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

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Antagonistic coevolution between maternal and fetal genes, and between maternally-derived 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 favor different degrees of proliferation of particular cell types in which they reside. As a result, the set of genes favoring greater proliferation will be selected to evade controls on cell-cycle progression imposed by the set of genes favoring 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.

Keywords: stem cells, trophoblast, parent–offspring conflict, imprinted gene network, comparative oncology

Cancer is an evolutionary problem. Natural selection within multicellular bodies favors somatic cell lineages that proliferate faster than their neighbors, 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 defenses 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. Anticancer 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 anticancer mechanisms.

Antagonistic coevolution between hosts and pathogens is the classic example of an evolutionary arms race. The evolution of new host defenses and new stratagems of pathogens to

evade these defenses could both have incidental pleiotropic effects that increased predisposition to cancer of hosts. However, pathogens, especially viruses, could also be directly selected to undermine anticancer adaptations of hosts. If host defenses against cancer are also deployed against viruses, then viruses will be selected to circumvent these defenses 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.

## Trophoblast and the subversion of extrinsic defenses

"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; Anonymous 1903]

Similarities between trophoblast and malignant cells have been noted for more than a century [11–17]. Shared features include rapid proliferation, invasion of neighboring tissues, deportation to distant sites, vasculogenic mimicry, induction of angiogenesis, and modulation of immune responses [18–21]. Trophoblast and malignant cells both utilize aerobic glycolysis [22, 23] and many cancers express 'trophoblast-specific' genes [24–27].

The β-subunit of chorionic gonadotropin (CGβ□is a quintessential product of trophoblast that is expressed by many trophoblastic and non-trophoblastic tumors [14, 28] and has been considered a 'definitive cancer biomarker' [16]. Although CGβ 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 placentation 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]. 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]. 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 tumors" [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 to 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. Preeclamptic 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 remodeling, smooth muscle cells undergo apoptosis and elastic elements of the extracellular matrix are degraded and replaced by fibrinoid [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 remodeling in first trimester, particularly the number of spiral arteries modified and how deeply their modification extends into the myometrium. Pregnancies in which remodeling 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 favor 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 remodeling of the endometrial segments of spiral arteries [54, 55]. Many researchers have succumbed to the temptation of conceptualizing vascular remodeling 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 remodeling. 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 tumor cells in intrasomatic selection to evade 'host' defenses and facilitate malignant spread [8].

## Genomic imprinting and the subversion of intrinsic defenses

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 depend 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 ($x$m:$y$p), 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 1 in 40,000 normal pregnancies, after 1 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 patrigene than when the same gene is a matrigene [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 favor different optimal sizes of a tissue.

Summers *et al*. applied the kinship theory to cancer [8]. 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 favor of the PEG associated with overgrowth and in favor of the MEG with undergrowth. IGF-II and p57 act respectively as an accelerator and brake on the $G_1$-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 tumors of childhood, including nephroblastoma, hepatoblastoma, adrenocortical carcinoma, rhabdomyosarcoma, pancreatoblastoma, and neuroblastoma [93, 94]. The tissues subject to overgrowth and embryonal tumors can be conjectured to be those in which patrigenes favor 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 estrogens 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 estrogens is unknown [96]. Whatever their precise function, placental estrogens are predicted to manipulate maternal physiology for fetal benefit [49]. Therefore, patrigenes are predicted to favor production of greater amounts of adrenal androgens than are matrigenes and to favor 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 tumors [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) [106–108]. These genes are expressed predominantly at the transition from proliferation to exit from the cell cycle [109]. 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 (biallelically expressed genes) [110]. 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 paralogs 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.

## 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*. proposed that early-life cancers are side effects of recent positive selection [5]. Childhood cancers are dominated by tumors 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 tumors should therefore occur in young animals of most species. Brain tumors, 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 tumors but not of leukemias, lymphomas or brain tumors that are numerically the most important childhood cancers. The reasons for this pattern deserve study. Children with SRS are relatively macrocephalic [111] and one of the few tumors reported from these children was a

brain tumor [112, 113]. *Igf2* appears to act as a MEG rather than a PEG in parts of the mouse brain [114]. Perhaps matrigenes, rather than patrigenes, favor greater expansion of some cell types within the brain [115].

Evolutionary hypotheses complement developmental explanations of age-specific cancer incidence. Non-epithelial tumors predominate in the first decade of life whereas epithelial tumors dominate at older ages [116]. 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 tumors have peak incidences around the onset of puberty when previously quiescent stem cells undergo rapid expansion [5, 117]. The age-specific incidence of pediatric cancers parallels changes in human growth velocity [118].

## Toward a truly comparative oncology

Comparisons of cancer rates between human populations requires 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 toward 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 tumors 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 [119, 120]. About 80% tumors in chickens are virally-induced whereas only 20% of cancers in humans have a clear viral etiology [121, 122]. Is this evidence that virally-induced tumors 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 [123]. 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) [124]. 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 [125]. 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 [126]. 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 [127, 128]. 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 [129] whereas blind mole-rats (*Spalax* spp.) are solitary with very low rates of cancer [130]. Studies of these and other species should illuminate whether mating system affects cancer rates.

Each species has its own distinctive spectrum of cancers [131]. Breast cancers, for example, kill many women but have not been reported in great apes [132]. Such differences argue for taxon-specific 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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