather than definitive [118,119]. About 80% of tumours in chickens are virally induced, whereas only 20% of cancers in humans have a clear viral aetiology [120,121]. Is this evidence that virally induced tumours form a smaller proportion of mammalian cancers because mammals are more vulnerable to other causes of cancer? Or is it evidence that modern poultry farming

creates ideal conditions for the spread of virulent viruses? The resolution of such questions will require epidemiological data on cancer incidence in multiple species.

Eutherian mammals vary in the extent to which trophoblast invades maternal tissues. Comparative studies of cancer rates in taxa with different degrees of placental invasiveness are needed [122]. A recent study found evidence that less invasive placentas are associated with lower rates of malignant cancer. Because reduced placental invasion is the evolutionarily derived state, the authors interpreted this association as evidence that selection on mothers to resist placental invasion reduces the risk of metastatic disease (positive pleiotropy) rather than that selection on placentas to invade maternal tissues increases risk (antagonistic pleiotropy) [123]. My preference is to view positive pleiotropy and antagonistic pleiotropy as two sides of a single coin rather than as competing hypotheses because placental invasiveness and endometrial resistance co-evolve. Hemochorial (highly invasive) placentas tend to be associated with small body size, whereas epitheliochorial (non-invasive) placentas tend to be associated with large body size [124]. Thus, non-invasive placentas that are conjectured to be associated with reduced risk of cancer are associated with larger bodies that provide more opportunities for malignancy.

Naked mole-rats develop very few cancers despite suffering other maladies of old age and thus challenge the idea that viviparity increases risk of cancer [125]. Summers *et al.* predicted that monogamous species should suffer less cancer than promiscuous species because conflict between matrigenes and patrigenes is less intense [8]. Naked mole-rat colonies appear to be founded by a single pair followed by close inbreeding within colonies [126,127]. Therefore, an individual's matrigenic and patrigenic alleles are often identical by descent and intragenomic conflict is greatly attenuated. *Fukomys damarensis* is a social mole-rat with extensive outbreeding and multiple paternity within litters [128], whereas blind mole-rats (*Spalax* spp.) are solitary with very low rates of cancer [129]. Studies of these and other species should illuminate whether mating system affects cancer rates.

Each species has its own distinctive spectrum of cancers [130]. Breast cancers, for example, kill many women but have not been reported in great apes [131]. Such differences argue for taxon- and organ-specific risks that may be developmental or environmental in origin. The fact that the rates of different kinds of cancer do not vary in unison across phylogeny argues against overly simplistic theories in which all cancers have a common cause.

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## References

- Nunney L. 2012 The real war on cancer: the evolutionary dynamics of cancer suppression. *Evol. Appl.* **6**, 11–19. (doi:10.1111/eva.12018)
- Caulin AF, Maley CC. 2011 Peto's paradox: evolution's prescription for cancer prevention. *Trends Ecol. Evol.* **26**, 175–182. (doi:10.1016/j.tree.2011.01.002)
- Williams GC. 1957 Pleiotropy, natural selection, and the evolution of senescence. *Evolution* **11**, 398–411. (doi:10.2307/2406060)
- Weinstein BS, Ciszek D. 2002 The reserve-capacity hypothesis: evolutionary origins and modern implications of a trade-off between tumor-suppression and tissue-repair. *Exp. Gerontol.* **37**, 615–627. (doi:10.1016/S0531-5565(02)00012-8)
- Leroi AM, Koufopanou V, Burt A. 2003 Cancer selection. *Nat. Rev. Cancer* **3**, 226–228. (doi:10.1038/nrc1016)
- Crespi BJ, Summers K. 2006 Positive selection in the evolution of cancer. *Biol. Rev.* **81**, 407–424. (doi:10.1017/S1464793106007056)

7. Ewald PW. 2009 An evolutionary perspective on parasitism as a cause of cancer. *Adv. Parasitol.* **68**, 21–43. (doi:10.1016/S0065-308X(08)00602-7)
8. Summers K, da Silva J, Farwell MA. 2002 Intragenomic conflict and cancer. *Med. Hypotheses*. **59**, 170–179. (doi:10.1016/S0306-9877(02)00249-9)
9. Gupta GP, Massagué J. 2006 Cancer metastasis: building a framework. *Cell* **127**, 679–695. (doi:10.1016/j.cell.2006.11.001)
10. Anonymous. 1903 Reviews of recent books. Tumeurs du placenta et tumeurs placentaires (placentomes malins). Par Dr. Paul Briquel. *J. Obstet. Gynaecol. Brit. Emp.* **4**, 592–593. (doi:10.1111/j.1471-0528.1903.tb12890.x)
11. Adami JG. 1902 Contribution to a discussion upon the parasitology of malignant growths (on *Syncytioma malignum*). *Clin. J.* **20**, 141–144.
