Biol. Rev.: Page 1 of 18. © 2006 *Cambridge Philosophical Society*
doi:10.1017/S1464793106007056 *Printed in the United Kingdom*

Positive selection in the evolution of cancer

Bernard J. Crespi[1] and Kyle Summers[2]

[1] *Behavioural Ecology Research Group*, *Department of Biology*, *Simon Fraser University*, *Burnaby*, *B. C. V5A 1 S6 Canada* (E-mail: crespi@sfu.ca);
[2] *Department of Biology*, *East Carolina University*, *Greenville*, *N. C.* 27858-4353 *USA* (E-mail: summersk@mail.ecu.edu)

(*Received* 20 *June* 2005; *revised* 27 *March* 2006; *accepted* 29 *March* 2006)

ABSTRACT

We hypothesize that forms of antagonistic coevolution have forged strong links between positive selection at the molecular level and increased cancer risk. By this hypothesis, evolutionary conflict between males and females, mothers and foetuses, hosts and parasites, and other parties with divergent fitness interests has led to rapid evolution of genetic systems involved in control over fertilization and cellular resources. The genes involved in such systems promote cancer risk as a secondary effect of their roles in antagonistic coevolution, which generates evolutionary disequilibrium and maladaptation. Evidence from two sources: (1) studies on specific genes, including *SPANX* cancer/testis antigen genes, several Y-linked genes, the *pem* homebox gene, centromeric histone genes, the breast cancer gene *BRCA1*, the angiogenesis gene *ANG*, cadherin genes, cytochrome P450 genes, and viral oncogenes; and (2) large-scale database studies of selection on different functional categories of genes, supports our hypothesis. These results have important implications for understanding the evolutionary underpinnings of cancer and the dynamics of antagonistically-coevolving molecular systems.

Key words: positive selection, antagonistic coevolution, oncogenes, tumour suppressors, molecular evolution.

CONTENTS

I. INTRODUCTION

Cancer is an evolutionary process at two levels: somatic selection of cancer genes and cells within individuals, and natural selection within populations of genes that predispose to cancer or help prevent it (Cairns, 1975; Graham, 1992; Greaves, 2000; Frank & Nowak, 2004). Analogies between the evolution of cancer cell lineages within the body and evolutionary change in populations via natural selection have been noted repeatedly in the scientific literature (e.g. Greaves, 2000), but there has recently been a surge in research that employs theory and methodology from evolutionary biology to address problems in the biology of cancer (e.g. Nunney, 1999, 2003; Maley & Forrest, 2001; Shibata, 2002; Weinstein & Ciszek, 2002; Michor *et al.*, 2004*a*, *b*; Frank, 2004*a*, *b*; Frank & Nowak, 2004; Crespi & Summers, 2005).

One of the most exciting aspects of the emerging integration of molecular evolutionary biology and medicine is the use of powerful analytical and statistical methods from the field of molecular evolution to investigate the evolutionary histories of specific genes involved in cancer predisposition and progression. Examples of cancer genes shown to be subject to positive selection (selection for amino acid changes) include *BRCA1*, involved in hereditary breast cancer (Huttley *et al.*, 2000; Fleming *et al.*, 2003; Pavlicek *et al.*, 2004), testis-specific *SPANX* genes, expressed in melanoma (Kouprina *et al.*, 2004), the angiogenin gene, involved in the angiogenesis that facilitates tumour growth via recruitment of supportive vasculature (Zhang & Rosenberg, 2002), *E-cadherin* and *VE-cadherin* genes, coding for cell-adhesion proteins mediating cell–cell interactions between mother and foetus during development, as well as cellular interactions in many forms of cancer (De Marzo *et al.*, 1999; Ilyas, 2000; Hendrix *et al.*, 2001; Hirohashi & Kanai, 2003; Summers & Crespi, 2005), and *TRPV6*, a calcium-transport gene associated with prostate cancer (Akey *et al.*, 2004; Stajich & Hahn, 2005). Positive selection has also been inferred for a substantial number of oncogenes in humans, chimpanzees and mice by Clark *et al.* (2003) in their broad-scale survey of selection across different functional gene categories. These results are intriguing, because it is not obvious why there should be a connection between cancer and positive selection.

Several authors have suggested that evolutionary conflicts, such as maternal-foetal conflict over resource allocation (Haig, 1993), or male–female conflict over fertilization (Chapman *et al.*, 2003) may have driven the positive selection of genes that are involved in the evolution and development of cancer (Zhang & Rosenberg, 2002; Kouprina *et al.*, 2004; Kleene, 2005; Nielsen *et al.*, 2005). Herein, we generalize these ideas to encompass diverse evolutionary situations involving antagonistic coevolution, which involves genetically-based conflict between parties with divergent fitness interests. Our main hypothesis is that antagonistic coevolution has led to rapid evolution in genetic, developmental and physiological systems of control over cellular resources, which creates evolutionary disequilibrium and organism-level maladaptation, manifested as increased cancer risk. We provide evidence bearing on this hypothesis from two sources: (1) molecular-evolutionary studies of positive selection (selection for amino acid changes that are inferred to be functional and adaptive) (Kreitman, 2000; Yang & Bielawski, 2000; Fay & Wu, 2003) on genes associated with cancer, and (2) large-scale database studies of positive selection on different functional categories of genes, some of which are cancer-related. We then discuss the evolutionary and clinical implications of our results, and provide suggestions for future integrative evolutionary-medical studies of carcinogenesis.

II. POSITIVE SELECTION IN THE EVOLUTION OF CANCER

Positive selection is often associated with antagonistic coevolution, driven by ongoing unresolved conflicts. These conflicts involve natural enemies such as hosts and parasites (e.g. Yeager & Hughes, 1999; Burrows *et al.*, 2004; Sawyer, Emerman & Malik, 2004), but also males and females or eggs and sperm competing over control of fertilization (e.g. Vacquier, 1998; Wyckoff, Wang & Wu, 2000), sexually-antagonistic genes favoured when expressed in one sex but disfavoured when expressed in the other sex (Rice, 1996; Rice & Holland, 1997), genes expressed in mothers and foetal offspring (Trivers, 1974; Haig, 1993; Crespi & Semeniuk, 2004), intragenomic elements with different avenues of maximizing fitness (Summers, de Silva & Farwell, 2002; Burt & Trivers, 2006), and genomically-imprinted genes that are expressed when either paternally or maternally derived (Haig, 2000, 2004). In each of these situations, more or less mutually-dependent parties are in conflict over fitness-related resources, and the conflict is driven by reciprocal genetic or epigenetic change over an evolutionary time scale.

We suggest that the connection between positive selection at the molecular level and cancer is driven by the strong, ongoing selection generated by evolutionary conflict (see also Ewald, 2000; Huttley *et al.*, 2000; Zhang & Rosenberg, 2002). By this hypothesis, most of the cancer genes that show evidence of positive selection have been subject to antagonistic coevolution, which varies in its dynamics and strength among lineages.

Why should antagonistically-coevolving genes be involved in the evolution of cancer? The genetic, developmental and physiological systems that are focal points for antagonistic coevolution, such as resource acquisition and use, cell replication, and tissue growth, are often critical components in the evolution of predisposition to cancer (Summers *et al.*, 2002; Hernandez *et al.*, 2003). Thus, strong selection in the context of antagonistic coevolution leads to evolutionary change in genes and traits related to conflict, and the pleiotropic effects of these changes may generate increased cancer risk. The negative fitness effects of cancer are selected against, but three factors, (1) the unrelenting nature of coevolutionary antagonism (Rice & Holland, 1997), (2) negative pleiotropic effects of strongly-selected alleles, and (3) weaker anticancer selection with increasing age

(Weinstein & Ciszek, 2002), maintain the association between conflict-related genes and cancer. Genomic imprinting, the expression *versus* silencing of genes depending on their parent of origin (Haig, 2000, 2004), provides an epigenetic equivalent to this pleiotropic genetic system. Here, genetic conflict between mothers and offspring over resource allocation during embryonic development (Haig, 1993, 2000) has led to systems of gene expression that also amplify cancer risk when disrupted either naturally via mutation and epigenetic alteration (Feinberg, 2000; Ohlsson *et al.*, 2003), or experimentally via the creation of androgenetic (exclusively paternal) cell lines (Hernandez *et al.*, 2003).