12. Bell WB. 1925 On the specific character of malignant neoplasia. *Lancet* **2**, 1003–1007.
13. Krebs ET, Gurchot C. 1946 Trophoblast elements in cancer. *Science* **104**, 302. (doi:10.1126/science.104.2700.302)
14. McManus LM, Naughton MA, Martinez-Hernandez A. 1976 Human chorionic gonadotropin in human neoplastic cells. *Cancer Res.* **36**, 3476–3481.
15. Yagel SY, Parhar RS, Jeffrey JJ, Lala PK. 1988 Normal nonmetastatic human trophoblast cells share *in vitro* invasive properties of malignant cells. *J. Cell. Physiol.* **136**, 455–462. (doi:10.1002/jcp.1041360309)
16. Regelson W. 1995 Have we found the 'definitive cancer biomarker'? *Cancer* **76**, 1299–1301. (doi:10.1002/1097-0142(19951015)76:8<1299::AID-CNCR2820760802>3.0.CO;2-L)
17. Novakovic B *et al.* 2008 Specific tumour-associated methylation in normal human term placenta and first-trimester trophoblasts. *Mol. Hum. Reprod.* **14**, 547–554. (doi:10.1093/molehr/gan046)
18. Rama S, Rao AJ. 2004 Trophoblast 'pseudo-tumorigenesis': significance and contributory factors. *Reprod. Biol. Endocrinol.* **2**, 15. (doi:10.1186/1477-7827-2-15)
19. Ferretti ME, Bruni L, Dangles-Marie V, Pecking AP, Bellet D. 2007 Molecular circuits shared by placental and cancer cells, and their implications in the proliferative, invasive and migratory capacities of trophoblasts. *Hum. Reprod. Update* **13**, 121–141. (doi:10.1093/humupd/dml048)
20. Holtan SG, Creedon DJ, Haluska P, Markovic SN. 2009 Cancer and pregnancy: parallels in growth, invasion, and immune modulation and implications for cancer therapeutic agents. *Mayo Clinic. Proc.* **84**, 985–1000. (doi:10.1016/S0025-6196(11)60669-1)
21. Perry JK, Lins RJ, Lobie PE, Mitchell MD. 2010 Regulation of invasive growth: similar epigenetic mechanisms underpin tumour progression and implantation in human pregnancy. *Clin. Sci.* **118**, 451–457. (doi:10.1042/CS20090503)
22. Bax BE, Bloxam DL. 1997 Energy metabolism and glycolysis in human placental trophoblast cells during differentiation. *Biochim. Biophys. Acta* **1319**, 283–292. (doi:10.1016/S0005-2728(96)300169-7)
23. Vander Heiden MG, Cantley LC, Thompson CB. 2009 Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* **324**, 1029–1033. (doi:10.1126/science.1160809)
24. Horne CHW, Reid IN, Milne GD. 1976 Prognostic significance of inappropriate production of pregnancy proteins by breast cancers. *Lancet* **2**, 279–282. (doi:10.1016/S0140-6736(76)90731-5)
25. Inaba N, Renk T, Wurster K, Rapp W, Bohn H. 1980 Pregnancy specific  $\beta$ 1-glycoprotein (SP1) and placental specific tissue proteins (PP5, PP10, PP11, PP12) in nontrophoblastic malignant tumours. Possible markers in oncology. *Klin. Wochenschr.* **58**, 789–791. (doi:10.1007/BF01478287)
26. Chassin D *et al.* 1994 Identification of genes overexpressed in tumors through preferential expression screening in trophoblasts. *Cancer Res.* **54**, 5217–5223.