As first described by Graham (1992) in his book *Cancer Selection*, strong selection in contexts other than antagonistic coevolution can also lead to increased cancer risk as a pleiotropic byproduct, although here the effects are expected to be less pronounced. For example, artificial selection for large size has led to greatly-increased cancer rates in some breeds of dogs (Graham, 1992; Leroi *et al.*, 2003), and pediatric cancers of humans appear to be concentrated in two tissues, brain and bone, that have undergone rapid phenotypic changes in their developmental trajectories along the human lineage (Graham, 1992; Leroi, Koufopanou & Burt, 2003). In these cases, rapid evolution drives the genotype away from the optimum, increasing the risk of cancer as a result (Galis & Metz, 2003; Leroi *et al.*, 2003). Such cases may typically be transitory, disappearing once the species or population has adapted to the changes, or they may lead to positive-feedback cycles of oncogene evolution, leading to improved tumour suppression, greater developmental precision and complexity, and further adaptive changes driving pleiotropic oncogene evolution (Graham, 1992). Antagonistic coevolution similarly leads to incessant pressure for positive genetic change, and little opportunity for adjustment to a new equilibrium because one does not exist over an evolutionary time scale. Hence, antagonistically-coevolving genes should be in a continual state of mild organism-level maladaptation, and may be particularly likely to contribute to the development of cancer as a result.

III. EVIDENCE FOR LINKS BETWEEN POSITIVE SELECTION, CANCER GENES, AND ANTAGONISTIC COEVOLUTION

Our hypothesis predicts the frequent coincidence of positive selection on a gene, involvement of the gene in the risk or progression of cancer, and evidence that forms of antagonistic coevolution are involved in how gene regulation or function has diversified. Genes may be implicated in cancer in various ways, such as the presence of hereditary variants associated with risk, the generation of somatic variants that promote carcinogenesis, the development of changes in levels of gene expression, or the co-option by cancer cells of developmental pathways that evolved for other purposes (e.g. Kleene, 2005). Such effects may involve oncogenes that directly promote tumour growth, 'gatekeeper' tumour-suppressor genes that prevent or suppress incipient cancers, 'caretaker' genes that inhibit loss of genetic stability, or 'landscaper' genes that maintain the integrity of phenotypic interactions between and within types of tissues (Hanahan & Weinberg, 2000; Michor *et al.*, 2004*a*; Michor, *et al.*, 2004*b*; Crespi & Summers, 2005). We expect that many cases of positive selection on such genes involve the genetic, epigenetic, or developmental breakdown of 'tug-of-war' systems, whereby conflict over cellular resources has led to the evolution of dynamic stalemates held at Nash equilibria by opposing selection (e.g. Haig, 1993). The human *IGF2* system provides the classic case of such tugs-of-war between mother and child during foetal development, and Haig (1993, 1999*a*, *b*) describes how some major pathologies of pregnancy, such as preeclampsia and gestational diabetes, may be driven by disruption of costly, coevolved stalemates. Other cases of positive selection may instead derive from strong divergent selection on aspects of life-history, such as developmental rates, lifespan, or tissue renewal or wound repair capacity, that are directly linked to the molecular-genetic systems containing oncogenes, tumour suppressors, and landscaper genes (e.g. Weinstein & Ciszek, 2002; Chang *et al.*, 2005; Hampton, 2005).

How common is the coincidence of positive selection, effects on cancer, and antagonistic coevolution? We present evidence from two approaches: (1) studies of positive selection on specific genes or gene families that are known to be directly related to cancer, and also are implicated in antagonistic coevolution, and (2) previous large-scale studies of positive selection across hundreds or thousands of genes that vary in function. The first approach links the three phenomena more or less directly, and the latter approach provides indirect evidence but helps to indicate where and how future studies might usefully proceed. We stress that because our hypothesis is novel and links three formerly-disparate processes, conclusive evidence for most cases must await future, targeted tests that integrate diverse data from molecular evolution, genetic conflict studies and carcinogenesis.

IV. POSITIVELY-SELECTED GENES INVOLVED IN CANCER AND GENETIC CONFLICT

(1) *SPANX* cancer/testis genes

SPANX is a family of X-linked, primate-specific cancer/testis associated genes (CTAs), so called because their expression is almost exclusively limited to normal testis, where they are involved in spermatogenesis, and melanoma tumour cells, where they apparently promote cancer cell growth (Zendman, Ruiter & Muijen, 2003; Kouprina *et al.*, 2004; Scanlan, Simpson & Old, 2004; Westbrook *et al.*, 2004; Kalejs & Erenpreisa, 2005). Their normal functions are largely unknown, although some evidence suggests roles for these and other CTA genes in spermatozoa development and function, cell cycle regulation, and apoptosis (Zendman *et al.*, 2003). *SPANX* gene expression is associated with aggressiveness of skin tumours, and these genes have been mapped to an X-chromosome location close to loci for

inherited testicular and prostate cancer risk (Zendman *et al.*, 2003*a*; Westbrook *et al.*, 2004).

Kouprina *et al.* (2004) inferred strong positive selection on *SPANX* genes in primates (including humans), with very rapid evolution at both non-synonymous and synonymous sites. They hypothesized that *SPANX* genes contribute to spermatozoa fitness, and that the rapid rate of synonymous site substitution evolved to achieve a high translation rate, as many CTA genes exhibit unusually high rates of expression. Kleene (2005) provides additional evidence that CTAs such as *SPANX* are subject to extremely strong selection in the context of sperm production rates, with sexual selection and intragenomic conflict as the main agents of evolutionary diversification. Thus, genetic pathways involving CTA genes, which evolved in the context of sexual conflict and sexual selection, are apparently co-opted by cancer cell lineages during somatic evolution, as developing cancer cells avoid apoptosis, dedifferentiate and take on properties of immortal male germ cells (Old, 2001; Kleene, 2005; Nielsen *et al.*, 2005).

ADAM2, another CTA gene subject to positive selection in mammals (Scanlan *et al.*, 2002; Torgerson, Kulathinal & Singh, 2002; Glassey & Civetta, 2004), is a sperm cell-surface adhesion protein integral to fertilization, and as such it is also a strong candidate for evolution by molecular sexual selection or sexual conflict (see also Civetta, 2003*a*, *b*). The large number (>100) of other mainly unexplored CTAs functionally related to *SPANX*, their clinical promise as targets of cancer immunotherapy (Old, 2001; Zendman *et al.*, 2003; Scanlan *et al.*, 2004), and their evolutionary implications as selfish genomic elements and reproductive genes subject to positive selection (Karn & Nachman, 1999; Wyckoff *et al.*, 2000; Swanson, Nielsen & Yang, 2003; Wang & Zhang, 2004) should motivate further studies of these gene families.

Clark *et al.* (2003) inferred positive selection on four ADAM family genes which do not show cancer/testis expression patterns, but instead exhibit important roles in angiogenesis (Bauvois, 2004), cell adhesion, and proteolysis. Two of these genes, *ADAM17* and *ADAMTS4*, exhibit highly disregulated expression in prostate and breast cancers, where they appear to play key roles in invasion and metastasis due to their protease activity (Okada, 2000; Karan *et al.*, 2003; Lendeckel *et al.*, 2005); moreover, *ADAM17* activity appears to be regulated by dihydrotestosterone in prostate cancer (Karan *et al.*, 2003). Based on the roles of various *ADAM* genes in implantation (Olson *et al.*, 1998; Hurskainen *et al.*, 1999), placentation (Shi *et al.*, 2000) and insulin-like growth factor production during foetal growth (Laigaard *et al.*, 2005), we hypothesize that maternal-foetal conflict has driven their molecular evolution. A matrix metalloprotease, *MMP26*, which exhibits similar dual functions in maternal-foetal interactions and cancer (Uria & Lopez-Otin, 2000, has also been shown to be subject to very strong positive selection (Nielsen *et al.*, 2005).

(2) Y-linked genes

Several researchers have noted that Y-linked genes associated with sexual selection and sexual conflict are related to cancer (e.g. Hurst, 1994*a*, *b*, Kleene, 2005). Hurst (1994*a*, *b*) described how genes on the Y chromosome, such as *Sry* and *Zfy*, are subject to the same kind of intragenomic conflict between the paternal and maternal genomes of an embryo that characterizes imprinted growth factor genes such as *IGF2* (Haig, 2004). This, in turn, is expected to generate antagonistic coevolution, and a variety of studies have found evidence of strong positive selection acting on both *Sry* and *Zfy* (e.g. Whitfield, Lovell-Badge & Goodfellow, 1993; Tucker & Lundrigan, 1993; Jansa, Lundrigen & Tucker, 2003; Tucker, Adkins & Rest, 2003; Wildman *et al.*, 2003). Both *Sry* and *Zfy* are associated with prostate cancer (Tricoli & Bracken, 1993; Tricoli *et al.*, 1993).