27. Simpson AJG, Caballero OL, Jungbluth A, Chen YT, Old LJ. 2005 Cancer/testis antigens, gametogenesis and cancer. *Nat. Rev. Cancer* **5**, 615–625. (doi:10.1038/nrc1669)
28. Stenman UH, Alfthan H, Hotakainen K. 2004 Human chorionic gonadotropin in cancer. *Clin. Biochem.* **37**, 549–561. (doi:10.1016/j.clinbiochem.2004.05.008)
29. Illes RK, Delves PJ, Butler SA. 2010 Does hCG or hCG $\beta$  play a role in cancer cell biology? *Mol. Cell. Endocrinol.* **329**, 62–79. (doi:10.1016/j.mce.2010.07.014)
30. Li Z, Li C, Du L, Zhou Y, Wu W. 2013 Human chorionic gonadotropin  $\beta$  induces migration and invasion via activating ERK1/2 and MMP-2 in human prostate cancer DU145 cells. *PLoS ONE* **8**, e54592. (doi:10.1371/journal.pone.0054592)
31. Maston GA, Ruvolo M. 2002 Chorionic gonadotropin has a recent origin within primates and an evolutionary history of selection. *Mol. Biol. Evol.* **19**, 320–335. (doi:10.1093/oxfordjournals.molbev.a004085)
32. Mossman HW. 1987 *Vertebrate fetal membranes*. New Brunswick, NJ: Rutgers University Press.
33. Rawn SM, Cross JC. 2008 The evolution, regulation, and function of placenta-specific genes. *Annu. Rev. Cell Dev. Biol.* **24**, 159–181. (doi:10.1146/annurev.cellbio.24.110707.175418)
34. Haig D. 2010 Fertile soil or no man's land: cooperation and conflict in the placental bed. In *Placental bed disorders* (eds R Pijnenborg, I Brosens, R Romero), pp. 165–173. Cambridge, UK: Cambridge University Press.
35. Marchand F. 1895 Über die sogenannten 'deciduellen' Geschwülste im Anschluss an normale Geburt, Abort, Blasenmole und Extrauterinschwangerschaft. *Monatsschr. Geburtsh. Gynäkol.* **1**, 419–438, 513–561.
36. Marchand F. 1898 Über das maligne Chorion-Epitheliom, nebst Mittheilung von 2 neuen Fällen. *Z. Geburtsh. Gynäkol.* **39**, 173–258.
37. Peters H. 1899 Über die Einbettung des menschlichen Eies und das früheste bisher bekannte menschliche Placentationsstadium. Leipzig, Germany: Franz Deutike.
38. Adami JG. 1901 The causation of cancerous and other new growths. *Brit. Med. J.* **1**, 621–628. (doi:10.1136/bmj.1.2098.621)
39. Beard J. 1902 Embryological aspects and etiology of cancer. *Lancet* **1**, 1758–1761. (doi:10.1016/S0140-6736(01)89936-0)
40. Beard J. 1904 Abstract of a lecture on the problems of cancer. *Lancet* **2**, 1200–1201.
41. Beard J. 1905 The cancer problem. *Lancet* **1**, 281–283. (doi:10.1016/S0140-6736(01)42822-4)
42. Beard J, Murray JA. 1895 On the phenomena of reproduction in animals and plants. Reducing division in metazoan reproduction. *Ann. Bot.* **9**, 448–455.
43. Haig D. 2008 Homologous versus antithetic alternation of generations and the origin of sporophytes. *Bot. Rev.* **74**, 395–418. (doi:10.1007/s12229-008-9012-x)
44. Peterson JC, Markle GE. 1979 Politics and science in the laetrile controversy. *Soc. Stud. Sci.* **9**, 139–166. (doi:10.1177/030631277900900201)
45. Haig D. 1993 Genetic conflicts in human pregnancy. *Q. Rev. Biol.* **68**, 495–532. (doi:10.1086/418300)
46. Haig D. 1996 Gestational drive and the green-bearded placenta. *Proc. Natl Acad. Sci. USA* **93**, 6547–6551. (doi:10.1073/pnas.93.13.6547)
47. Haig D. 1996 Altercation of generations: genetic conflicts of pregnancy. *Am. J. Reprod. Immunol.* **35**, 226–232. (doi:10.1111/j.1600-0897.1996.tb00035.x)
48. Haig D. 2007 Putting up resistance: maternal-fetal conflict over the control of uteroplacental blood flow. In *Endothelial biomedicine* (ed. WC Aird), pp. 135–141. Cambridge, UK: Cambridge University Press.
49. Haig D. 1996 Placental hormones, genomic imprinting, and maternal–fetal communication. *J. Evol. Biol.* **9**, 357–380. (doi:10.1046/j.1420-9101.1996.9030357.x)
50. Bright AS, Maser AH. 1961 Advanced abdominal pregnancy. Review of the recent literature and report of a case. *Obstet. Gynaecol.* **17**, 316–324.
51. Harris LK. 2010 Trophoblast-vascular cell interactions in early pregnancy: how to remodel a vessel. *Placenta* **31**, S93–S98. (doi:10.1016/j.placenta.2009.12.012)
52. Khong TY, de Wolf F, Robertson WB, Brosens I. 1986 Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational-age infants. *Brit. J. Obstet. Gynaecol.* **93**, 1049–1059. (doi:10.1111/j.1471-0528.1986.tb07830.x)
53. Brosens I, Khong TY. 2010 Defective spiral artery remodeling. In *Placental bed disorders* (eds R Pijnenborg, I Brosens, R Romero), pp. 11–21. Cambridge, UK: Cambridge University Press.
54. Smith SD, Dunk CE, Aplin JD, Harris LK, Jones RL. 2009 Evidence for immune cell involvement in decidual spiral artery remodeling in early human pregnancy. *Am. J. Pathol.* **174**, 1959–1971. (doi:10.2353/ajpath.2009.080995)
55. Hazan AD, Smith SD, Jones RL, Whittle W, Lye SJ, Dunk CE. 2010 Vascular–leukocyte interactions. Mechanisms of human decidual spiral artery remodeling *in vitro*. *Am. J. Pathol.* **177**, 1017–1030. (doi:10.2353/ajpath.2010.091105)

56. Randall S, Buckley CH, Fox H. 1987 Placentation in the fallopian tube. *Int. J. Gynecol. Pathol.* **6**, 132–139. (doi:10.1097/00004347-198706000-00005)
57. Fisher SJ, Leitch MS, Kantor MS, Basbaum CB, Kramer RH. 1985 Degradation of extracellular matrix by the trophoblastic cells of first-trimester human placentas. *J. Cell. Biochem.* **27**, 31–41. (doi:10.1002/jcb.240270105)
58. Abrahams VM, Straszewski-Chavez SL, Guller S, Mor G. 2004 First trimester trophoblast cells secrete Fas ligand which induces immune cell apoptosis. *Mol. Hum. Reprod.* **10**, 55–63. (doi:10.1093/molehr/gah006)
59. Straszewski-Chavez SL, Abrahams VM, Funai EF, Mor G. 2004 X-linked inhibitor of apoptosis (XIAP) confers human trophoblast cell resistance to Fas-mediated apoptosis. *Mol. Hum. Reprod.* **10**, 33–41. (doi:10.1093/molehr/gah001)
60. Marchand F. 1903 On malignant chorionepithelioma. *J. Obstet. Gynaecol. Brit. Emp.* **4**, 74–79. (doi:10.1111/j.1471-0528.1903.tb11781.x)