Other genes on the Y chromosome should also experience the effects of sexual conflict, and several of them have been linked to prostate cancer (e.g. Dasari *et al.*, 2001). For example, *DAZ* (deleted in azoospermia), a Y-linked gene essential in spermatogenesis (Reynolds & Cooke, 2005), has been inferred to be subject to positive selection in humans and other primates (Bielawski & Yang, 2001; Wildman *et al.*, 2003); moreover, Teng *et al.* (2002) and Becherini *et al.* (2004) found pronounced ethnic differences in the frequency of a functional SNP (single-nucleotide polymorphism of *DAZL*, the autosomal homologue of *DAZ*, which are suggestive of positive selection. The *DAZ* gene exhibits deregulated expression in prostate cancer (Dasari *et al.*, 2001, 2002), and we suggest that this link to cancer is driven by sexual conflict or sexual selection.

(3) Homebox genes

Homeobox genes encode transcription factors that direct various crucial developmental processes, such as the patterning of body plans, the control of cell growth (Cillo *et al.*, 1999) and the determination of stem cell fate (Lansdorp, 1997). Altered homeobox gene expression is found in many cancers, apparently due to disregulation of their roles in cell proliferation, differentiation, and migration (Cillo *et al.*, 1999; Galis, 1999; Rao *et al.*, 2002). Most homeobox genes are highly conserved among species. However, the *pem* homeobox gene, a member of the *PEPP* homeobox subfamily, has been shown to evolve very rapidly in rodents, under the effects of positive selection, especially in the N-terminal region (Maiti *et al.*, 1996; Sutton & Wilkinson, 1997; Wang & Zhang, 2004). This X-linked gene is expressed in primordial germ cells and placental membranes during embryogenesis, and reproductive tissues (testis and ovaries) during adulthood; it is also expressed in diverse tumour types, where it promotes tumour cell growth and interacts with the tumour-suppressor gene *menin* (Pitman *et al.*, 1998; Rao *et al.*, 2002). The function of the gene is unclear, but it appears to regulate placental development and the development of sperm and egg cells in some manner (Pitman *et al.*, 1998; Rao *et al.*, 2002), even though it is not essential for normal development in mice (Pitman *et al.*, 1998).

We suggest that the *pem* gene has been subject to positive selection in the same context as other X-linked cancer/testis antigen genes such as *SPANX*: sexual selection, sexual antagonism, and possibly sex-chromosomal meiotic drive

(Wang & Zhang, 2004; Kleene, 2005). One of the few other X-linked homeobox genes known to be subject to positive selection, *OdsH*, affects levels of sperm production in *Drosophila*, although, like the *pem* gene, it is functionally non-essential (Sun *et al.*, 2004). *OdsH* is also a 'speciation' gene that mediates the evolution of hybrid sterility in *Drosophila mauritiana* and its relatives (Ting *et al.*, 1998; Sun, Ting & Wu, 2004). The similarities between cancer/testis antigen genes, and X-linked, testis-expressed homeobox genes such as *pem*, *OdsH*, and *TGIFlX* (Wang & Zhang, 2004) suggest that the molecular changes accompanying speciation, especially those that affect male reproductive function (Civetta & Singh, 1995; Tsaur & Wu, 1997; Vacquier, 1998; Wyckoff *et al.*, 2000; Swanson *et al.*, 2003), engender increased cancer risk.

Numerous other homeobox genes have been shown to be subject to positive selection (Van de Peer *et al.*, 2001; Clark *et al.*, 2003 for *HOXA5, A11, C4, C6, D4* and *D10*; Fares *et al.*, 2003) and are aberrantly expressed in cancer cells (e.g. Boström *et al.*, 2000; Naora *et al.*, 2001; Miller *et al.*, 2003*a*, *b*). These links between positive selection and cancer for *HOX* genes fit with Graham's (1992) hypothesis that rapid morphological evolution increases cancer risk (see also Thaler, 1999; Galis & Metz, 2003; Kavanagh, 2003; Leroi *et al.*, 2003). We hypothesize that positively-selected *HOX* genes will also show evidence of pleiotropic effects on morphogenesis and cancer risk, or antagonistic coevolution, upon further study.

(4) Centromeric histone genes

Histones that bind and structure DNA are in general among the most conserved of proteins, but some centromeric histones evolve very rapidly and have been demonstrated to be subject to strong positive selection in diverse animals and plants (Malik & Henikoff, 2002; Cooper & Henikoff, 2004; Talbert, Bryson & Henikoff, 2004). During meiosis, these centromeric histones form a crucial part of the cellular machinery distributing chromosomes to developing gametes. In females, only one of four products survives to be included in the egg nucleus, and this strong selection has apparently led to the recurrent evolution of 'driving' centromeric histone variants that gain preferential access to the developing oocyte (Henikoff, Ahmad & Malik, 2001; Malik & Henikoff, 2002; Talbert *et al.*, 2004). This centromeric drive is, however, opposed by marked reductions in male fertility that stem from such disparities in centromere strength, which leads to antagonistic coevolution of drivers and suppressors, positive selection (Malik & Henikoff, 2001, 2002; Daniel, 2002; Cooper & Henikoff, 2004), and apparent strong effects on karyotype evolution and speciation (Borodin, 2001; Henikoff *et al.*, 2001; Amor & Choo, 2002; Amor *et al.*, 2004; O'Neill, Eldridge & Metcalfe, 2004).

Centromeric histones also play critical roles in the maintenance of genomic integrity across the cell cycle (e.g. Liang *et al.*, 2004; Shah *et al.*, 2004), and as such function as genomic 'caretakers' helping to prevent carcinogenesis. Moreover, some centromeric histones are overexpressed in tumours (e.g. Collins, Furuyama & Biggins, 2004; Atalay *et al.*, 2005) and one of the positively-selected centromeric histones, *CENP-C*, generates aneuploid cells when subject to mitotic dysfunction (Jabs *et al.*, 1993). Such aneuploidy is a hallmark of chromosomal instability, a major cause of cancer progression (Michor *et al.*, 2004*a*, *b*). Selection for constant expansion of heterochromatin repeats, to facilitate the function of centromeres, may also lead to the retention of mechanisms of replication that foster instability of microsatellite repeats (Henikoff, 2000), another major contributor to carcinogenesis (e.g., Breivik, 2005). Considered together, this evidence suggests that centromeric drive can increase cancer risk via effects on genomic stability.

(5) Breast cancer genes

The *BRCA1* gene is a central component of pathways regulating the cell cycle, DNA repair, and cell replication (Deng & Brodie, 2000; Deng & Wang, 2003). This gene acts as a tumour suppressor, as loss of heterozygosity is found in familial breast and ovarian cancers, but it also exhibits crucial functions during development. Thus, human female *BRCA1* heterozygotes exhibit substantially lower birth mass than homozygotes (Jernström *et al.*, 1998), null *BRCA1* mice die in early embryogenesis with severe growth defects, and the gene exhibits its greatest expression in the highly-proliferative terminal end buds of the breast epithelium in pubertal mice (Jernström *et al.*, 1998; Deng & Brodie, 2000; Huttley *et al.*, 2000).

Intragenomic conflict may play a role in generating a substantial proportion of the genetic variation associated with hereditary predisposition to breast cancer. The *BRCA1* gene contains a particularly high frequency of *Alu* repeat elements (129, making up approximately 42% of the sequence). These are classic 'selfish genes' that can increase in frequency through transposition (Miki, 1998; Kolomietz *et al.*, 2002; Jurka, 2004). These elements are involved in a variety of rearrangements that have been identified in patients with an inherited predisposition to breast and ovarian cancer (Pavlicek *et al.*, 2004 and references therein), as well as being directly involved in the evolution of other forms of cancer and additional diseases among primates (Martinez *et al.*, 2001).

Positive selection has been inferred for exon 11 of *BRCA1* by Huttley *et al.* (2000), Yang & Nielsen (2002) and Fleming *et al.* (2003), and for the whole gene by Pavlicek *et al.* (2004) using a larger sample of eutherian mammals (see also Wildman *et al.*, 2003). Huttley *et al.* (2000) and Yang & Nielsen (2002) also presented evidence for positive selection along the chimpanzee and human lineages. Deviations from Hardy-Weinberg equilibrium (Huttley *et al.*, 2000) for extant *BRCA1* alleles, as well as inferences of recent allele ages (Slatkin, 2000; Slatkin & Rannala, 2000), provide evidence that strong selection is also ongoing at this locus in human populations. Hurst & Pál (2001) also inferred the presence of purifying selection on silent sites in *BRCA1*, perhaps as a consequence of selection on patterns of codon usage.

Two related and non-exclusive evolutionary hypotheses may help explain the coincidence of positive selection and increased cancer risk for *BRCA1*. First, based on the

evidence that *BRCA1* plays a central role in both DNA repair and cell proliferation in breast and brain tissue (Xu *et al.*, 1999; Korhonen *et al.*, 2003; Foulkes, 2004), we hypothesize that this gene mediates a tradeoff between DNA repair and cell proliferation rates (Breivik & Gaudernack, 2004; Breivik, 2005), analogous to the tradeoff of cancer risk with apoptosis and cellular senescence that mediates ageing (Campisi, 2005). The nature of this repair-proliferation tradeoff may vary among species, leading to the observed adaptive molecular evolution in the human and chimpanzee lineages driven by selection on such factors as lifespan, mating system, brain development, or breast development.

A diverse set of evidence suggests that the optimum for the tradeoff between DNA repair and cell proliferation rate varies between males and females. Thus, *BRCA1* interacts with *BRCA2* (Huttley *et al.*, 2000), and many alleles at both *BRCA1* and *BRCA2* are associated with human breast cancer (Pavlicek *et al.*, 2004). *BRCA2*, which is also involved in DNA repair and growth during early development, may be subject to sexually antagonistic selection in that in humans, alleles appear to affect foetal survival in a sex-dependent manner (Healey *et al.*, 2000; see also Teare *et al.*, 2004). de la Hoya *et al.* (2003) and Kotar *et al.* (2004) also present evidence for biased offspring sex ratios in women with *BRCA1* or *BRCA2* mutations, which may be due to sex differences in prenatal viability, or, perhaps, to ascertainment biases in sampling. Finally, *BRCA1* genotype is known to affect birth mass of its female bearers (Jernström *et al.*, 1998), and similar links between *BRCA2* allele (truncation), sex ratio, birth mass and cancer have been found in mice (Connor *et al.*, 1997; Friedman *et al.*, 1998). This evidence from studies of viability, sex ratios, and birth mass are consistent with the hypothesis that *BRCA1* and *BRCA2* alleles exhibit sexually-antagonistic effects during human development due to repair-proliferation tradeoffs. By this hypothesis, genes for more-rapid proliferation (in rapid growth or wound-healing, for example) may be more favoured in one sex than another, ultimately as a result of sexual selection or other factors differing between the sexes; effects on cancer would then derive from disruption of the tradeoff via somatic mutation, leading to proliferation with less-effective DNA repair. This hypothesis is also consistent with the relatively high degree of positive selection on other genes involved in cell proliferation and DNA repair noted in Clark *et al.* (2003), but it requires targeted tests and elucidation of molecular mechanisms.

Second, relative breast size is considerably higher in humans than in other primates, and, indeed, breasts develop prematurely (prior to pregnancy) in nulliparous humans (Cant, 1981; Caro, 1987; Caro & Sellen, 1990). Whatever the selective pressures for increased breast size in the human lineage, which may include mate choice by males (Jasienska *et al.*, 2004) and natural selection for fat reserves (Caro & Sellen, 1990; Pawlowski, 1999; Arieli, 2004), this rapid evolutionary increase in size may have selected for alleles promoting accelerated breast development, which have the pleiotropic effect of increased cancer risk. Similar considerations apply to other rapidly-evolved aspects of human morphology, such as brain size and bone growth (Graham, 1992; Leroi *et al.*, 2003), and possibly the prostate (Hamilton, 1990). This hypothesis is also consistent with high *BRCA1* expression in the rapidly-proliferating breast epithelium of pubertal mice (Jernström *et al.*, 1998), and with Huttley *et al.*'s (2000) hypothesis that new alleles introduced at the *BRCA1* locus disrupt coadapted gene complexes.

(6) Angiogenesis gene *ANG*

The angiogenin gene (*ANG*) has a critical role in tissue vascularization of the developing placenta and embryo, maternal immune tolerance of the foetus, and vascular and tissue homeostasis (Zhang & Rosenberg, 2002; Brion & Badet, 2003). This gene also exhibits elevated expression in many types of tumours, its expression levels are directly related to cancer progression, and *ANG* antagonists inhibit cancer growth (Zhang & Rosenberg, 2002).

Given its role in placental development, *ANG* may be subject to the parent-offspring conflicts over resource transfer that are an integral part of placentation and pregnancy (Haig, 1993, 1999*a*, *b*; Zhang & Rosenberg, 2002; Crespi & Semeniuk, 2004), with cancer as a side effect of the 'tug-of-war' over the levels of placental development. Indeed, invasive placentation shares many biochemical and physiological features with the development of cancer (Pearson, 1981; Adamson, 1987; Old, 2001; Zygmunt *et al.*, 2003), and stimulation of blood vessel formation may be similar between these two processes. This hypothesis could be tested further by comparing *ANG* evolution in eutherian mammal lineages with invasive *versus* non-invasive placentation (Mossman, 1987), and via analysis of the functional effects of *ANG* mutants during placentation and carcinogenesis. *ANG* is also involved in reproductive functions (Ferrara, 2000), which suggest that it may also be subject to selection in the context of sexual antagonism.

Zhang & Rosenberg (2002) and Wildman *et al.* (2003) demonstrated elevated ratios of nonsynonymous to synonymous nucleotide substitution rates (dN/dS) in *ANG* in primates. Zhang & Rosenberg (2002) also showed that substitutions causing change in the protein charge occurred in regions likely to affect crucially the interaction of angiogenin with a variety of other proteins, including actin, angiostatin, elastase, heparin, plasminogen and RNase inhibitor. Hence, the substitutions under positive selection are likely to affect the activity of angiogenin in functionally important protein–protein interactions. Zhang & Rosenberg (2002) suggested that the positive selection they detected may be driven by conflicts between maternal and foetal interests, following arguments by Haig (1993).

(7) Cadherins

Cadherins are a multigene family of proteins that mediate homotypic cell–cell adhesion and signal transduction (Wheelock & Damsky, 1997; Gallin, 1998; Nollet, Kools & van Roy, 2000; King, Hittinger & Carroll, 2003; Wheelock & Johnson, 2003). They play fundamental roles during mammalian placentation and morphogenesis, as well and controlling tissue architecture and integrity, including the

organization of stem cell compartments (Nelson & Nusse, 2004). Cadherin expression is also closely associated with the development and metastasis of cancer; for example, *vascular endothelial* (*VE*) *cadherin* is highly expressed in aggressive melanomas, where it causes cells to adopt a vascular phenotype that mimics embryonic vascular networks (Hendrix *et al.*, 2001), and *E-cadherin* abnormalities are found in nearly all invasive human cancers (Mareel & Van Roy, 1998). *VE-cadherin* also enhances placental invasiveness, by causing invading cytotrophoblast (a developing placental cell type) to adopt the vascular phenotype of the maternal tissues in the spiral arteries that they replace (Zhou *et al.*, 1997).

Summers & Crespi (2005) present evidence that three cadherin genes, *E-cadherin*, *P-cadherin*, and *VE-cadherin*, that are strongly expressed during placentation, have been subject to positive selection. By contrast, a 'control' cadherin that is not expressed in the placenta, *H-cadherin*, showed no evidence of selection. These results provide support for the hypothesis that the cadherin genes involved in maternal-foetal interactions have been subject to antagonistic coevolution, possibly in the context of 'green-beard' mutations that result in 'selfish' alleles effecting their own increased reproduction but being subject to suppressing mutations by unlinked genes (Hamilton, 1964; Haig, 1996). More generally, ongoing maternal-foetal 'tugs-of-war' over resources (Haig, 1993, 1999*a*, *b*) may have led to the evolution of genetic pathways, normally expressed in the invasive placenta and uterus, that are co-opted by cancer cells during somatic selection for proliferation and degradation of tissue integrity surrounding tumours (e.g. Bischof, Meisser & Campana, 2000; Lala *et al.*, 2002).

Clark *et al.* (2003) provided evidence for positive selection on five additional cadherin genes, one of which, *PCDH7*, appears to be related to the development of some cancers (Yoshida *et al.*, 1998). Similarly, Wildman *et al.* (2003) found evidence of positive selection on the cell-adhesion gene *ICAM1* in some primates; aberrant expression of this gene is associated with breast cancer (Kammerer *et al.*, 2004). *ICAM1* is also intimately involved in maternal-foetal interactions during pregnancy, where it also plays an important role in pathological situations such as preeclampsia, aberrant inflammatory reactions, and infection of the placenta with malarial parasites (Maubert, Guilbert & Deloron, 1997; Xiao *et al.*, 1997; Oyama, 2001).