61. Kajii T, Ohama K. 1977 Androgenetic origin of hydatidiform mole. *Nature* **268**, 633–634. (doi:10.1038/268633a0)
62. Wake N, Takagi N, Sasaki M. 1978 Androgenesis as a cause of hydatidiform mole. *J. Natl Cancer Inst.* **60**, 51–53.
63. Benirschke K, Burton GJ, Baergen RN. 2012 *Pathology of the human placenta*. New York, NY: Springer.
64. Vassilakos P, Riotton G, Kajii T. 1977 Hydatidiform mole: two entities. *Am. J. Obstet. Gynecol.* **126**, 167–170.
65. Zaragoza MV, Surti U, Redline RW, Millie E, Chakravarti A, Hassold TJ. 2000 Parental origin and phenotype of triploidy in spontaneous abortions: predominance of diandry and association with the partial hydatidiform mole. *Am. J. Hum. Genet.* **66**, 1807–1820. (doi:10.1086/302951)
66. Witters I, Fryns JP. 2008 Triploidy: 109 prenatal diagnoses. *Ultrasound* **16**, 21–23. (doi:10.1179/174313408X259427)
67. Murdoch S *et al.* 2006 Mutations in *NALP7* cause recurrent hydatidiform moles and reproductive wastage in humans. *Nat. Genet.* **38**, 300–301. (doi:10.1038/ng1740)
68. Parry DA *et al.* 2011 Mutations causing familial biparental hydatidiform mole implicate *C6orf221* as a possible regulator of genomic imprinting in the human oocyte. *Am. J. Hum. Genet.* **89**, 451–458. (doi:10.1016/j.ajhg.2011.08.002)
69. Fallahian M, Sebire NJ, Savage PM, Seckl MJ, Fisher RA. 2013 Mutations in *NLRP7* and *KHDC3L* confer a complete hydatidiform mole phenotype on digynic triploid conceptions. *Hum. Mut.* **34**, 301–308. (doi:10.1002/humu.22228)
70. Lurain JR. 2010 Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. *Am. J. Obstet. Gynecol.* **203**, 531–539. (doi:10.1016/j.ajog.2010.06.073)
71. Haig D, Westoby M. 1989 Parent-specific gene expression and the triploid endosperm. *Am. Nat.* **134**, 147–155. (doi:10.1086/284971)
72. Trivers R, Burt A. 1999 Kinship and genomic imprinting. In *Genomic imprinting* (ed. R Ohlsson), pp. 1–21. Berlin, Germany: Springer.
73. Haig D. 1992 Genomic imprinting and the theory of parent-offspring conflict. *Sem. Dev. Biol.* **3**, 153–160.
74. Pateras IS, Apostolopoulou K, Niforou K, Kotsinas A, Gorgoulis VG. 2009 *p57<sup>Kip2</sup>*: ‘Kip’ing the cell under control. *Mol. Cancer Res.* **7**, 1902–1919. (doi:10.1158/1541-7786.MCR-09-0317)
75. Borriello A, Caldarelli I, Bencivenga D, Criscuolo M, Cucciolla V, Tramontano A, Oliva A, Perrotta S, Della Ragione F. 2011 *p57<sup>Kip2</sup>* and cancer: time for a critical appraisal. *Mol. Cancer Res.* **9**, 1269–1284. (doi:10.1158/1541-7786.MCR-11-0220)
76. Livingstone C. 2013 IGF2 and cancer. *Endocr. Relat. Cancer* **20**, R321–R339. (doi:10.1530/ERC-13-0231)
77. Kavanagh E, Joseph B. 2011 The hallmarks of CDKN1C (*p57*, *KIP2*) in cancer. *Biochim. Biophys. Acta* **1816**, 50–56. (doi:10.1016/j.bbcan.2011.03.002)
78. Yan Y, Frisén J, Lee MH, Massagué J, Barbacid M. 1997 Ablation of the CDK inhibitor gene *p57<sup>Kip2</sup>* results in increased apoptosis and delayed differentiation during mouse development. *Genes Dev.* **11**, 973–983. (doi:10.1101/gad.11.8.973)
79. Ma Y, Cress WD. 2007 Transcriptional upregulation of *p57* (*Kip2*) by the cyclin-dependent kinase inhibitor BMS-387032 is E2F dependent and serves as a negative feedback loop limiting cytotoxicity. *Oncogene* **26**, 3532–3540. (doi:10.1038/sj.onc.1210143)
80. Eggermann T, Eggermann K, Schönherr N. 2008 Growth retardation versus overgrowth: Silver–Russell syndrome is genetically opposite to Beckwith–Wiedemann syndrome. *Trends Genet.* **24**, 195–204. (doi:10.1016/j.tig.2008.01.003)