(8) Cytochrome P450 genes

The cytochrome P450 heme-thiolate enzymes comprise a gene superfamily with over 2700 genes known overall, including 57 from humans (Lewis, 2004). These enzymes are involved in two main functions: (1) synthesis and degradation of hormones (including steroids), lipids, prostoglandins, and vitamin D, and (2) metabolism of various 'exogenous' chemicals, including carcinogens and toxins, which can entail both detoxification and activation to harmful metabolites (Negishi *et al.*, 1996; Lewis, Watson & Lake, 1998; Lewis, 2004). Much of the high diversity of this gene family, for the enzymes acting on exogenous substrates, apparently arose via evolutionary antagonism in the context of plant-animal metabolic coevolution (Gonzalez & Nebert, 1990; Nebert, 1997; Lewis *et al.*, 1998). Such coevolution of exogenous chemicals with the enzymes that metabolize them, and the central role of cytochome P450 enzymes in the metabolism of sex hormones such as testosterone and oestrogen, suggest that many of these enzymes should be subject to positive selection.

Some cytochrome P450 genes should, by our hypothesis, mediate cancer risk in the context of sexual selection, sexual conflict, local dietary adaptation (Nebert, 1997), or negative pleiotropic effects of detoxification (Negishi *et al.*, 1996). Sexual conflict and sexual selection in particular may drive the evolution of genes involved in sex steroid metabolism via the extensive pleiotropic effects of hormones like testosterone and estrogen, and their effects in mediating the risk of cancer in reproductive tissues. For example, the development of cancers of the prostate (Taplin & Balk, 2004), breast (Rebbeck *et al.*, 1999; Giguere *et al.*, 2001; Haiman *et al.*, 2002; Suter *et al.*, 2003) and ovary (Silva *et al.*, 1997; Risch, 1998; Modugno, 2004) is strongly influenced by androgen levels and alleles at the androgen receptor gene, and such effects may differ in direction between the sexes (e.g. Ingles *et al.*, 1997; Ferro *et al.*, 2002). More generally, research on *Drosophila* species indicates that the expression of sexually antagonistic genes in the 'wrong' sex is pervasive and can impose significant fitness costs on adults (Chippindale, Gibson & Rice, 2001; Rice & Chippindale, 2001).

Wooding *et al.* (2002) found evidence of positive selection among human populations on *CYP1A2*, which metabolises oestrogens and other compounds such as caffeine, and exhibits polymorphisms and expression patterns related to prostate cancer (Weber, 1995; Sterling & Cutroneo, 2004). Similarly, adaptive molecular evolution has been inferred in rodent *CYP2A4* and *CYP2A5* genes, which are involved in steroid metabolism and the metabolism of exogenous compounds (Negishi *et al.*, 1996); Gotoh (1992) also demonstrated that substrate-recognition regions of the *CYP2* gene family exhibit relatively more non-synonymous than synonymous changes compared to other sites. Expression levels and polymorphisms of various *CYP2* family genes, including *CYP2A5*, are associated with cancer risk in mice and humans (e.g. Chomarat *et al.*, 1997; Wastl *et al.*, 1998; Agundez, 2004). Clark *et al.* (2003) inferred positive selection on four *CYP* genes, two of which, *CYP27A1* and *CYP27B1*, are associated with prostate, colon, and breast cancer, apparently via their roles in vitamin D metabolism (Kállay *et al.*, 2002; Farhan, Wahala & Cross, 2003; Cross *et al.*, 2004). Further studies should elucidate the apparent links between antagonistic coevolution and cancer risk for cytochrome P450 genes, which may be especially important given that over 90% of drugs in human clinical use are metabolized by genes in the *CYP1*, *CYP2* and *CYP3* gene families (Lewis, 2004), and approximately 40% of human P450-dependent drug metabolism is enacted by enzymes that are polymorphic (Ingelman-Sundberg, Oscarson & McLellan, 1999). Such links may also mediate the strong effects of recent evolutionary changes in the human diet on increased prostate and breast cancer risk (Coffey, 2001; Cordain *et al.*, 2005; Michels, 2005).

(9) Genes in oncogenetic viruses

Viruses cause approximately 15 % of cancers, via the effects of their own oncogenes or insertion into regions of DNA near host proto-oncogenes, leading to alterations of cell cycle control that favour viral replication (Eick & Hermeking, 1996; Slev & Potts, 2002). Many viruses also deactivate or degrade host systems for apoptosis such as *p53*, and indeed some anticancer adaptations may have evolved in the context of selection on hosts to induce suicide in virus-infected cells with corrupted control of proliferation (Vaux, Haeker & Strasser, 1994; Eick & Hermeking, 1996; LeGrand, 2001).

Virus-host interactions are by default subject to antagonistic coevolution where the virus causes acute disease or cancer. Positive selection on oncoviruses, apparently driven by immunogenicity or degree of virulence (Ewald, 1994, 2000) has been reported for Epstein Barr virus (Midgley *et al.*, 2003; Burrows *et al.*, 2004), papillomavirus (DeFilippis, Ayala & Villareal, 2002; Chen *et al.*, 2005), and human T cell leukemia virus (Salemi, Desmyter & Vandamme, 2000). Bannert & Kurth (2004) describe how various mobile retroelements similarly insert into host proto-oncogenes or tumour-suppressor genes and promote cancer, and they estimate that one-quarter of all human promotors retain sequences derived from such elements. As such, intragenomic conflict driven by endogenous genetic elements, including such ubiquitous elements as Alu repeats (Miki, 1998; Kolomietz *et al.*, 2002), may substantially increase cancer risks (see also Summers *et al.*, 2002).

Taken together, these data for Y-linked genes, *SPANX*, homeobox genes, centromeric histones, *BRCA1*, *ANG*, cadherins, cytochrome P450 genes, and viral genes provide considerable evidence for strong links between positive selection and the evolution of increased cancer risk, driven by antagonistic coevolution. We also note that at least three of the positively-selected genes discussed above, *ANG*, *pem* and *OdsH*, have been shown to be non-essential in at least some species (Pitman *et al.*, 1998; Zhang & Zhang, 2003; Sun *et al.*, 2004), which is consistent with their hypothesized role in coevolutionary conflict because in some lineages one party may 'win'.

V. LARGE-SCALE DATABASE STUDIES OF POSITIVE SELECTION

As part of their extensive survey testing for positive selection on 7645 genes using human-chimpanzee-mouse trios, Clark *et al.* (2003) listed the biological processes showing the strongest evidence for positive selection along the chimp and human lineages. For the chimpanzee lineage, the biological functions 'Oncogenesis' and 'Other oncogenesis' both exhibited some of the strongest evidence for selection ($P<0.05$ on average, across 240 genes). Overall, four (15 %) of 27 tumour suppressor genes, and 10 (20 %) of 51 oncogenes or oncogenesis genes in this data set exhibited $P<0.05$ for either the human or chimpanzee lineage, under their model 2.

Nielsen *et al.* (2005) analysed 13 731 genes to test for positive selection in the human and chimpanzee lineages in relation to gene function. They noted a large proportion of cancer-related genes among the 50 genes with the strongest inferred positive selection, including genes involved in tumour suppression, apoptosis and cell cycle control. Some of these genes also exhibited testis-specific expression, leading the authors to suggest that genetic conflict between selection for apoptosis-avoidance in the germ line, and anticancer selection in adults, has driven the observed positive selection (see also Waters, Shen & Glickman, 2000). Their hypothesis is supported by the observation that some specific genetic pathways, such as *Fas*-mediated apoptosis, are involved in both control of cancer and spermatogenesis (Nielsen *et al.*, 2005), by LeGrand's (2001) arguments regarding the role of genetic conflict in the evolution of apoptosis, and by Kleene's (2005) evidence that the genetic pathways of spermatogenesis may coincide with those used by cancer cells to increase their survival and replication. Nielsen *et al.* (2005) also found a striking excess of genes expressed in the testis among their positively-selected sample ($P=0.002$), and a similar trend for prostate-expressed genes ($P=0.092$, the fourth lowest P value in a list of 28 tissues).

Diller, Gilbert & Kocher (2002) used the draft human genome to discern areas of low nucleotide diversity (reduced genetic variation among individuals) that indicate recent (200 000 years before present or less) selective sweeps in the human lineage. They found evidence for selective sweeps for 89 genes, 13 of which (15 %) are known to be associated with cancer (see Table 2 in Diller *et al.*, 2002), and an additional three of which regulate apoptosis. Costas *et al.* (2005) conducted similar tests for selective sweeps in humans, finding notable evidence for a recent history of selection on four genes related to cancer, *DCC, EGF*, *MADH2*, and *XRCC3*, all of which also show some evidence of positive selection from Clark *et al.*'s (2003) comparative study.

These large-scale database studies provide evidence that positive selection is common on genes involved in cancer. Future studies including more taxa and finer distinctions of gene function and tissue expression should clarify and refine these nascent patterns.

VI. DISCUSSION

We have presented a hypothesis linking positive selection, antagonistic coevolution, and cancer, which is supported by evidence from a wide range of genes in previous studies. Our main premise is that ongoing conflict between more or less antagonistic parties, such as competing males, females and males, mothers and offspring, intragenomic elements, and hosts and parasites, has led to the evolution of genes and molecular pathways that increase cancer risk. This increased risk is generated via tugs-of-war over resources, coevolutionary arms races, and antagonistic pleiotropy, which lead to evolutionary and developmental disequilibrium in genetic systems controlling cell proliferation and

apoptosis. The evidence for the hypothesis is circumstantial but extensive and diverse. Although many cancer-related genes are not positively-selected, and many positively-selected genes are unrelated to cancer, the coincidence of the two phenomena is striking, as was also noted by Nielsen *et al.* (2005) in his recent analysis of 13 731 genes in humans and chimpanzees. In many of the cases that we describe, the linkage clearly occurs in situations of antagonistic coevolution. For many other genes, further studies focused by the predictions of our hypothesis may reveal such evidence of ongoing conflicts, and targeted molecular studies may uncover the precise mechanisms whereby antagonistic coevolution and cancer are associated.

(1) Mechanisms linking antagonistic coevolution with cancer

Alleles may be associated with cancer in several different ways, with important implications for their evolutionary dynamics. First, a locus may exhibit polymorphism, with some alleles engendering higher cancer risk, as for *BRCA1*. Such polymorphisms may be the result of several processes: (1) continual allelic turnover driven by selection, with new alleles replacing others; (2) frequency-dependent selection causing fluctuations in some set of alleles, as in some host-parasite interactions; (3) balancing selection keeping frequencies more or less stable, or (4) local adaptation to the environment, as in *p53* (Beckman *et al.*, 1994), genes related to vitamin D metabolism (Holick, 2003; Price, Franks & Figg, 2004), *TRPV6* (Akey *et al.*, 2004; Wissenbach *et al.*, 2004; Stajich & Hahn, 2005), and cytochrome oxidase P450 family genes other than *CYP17* (e.g. Kalow, 1997; Garte, 1998; Agundez, 2004). The antagonistic coevolution hypothesis predicts that transient polymorphisms are driven by selection related to genetic conflict, that balanced polymorphisms may be maintained by opposing selective pressures related to cancer and antagonism in various contexts, and that for local adaptations, links to cancer will be most pronounced in cases where the gene-environment association is recent or otherwise subject to effects causing disequilibrium.

Second, alleles may exhibit altered patterns of expression in cancerous *versus* normal tissues, upward or downward, to enhance the survival or reproduction of cancer cells, as for *ANG, SPANX*, cadherins, homeobox genes, and centromeric histone genes. For such cases, we hypothesize that antagonistic coevolution has led to the evolution of genetic and epigenetic (Ohlsson *et al.*, 2003) pathways that are readily coopted or subverted by cancer cells, because they allow for rapid cell proliferation or avoidance of control by tumour suppressors or the immune system. Such subversion is seen most clearly in virus-host coevolutionary interactions, for the linkages between invasive placentation or embryonic development and cancer (Pearson, 1981, 1982; da Costa, 2001; Old, 2001; Lala *et al.*, 2002; Zygmunt *et al.*, 2003), and for the associations between gametogenesis and cancer (Kleene, 2005). Signal transduction (i. e., communication within and between cells; see also Krakauer & Pagel, 1996; Møller & Pagel, 1998) represents one of the main mechanisms mediating carcinogensis; signal transduction genes have been strongly positively selected in the human and chimpanzee lineages (Clark *et al.*, 2003), and modeling of this process using complex adaptive systems theory (Schwab & Pienta, 1997) is leading to novel insights regarding the somatic evolution of cancer. The key to analysing cases of altered expression of antagonistically-coevolving genes is to functionally link the expression changes to the primary evolved role of the gene, and to the cancerous phenotype, as many such changes may be irrelevant to cancer progression.

Third, some genes, such as *BRCA1* and *BRCA2*, are characterized by mutations during the development of cancer. In such cases, codon sites that are under positive selection are likely to be exhibit functional importance for the protein (e.g. Fleming *et al.*, 2003), and mutations at these sites are thus more likely to be associated with cancer. Indeed, identification of positively-selected sites in oncogenes and tumour-suppressor gene may be a useful guide to functional importance, at least as useful as comparing amino acid sites for conservation between taxa.

(2) Arenas of antagonistic coevolution

Our survey of positive selection in cancer-related genes suggests that specific forms of antagonistic coevolution are directly related to how such genes are involved in carcinogenesis. Thus, maternal-foetal conflict apparently leads to genetic programs in invasive placentation that can be coopted by somatically-evolving cancer cells lineages (Pearson, 1981; Adamson, 1987; Bischof *et al.*, 2000; Old, 2001; Lala *et al.*, 2002; Zygmunt *et al.*, 2003), and rapid evolution of genes involved in placentation (Crespi & Semeniuk, 2004) that exhibit antagonistic pleiotropy. Such effects may underlie positive selection on the *ANG*, *ADAM* and cadherin genes described above. Meiotic drive may lead to systems of cellular interaction during gametogenesis that involve conflict over cell proliferation and survival, as in CTA genes (Kleene, 2005), centromeric drive may indirectly contribute to chromosomal instability in cancer (Michor, 2005), and gestational drive (Haig, 1996) could lead to novel mechanisms of maternal-foetal physiological interaction. Male–female conflict may generate evolutionary disequilibrium in hormonal regulation, especially involving testosterone and estrogen in their effects on reproductive tissues such as prostate, testis, ovary, and breast (e.g. Ilekis *et al.*, 1997; Silva *et al.*, 1997; Risch, 1998; Edmondson, Monaghan & Davies, 2002), while intrasexual conflict, such as male–male competition, could lead to selection on growth factor genes such as *IGF1* and *IGF2* (Smith & Hurst, 1998) that fuel the growth of tumours (Giovannucci, 2003; Larsson, Girnita & Girnita, 2005). These aspects of sexual selection may be represented in the evolution of the *BRCA1* and *BRCA2* genes, and in the roles of insulin-like growth factors in promoting growth of prostate and breast cancers (Giovannucci, 2003; Pandini *et al.*, 2005). Conflicts of genomic imprinting, between paternal and maternal genes, often involve enhancement or suppression of cell growth (Tycko & Morison, 2002; Hernandez *et al.*, 2003). These conflicts have created in mammals a new avenue for mutation and

epigenetic alteration to promote cancer; indeed, loss of imprinting in growth-related genes drives the development of many forms of cancer (Feinberg, 2000; Ohlsson *et al.*, 2003; Farrell, 2005). The molecular evolutionary dynamics of imprinted genes remains to be elucidated, but may involve selection on patterns of gene regulation and expression, rather than the amino acid substitutions that are the usual hallmark of positive selection (Smith & Hurst, 1998).

Host–parasite conflict, especially between viruses and vertebrates, may generate disequilibrium that impacts the evolution of cancer in two main ways. First, positive selection on viruses involves genes related to apoptosis, telomerase regulation, and cell proliferation, whereby these parasites target cellular machinery for programmed death or cellular senescence of infected cells (e.g. Eick & Hermeking, 1996; LeGrand, 2001). Second, increased selection imposed on hosts by viruses should foster the evolution of enhanced immune function (e.g. Slev & Potts, 2002). Virally-impaired regulation of cell replication directly increases cancer risk, but over evolutionary time host–parasite coevolution could also reduce the incidence of cancer, by making cells more prone to apoptosis or by enhancing the suppression of cancer by immunosurveillance (Dunn, Old & Schreiber, 2004). In general, the dynamics of antagonistic coevolution between hosts and parasites (Ewald, 1994, 2000) may differ from those enacted during the evolution of a single species: for host and parasites there is less scope for constraining effects of mutual interests, unlike in pregnancy (Haig, 1993).

These hypotheses linking forms of antagonistic coevolution with mechanisms of carcinogenesis are speculative but they make clear predictions, which are testable via analyses of positive selection combined with studies of normal and disrupted physiological function.