81. Arboleda VA *et al.* 2012 Mutations in the PCNA-binding domain of *CDKN1C* cause IMaGe syndrome. *Nat. Genet.* **44**, 788–792. (doi:10.1038/ng.2275)
82. Jacob KJ, Robinson WP, Lefebvre L. 2013 Beckwith–Wiedemann and Silver–Russell syndromes: opposite developmental imbalances in imprinted regulators of placental function and embryonic growth. *Clin. Genet.* **84**, 326–334. (doi:10.1111/cge.12143)
83. Hatada I *et al.* 1996 An imprinted gene *p57<sup>KIP2</sup>* is mutated in Beckwith–Wiedemann syndrome. *Nat. Genet.* **14**, 171–173. (doi:10.1038/ng1096-171)
84. Romanelli V *et al.* 2010 *CDKN1C* (*p57<sup>Kip2</sup>*) analysis in Beckwith–Wiedemann syndrome (BWS) patients: genotype-phenotype correlations, novel mutations, and polymorphisms. *Am. J. Med. Genet.* **152A**, 1390–1397. (doi:10.1002/ajmg.a.33453)
85. Brioude F *et al.* 2013 *CDKN1C* mutation affecting the PCNA-binding domain as a cause of familial Russell Silver syndrome. *J. Med. Genet.* **50**, 823–830. (doi:10.1136/jmedgenet-2013-101691)
86. Hamajima N, Johmura Y, Suzuki S, Nakanishi M, Saitoh S. 2013 Increased protein stability of CDKN1C causes a gain-of-function phenotype in patients with IMaGe syndrome. *PLoS ONE* **8**, e75137. (doi:10.1371/journal.pone.0075137)
87. Eggermann T *et al.* 2014 *CDKN1C* mutations: two sides of the same coin. *Trends Mol. Med.* **20**, 614–622. (doi:10.1016/j.molmed.2014.09.001)
88. Weksberg R, Shen DR, Fei YL, Song QL, Squire J. 1993 Disruption of insulin-like growth factor 2 imprinting in Beckwith–Wiedemann syndrome. *Nat. Genet.* **5**, 143–150. (doi:10.1038/ng1093-143)
89. Algar EM, St. Heaps L, Darmanian A, Dagar V, Prawitt D, Peters GB, Collins F. 2007 Paternally inherited submicroscopic duplication at 11p15.5 implicates insulin-like growth factor II in overgrowth and Wilms’ tumorigenesis. *Cancer Res.* **67**, 2360–2365. (doi:10.1158/0008-5472.CAN-06-3383)
90. Yamazawa K *et al.* 2008 Molecular and clinical findings and their correlations in Silver–Russell syndrome: implications for a positive role of *IGF2* in growth determination and differential imprinting regulation of the *IGF2-H19* domain in bodies and placentas. *J. Mol. Med.* **86**, 1171–1181. (doi:10.1007/s00109-008-0377-4)
91. Caspary T, Cleary MA, Perlman EJ, Zhang P, Elledge SJ, Tilghman SM. 1999 Oppositely imprinted genes *p57<sup>KIP2</sup>* and *Igf2* interact in a mouse model of Beckwith–Wiedemann syndrome. *Genes Dev.* **13**, 3115–3124. (doi:10.1101/gad.13.23.3115)
92. Weksberg R, Shuman C, Beckwith JB. 2010 Beckwith–Wiedemann syndrome. *Eur. J. Hum. Genet.* **18**, 8–14. (doi:10.1038/ejhg.2009.106)
93. Wiedemann HR. 1983 Tumours and hemihypertrophy associated with Wiedemann–Beckwith syndrome. *Eur. J. Pediatr.* **141**, 129. (doi:10.1007/BF00496807)
94. Cohen MM. 2005 Beckwith–Wiedemann syndrome: historical, clinicopathological, and etiopathogenetic perspectives. *Pediatr. Dev. Pathol.* **8**, 287–304. (doi:10.1007/s10024-005-1154-9)
95. Mesiano S, Jaffe RB. 1997 Developmental and functional biology of the primate fetal adrenal cortex. *Endocr. Rev.* **18**, 378–403. (doi:10.1210/er.18.3.378)
96. Rainey WE, Rehman KS, Carr BR. 2004 The human fetal adrenal: making adrenal androgens for placental estrogens. *Semin. Reprod. Med.* **22**, 327–336. (doi:10.1055/s-2004-861549)
97. Rainey WE, Carr BR, Wang ZN, Parker CR. 2001 Gene profiling of human fetal and adult adrenals. *J. Endocrinol.* **171**, 209–215. (doi:10.1677/joe.0.1710209)
98. Giordano TJ *et al.* 2003 Distinct transcriptional profiles of adrenocortical tumors uncovered by DNA microarray analysis. *Am. J. Pathol.* **162**, 521–531. (doi:10.1016/S0002-9440(10)63846-1)