(3) Purifying selection and positive selection

Thomas *et al.* (2003) tested for positive and purifying selection in 331 human genes implicated in disease and an appropriate set of non-disease genes, and they found that genes involved in disease in general, and cancer-related genes in particular, appear to be under stronger purifying selection than other genes. Two hypotheses may help explain the discordance between their findings and the results described above. First, Thomas *et al.* (2003) used a considerably less precise method for inferring selection: pairwise comparison between sequence data from the human and mouse genome projects, supplemented with some human–rat genome comparisons. Such comparisons do not identify specific codons under selection, but rather provide a measure of the average form of selection across the entire gene for each between-species pairwise comparison. By contrast, the studies discussed above, where positive selection was inferred, used codon-specific and branch-specific methods to detect selection (e.g. Huttley *et al.*, 2000; Summers & Crespi, 2005). Hence, strong purifying selection may be acting across most of the gene for cancer-related genes, and yet these genes may also have specific, functionally important regions that are under positive selection.

Second, many genes that are ultimately mutated within individuals over the course of a particular case of cancer progression are highly conserved across species (e.g. in *BRCA1*, Fleming *et al.*, 2003; Pavlicek *et al.*, 2004). Such genes are essential (i.e., lethal in knockout experiments), and as such will be subject to strong purifying selection (Thomas *et al.*, 2003), but they may still be involved in carcinogenesis because they commonly mutate during somatic selection. The evolution of cancer cell lineages within the body involves a large series of mutations that accrue cumulatively over a long period (Greaves, 2000). Many of these mutations occur during periods when the cancer cell lineages are in a destabilized, hypermutagenic state that characterizes the progression of many cancers (e.g. Breivik & Gaudernack, 2004; Frank & Nowak, 2004; Breivik, 2005). The early progression of cancer is likely to be driven by a small subset of genes relative to the total number that ultimately are mutated. We propose that genes that are under positive selection are likely to be an important component of this subset of genes that initiate cancer and drive clonal expansion, due to their capacities in the control of cell proliferation.

(4) Evolutionary and clinical implications

Our study has several important implications for the evolutionary biology of cancer. First, other genes that are known to be positively selected, and potentially subject to antagonistic coevolution, may usefully be screened for a role in elevating cancer risk, via hereditary variants, somatic mutation, or altered expression. Conversely, known oncogenes, tumour-suppressors and other cancer-related genes should be sequenced in a wide range of related species (and extensively within humans) and tested for positive selection, which may direct researchers to additional sites of functional importance and provide insight into the selective pressures driving the inferred molecular-evolutionary changes. Such analyses may involve testing for positive selection among species in cancer genes that are either fixed or polymorphic in humans (Loktionov, 2004; Zhu *et al.*, 2004), testing for selective sweeps along the human lineage, and analysing the somatic molecular-evolutionary changes that typify cancer progression.

Second, rates and patterns of adaptive molecular change can be linked to physiological, developmental, behavioural and life-historical aspects of the phenotype, such as male and female lifespan, forms of placentation, and sexual selection and sexual conflict intensity, to infer the nature of the evolved linkages between phenotypic selection and the molecular mechanisms of cancer. The evidence that we have presented is necessarily correlative, as the genetic systems involved have yet to be deeply investigated by both molecular-evolutionary biologists and researchers studying cancer. It is only through such multidisciplinary analyses that the study of cancer will develop its own natural history, evolutionary underpinnings, and predictive understanding of how diverse forms

of selection drive molecular evolution both within and between organisms.

VII. CONCLUSIONS

(1) Application of evolutionary theory for intragenomic conflict and antagonistic coevolution to the microevolution of cancer-related genes suggests that such genes should often exhibit signatures of positive selection, with relatively high rates of amino acid substitution among species. Such positive selection at the molecular level can be driven by diverse forms of conflict between evolutionary agents, including parent-offspring conflict, maternal-foetal conflict, sexual conflict, sexual selection, and host–parasite conflict. These conflicts lead to evolutionary disequilibrium, molecular-level arms races, and tugs-of-war over cellular resources, which generate genetic, epigenetic, and developmental systems more vulnerable to the development of cancer.

(2) A large suite of genes exhibits three coincident features, (a) involvement in cancer, (b) positive selection among species, and (c) expression in arenas of evolutionary conflict, which taken together provide strong evidence for antagonistic coevolution driving cancer risk. These genes include *SPANX* cancer/testis associated genes, Y-linked genes, some homeobox genes, centromeric histone genes, the breast cancer genes *BRCA1* and *BRCA2*, the angiogenesis gene *ANG*, some cadherins, some cytochrome P450 genes, and some genes in oncogenetic viruses.

(3) Large-scale database studies of positive selection show that positive selection is commonly inferred for genes that are implicated in carcinogenesis, via their involvement on tumour suppression, apoptosis, and cell proliferation. These results demonstrate apparent generality to the links between antagonistic coevolution, cancer, and positive selection, and they suggest that signatures of selection, in genes potentially involved in evolutionary conflicts, may provide useful guides to identification of genes involved in cancer risk.

(4) Evolutionary-genomic approaches to the analysis of carcinogenesis, that include analyses at the levels of somatic selection, within-population selection, and among-species divergence, should provide novel insights into both cancer risk and the evolution of intragenomic conflicts.

VIII. ACKNOWLEDGEMENTS

We are grateful to NSERC for financial support, and we thank F. Breden, C. Maley, A. Mooers and two anonymous reviewers for helpful comments.

IX. REFERENCES

Adamson, E. D. (1987). Expression of proto-oncogenes in the placenta. *Placenta* **8**, 449–466.

Agundez, J. A. (2004). Cytochrome P450 gene polymorphism and cancer. *Current Drug Metabolism* **5**, 211–224.

Akey, J. M., Eberle, M. A., Rieder, M. J., Carlson, C. S., Shriver, M. D., Nickerson, D. A. & Kruglyak, L. (2004). Population history and natural selection shape patterns of genetic variation in 132 genes. *PloS Biology* **2**, e286.

Amor, D. J., Bentley, K., Ryan, J., Perry, J., Wong, L., Slater, H. & Choo, K. H. (2004). Human centromere repositioning "in progress". *Proceeding of the National Academy of Sciences U.S.A.* **101**, 6542–6547.

Amor, D. J. & Choo, K. H. (2002). Neocentromeres: role in human disease, evolution, and centromere study. *American Journal of Human Genetics* **71**, 695–714.

Arieli, R. (2004). Breasts, buttocks and the camel hump. *Israel Journal of Zoology* **50**, 87–91.

Atalay, C., Atalay, G., Yilmaz, K. B. & Altinok, M. (2005). The role of anti-CENP-B and anti-SS-B antibodies in breast cancer. *Neoplasma* **52**, 32–35.

Bannert, N. & Kurth, R. (2004). Retroelements and the human genome: new perspectives on an old relation. *Proceedings of the National Academy of Sciences of U.S.A.* **101**, 14572–14579.

Bauvois, B. (2004). Transmembrane proteases in cell growth and invasion: new contributors to angiogenesis? *Oncogene* **23**, 317–329.

Becherini, L., Guarducci, E., Degl'Innocenti, S., Rotondi, M., Forti, G. & Krausz, C. (2004). DAZL polymorphisms and susceptibility to spermatogenic failure: an example of remarkable ethnic differences. *Journal of Andrology* **27**, 375–381.

Beckman, G., Birgander, R., Själander, A., Saha, N., Holmberg, P. A., Kivelä, A. & Beckman, L. (1994). Is p53 polymorphism maintained by natural selection? *Human Heredity* **44**, 266–270.

Bielawski, J. P. & Yang, Z. (2001). Positive and negative selection in the DAZ gene family. *Molecular Biology and Evolution* **18**, 523–529.

Bischof, P., Meisser, A. & Campana, A. (2000). Mechanisms of endometrial control of trophoblast invasion. *Journal of Reproductive Fertility* **55**, 65–71.

Borodin, P. M. (2001). Speciation and centromere evolution. *Science* **294**, 2478–2480.

Boström, K., Tintut, Y., Kao, S. C., Stanford, W. P. & Demer, L. L. (2000). HOXB7 overexpression promotes differentiation of C3H10T1/2 cells to smooth muscle cells. *Journal of Cellular Biochemistry* **78**, 210–221.

Breivik, J. (2005). The evolutionary origin of genetic instability in cancer deveopment. *Seminar in Cancer Biology* **15**, 51–60.

Breivik, J. & Gaudernack, G. (2004). Resolving the evolutionary paradox of genetic instability: a cost-benefit analysis of DNA repair in changing environments. *FEBS Letters* **563**, 7–12.