99. West AN *et al.* 2007 Gene expression profiling of childhood adrenocortical tumors. *Cancer Res.* **67**, 600–608. (doi:10.1158/0008-5472.CAN-06-3767)
100. Vilain E, Le Merrer M, Lecointre C, Desangles F, Kay MA, Maroteaux P, McCabe ERB. 1999 IMaGe, a new clinical association of Intrauterine growth retardation, Metaphyseal dysplasia, Adrenal hypoplasia congenita, and Genital anomalies. *J. Clin.*



- Endocrinol. Metab.* **84**, 4335–4340. (doi:10.1210/jcem.84.12.6186)
101. Bendall SC *et al.* 2007 IGF and FGF cooperatively establish the regulatory stem cell niche of pluripotent human cells *in vitro*. *Nature* **448**, 1015–1021. (doi:10.1038/nature06027)
  102. Malaguarnera R, Belfiore A. 2014 The emerging role of insulin and insulin-like growth factor signaling in cancer stem cells. *Front. Endocrinol.* **5**, 10. (doi:10.3389/fendo.2014.00010)
  103. Zacharek SJ *et al.* 2011 Lung stem cell self-renewal relies on BMI1-dependent control of expression at imprinted loci. *Cell Stem Cell* **9**, 272–281. (doi:10.1016/j.stem.2011.07.007)
  104. Furutachi S, Matsumoto A, Nakayama KI, Gotoh Y. 2013 p57 controls adult neural stem cell quiescence and modulates the pace of lifelong neurogenesis. *EMBO J.* **32**, 970–981. (doi:10.1038/emboj.2013.50)
  105. Varrault A *et al.* 2006 *Zac1* regulates an imprinted gene network critically involved in the control of embryonic growth. *Dev. Cell* **11**, 711–722. (doi:10.1016/j.devcel.2006.09.003)
  106. Lui JC, Finkelstein GP, Barnes KM, Baron J. 2008 An imprinted gene network that controls mammalian somatic growth deceleration in multiple organs. *Am. J. Physiol.* **295**, R189–R196. (doi:10.1152/ajpregu.00182.2008)
  107. Berg JS *et al.* 2011 Imprinted genes that regulate early mammalian growth are coexpressed in somatic stem cells. *PLoS ONE* **6**, e26410. (doi:10.1371/journal.pone.0026410)
  108. Al Adhami H *et al.* 2015 A systems-level approach to parental genomic imprinting: the imprinted gene network includes extracellular matrix genes and regulates cell cycle exit and differentiation. *Genome Res.* **25**, 353–367. (doi:10.1101/gr.175919.114)
  109. Haig D. 2006 Intragenomic politics. *Cytogenet. Genome Res.* **113**, 68–74. (doi:10.1159/000090816)
  110. Wollmann H, Kirchner T, Enders H, Preece MA, Ranke MB. 1995 Growth and symptoms in Silver–Russell syndrome: review on the basis of 386 patients. *Eur. J. Ped.* **154**, 958–968. (doi:10.1007/BF01958638)
  111. Fenton E, Refai D, See W, Rawluk DJ. 2008 Supratentorial juvenile pilocytic astrocytoma in a young adult with Silver–Russell syndrome. *Br. J. Neurosurg.* **22**, 776–777. (doi:10.1080/02688690802044076)
  112. Lim DHK, Maher ER. 2010 Genomic imprinting syndromes and cancer. *Adv. Genet.* **70**, 145–175. (doi:10.1016/B978-0-12-380866-0.60006-X)
  113. Gregg C, Zhang J, Weissbourd B, Luo S, Schroth GP, Haig D, Dulac C. 2010 High-resolution analysis of parent-of-origin allelic expression in the mouse brain. *Science* **329**, 643–648. (doi:10.1126/science.1190830)
  114. Allen ND, Logan K, Lally G, Drage DJ, Norris ML, Keverne EB. 1995 Distribution of parthenogenetic cells in the mouse brain and their influence on brain development and behavior. *Proc. Natl Acad. Sci. USA* **92**, 10 782–10 786. (doi:10.1073/pnas.92.23.10782)
  115. Miller RW, Young JL, Novakovic B. 1994 Childhood cancer. *Cancer* **75**, 395–405. (doi:10.1002/1097-0142(19950101)75:1+ <395::AID-CNCR2820751321>3.0.CO;2-W)
  116. Poynter JN. 2014 Epidemiology of germ cell tumors. In *Pediatric germ cell tumors* (eds AL Frazier, JF Amatruda), pp. 17–36. Berlin, Germany: Springer.
  117. Crespi B. 2011 The evolutionary biology of child health. *Proc. R. Soc. B* **278**, 1441–1449. (doi:10.1098/rspb.2010.2627)
  118. Lombard LS, Witte EJ. 1959 Frequency and types of tumors in mammals and birds of the Philadelphia Zoological Garden. *Cancer Res.* **19**, 127–141.
  119. Effron M, Griner L, Benirschke K. 1977 Nature and rate of neoplasia found in captive wild mammals, birds, and reptiles at necropsy. *J. Natl Cancer Inst.* **59**, 185–198.
  120. Beard JW. 1963 Viral tumors of chickens with particular reference to the leukosis complex. *Ann. NY Acad. Sci.* **108**, 1057–1085. (doi:10.1111/j.1749-6632.1963.tb13436.x)
  121. Ewald PW, Ewald HAS. 2012 Toward a general evolutionary theory of oncogenesis. *Evol. Appl.* **6**, 70–81. (doi:10.1111/eva.12023)
  122. Stearns SC. 2012 Evolutionary medicine: its scope, interest and potential. *Proc. R. Soc. B* **279**, 4305–4321. (doi:10.1098/rspb.2012.1326)
  123. D'Souza AW, Wagner GP. 2014 Malignant cancer and invasive placentation. A case for positive pleiotropy between endometrial and malignancy phenotypes. *Evol. Med. Pub. Health* **2014**, 136–145. (doi:10.1093/emph/eou022)
  124. Elliot MG, Crespi BJ. 2009 Phylogenetic evidence for early hemochorial placentation. *Placenta* **30**, 949–967. (doi:10.1016/j.placenta.2009.08.004)
  125. Delaney MA, Nagy L, Kinsel MJ, Treuting PM. 2013 Spontaneous histologic lesions of the adult naked mole-rat (*Heterocephalus glaber*): a retrospective survey of lesions in a zoo population. *Vet. Pathol.* **50**, 607–621. (doi:10.1177/0300985812471543)
  126. Reeve HK, Westneat DF, Noon WA, Sherman PW, Aquadro CF. 1990 DNA 'fingerprinting' reveals high levels of inbreeding in colonies of the eusocial naked mole-rat. *Proc. Natl Acad. Sci. USA* **87**, 2496–2500. (doi:10.1073/pnas.87.7.2496)
  127. Braude S. 2000 Dispersal and new colony formation in wild naked mole-rats: evidence against inbreeding as the system of mating. *Behav. Ecol.* **11**, 7–12. (doi:10.1093/beheco/11.1.7)
  128. Burland TM, Bennett NC, Jarvis JUM, Faulkes CG. 2004 Colony structure and parentage in wild colonies of co-operatively breeding Damaraland mole-rats suggest incest avoidance alone may not maintain reproductive skew. *Mol. Ecol.* **13**, 2371–2379. (doi:10.1111/j.1365-294X.2004.02233.x)
  129. Manov I, Hirsh M, Iancu TC, Malik A, Sotnichenko N, Band M, Avivi A, Shamsi I. 2013 Pronounced cancer resistance in a subterranean rodent, the blind mole-rat, *Spalax*: *in vivo* and *in vitro* evidence. *BMC Biol.* **11**, 91. (doi:10.1186/1741-7007-11-91)
  130. Cotchin E. 1962 Problems of comparative oncology with special reference to the veterinary aspects. *Bull. WHO* **26**, 633–648.
  131. Finch CE. 2010 Evolution of the human lifespan and diseases of aging: roles of infection, inflammation, and nutrition. *Proc. Natl Acad. Sci. USA* **107**(Suppl. 1), 1718–1724. (doi:10.1073/pnas.0909606106)