Brion, D. E. & Badet, J. (2003). Angiogenin distribution in human term placenta, and expression by cultured trophoblastic cells. *Angiogenesis* **6**, 317–330.

Burrows, J. M., Bromham, L., Woolfit, M., Piganeau, G., Tellam, J., Connolly, G., Webb, N., Poulsen, L., Cooper, L., Burrows, S. R., Moss, D. J., Haryana, S. M., Ng, M., Nicholls, J. M. & Khanna, R. (2004). Selection pressure-driven evolution of the Epstein-Barr virus-encoded oncogene LMP1 in virus isolates from Southeast Asia. *Journal of Virology* **78**, 7131–7713.

Burt, A. & Trivers, R. L. (2006). *Genes in Conflict: the Biology of Selfish Genetic Elements*. Cambridge, Belknap Press.

Cairns, J. (1975). Mutation selection and the natural history of cancer. *Nature* **255**, 197–200.

Campisi, J. (2005). Senescent cells, tumor suppression, and organismal aging: good citizens, bad neighbors. *Cell* **120**, 513–522.

Cant, J. G. H. (1981). Hypotheses for the evolution of human breasts and buttocks. *American Naturalist* **117**, 199–204.

Caro, T. M. (1987). Human breasts: unsupported hypotheses reviewed. *Human Evolution* **2**, 271–282.

Caro, T. M. & Sellen, D. W. (1990). The reproductive advantages of fat in women. *Ethology and Sociobiology* **11**, 51–66.

Chang, H. Y., Nuyten, D. S., Sneddon, J. B., Hastie, T., Tibshirani, R., Sorlie, T., Dai, H., He, Y. D., van't Veer, L. J., Bartelink, H., van de Rijn, M., Brown, P. O. & van de Vijver, M. J. (2005). Robustness, scalability, and integration of a wound-response gene expression signature in predicting breast cancer survival. *Proceeding of the National Academy of Sciences U.S.A.* **102**, 3738–3743.

Chapman, T., Arnqvist, G., Bangham, J. & Rowe, L. (2003). Sexual conflict. *Trends in Ecology and Evolution* **18**, 41–47.

Chen, Z., Terai, M., Fu, L., Herrero, R., DeSalle, R. & Burk, R. D. (2005). Diversifying selection in human papillomavirus type 16 lineages based on complete genome analyses. *Journal of Virology* **79**, 7014–7023.

Chippindale, A. K., Gibson, J. R. & Rice, W. R. (2001). Negative genetic correlation for adult fitness between sexes reveals ontogenetic conflict in *Drosophila*. *Proceeding of the National Academy of Sciences U.S.A.* **98**, 1671–1675.

Chomarat, P., Sipowicz, M. A., Diwan, B. A., Fornwald, L. W., Awasthi, Y. C., Anver, M. R., Rice, J. M., Anderson, L. M. & Wild, C. P. (1997). Distinct time courses of increase in cytochromes P450 1A2, 2A5 and glutathione S-transferases during the progressive hepatitis associated with *Helicobacter hepaticus*. *Carcinogenesis* **18**, 2179–2190.

Cillo, C., Faiella, A., Cantile, M. & Boncinelli, E. (1999). Homeobox genes and cancer. *Experimental Cell Research* **248**, 1–9.

Civetta, A. (2003*a*). Shall we dance or shall we fight? Using DNA sequence data to untangle controversies surrounding sexual selection. *Genome* **46**, 925–929.

Civetta, A. (2003*b*). Positive selection within sperm-egg adhesion domains of fertilin: an ADAM gene with a potential role in fertilization. *Molecular Biology and Evolution* **20**, 21–29.

Civetta, A. & Singh, R. S. (1995). High divergence of reproductive tract proteins and their association with post-zygotic reproductive isolation in *Drosophila melanogaster* and *Drosophila virilis* group species. *Journal of Molecular Evolution* **4**, 1085–1095.

Civetta, A. & Singh, R. S. (1998). Sex-related genes, directional sexual selection, and speciation. *Molecular Biology and Evolution* **15**, 901–909.

Clark, A. G., Glanowski, S., Nielsen, R., Thomas, P. D., Kejariwal, A., Todd, M. A., Tanenbaum, D. M., Civello, D., Lu, F., Murphy, B., Ferriera, S., Wang, G., Zheng, X. G., White, T. J., Sninsky, J. J., Adams, M. D. & Cargill, M. (2003). Inferring nonneutral evolution from human-chimp-mouse orthologous gene trios. *Science* **302**, 1960–1963.

Coffey, D. S. (2001). Similarities of prostate and breast cancer: evolution, diet, and estrogens. *Urology* **57**, 31–38.

Collins, K. A., Furuyama, S. & Biggins, S. (2004). Proteolysis contributes to the exclusive centromere localization of the yeast Cse4/CENP-A histone H3 variant. *Current Biology* **14**, 1968–1972.

Connor, F., Berwistle, D., Mee, P. J., Ross, G. M., Swift, S., Grigorieva, E., Tybulewicz, V. L. & Ashworth, A. (1997). Tumorigenesis and a DNA repair defect in mice with a truncating Brca2 mutation. *Nature Genetics* **17**, 423–430.

Cooper, J. L. & Henikoff, S. (2004). Adaptive evolution of the histone fold domain in centromeric histones. *Molecular Biology and Evolution* **21**, 1712–1718.

Cordain, L., Eaton, S. B., Sebastian, A., Mann, N., Lindeberg, S., Watkins, B. A., O'Keefe, J. H. & Brand-Miller, J. (2005). Origins and evolution of the Western diet: health implications for the 21st century. *American Journal of Clinical Nutrition* **81**, 341–354.

Costas, J., Salas, A., Phillips, C. & Carracedo, A. (2005). Human genome-wide screen of haplotype-like blocks of reduced diversity. *Gene* **349**, 219–225.

Crespi, B. & Semeniuk, C. (2004). Parent-offspring conflict in the evolution of vertebrate reproductive mode. *American Naturalist* **163**, 635–653.

Crespi, B. & Summers, K. (2005). Evolutionary biology of cancer. *Trends in Ecology and Evolution* **20**, 545–552.

Cross, H. S., Kállay, E., Lechner, D., Gerdenitsch, W., Adlercreutz, H. & Armbrecht, H. J. (2004). Phytoestrogens and vitamin D metabolism: a new concept for the prevention and therapy of colorectal, prostate, and mammary carcinomas. *Journal of Nutrition* **134**, 1207S–1212S.

da Costa, L. F. (2001). Return of de-differentiation: why cancer is a developmental disease. *Current Opinion in Oncology* **13**, 58–62.

Daniel, A. (2002). Distortion of female meiotic segregation and reduced male fertility in human Robertsonian translocations: consistent with the centromere model of co-evolving centromere DNA/centromeric histone (CENP-A). *American Journal of Medical Genetics* **111**, 450–452.

Dasari, V. K., Deng, D., Perinchery, G., Yeh, C. C. & Dahiya, R. (2002). DNA methylation regulates the expression of Y chromosome specific genes in prostate cancer. *The Journal of Urology* **167**, 335–338.

Dasari, V. K., Goharderakhshan, R. Z., Perinchery, G., Li, L. C., Tanaka, Y., Alonzo, J. & Dahiya, R. (2001). Expression analysis of Y chromosome genes in human prostate cancer. *The Journal of Urology* **165**, 1335–1341.

DeFilippis, V. R., Ayala, F. J. & Villarreal, L. P. (2002). Evidence of diversifying selection in human papillomavirus type 16 E6 but not E7 oncogenes. *Journal of Molecular Evolution* **55**, 491–499.

de la Hoya, M., Fernandez, J. M., Tosar, A., Godino, J., Sanchez de Abajo, A., Vidart, J. A., Perez-Segura, P., Diaz-Rubio, E. & Caldes, T. (2003). Association between BRCA1 mutations and ratio of female to male births in offspring of families with breast cancer, ovarian cancer, or both. *Journal of the American Medical Association* **290**, 929–931.

De Marzo, A. M., Knudsen, B., Chan-Tack, K. & Epstein, J. I. (1999). E-cadherin expression as a marker of tumor aggressiveness in routinely processed radical prostatectomy specimens. *Urology* **53**, 707–713.

Deng, C.-X. & Brodie, S. G. (2000). Roles of BRCA1 and its interacting proteins. *BioEssays* **22**, 728–737.

Deng, C.-X. & Wang, R.-H. (2003). Roles of BRCA1 in DNA damage repair: a link between development and cancer. *Human Molecular Genetics* **12**, R113–R123.

Diller, K. C., Gilbert, W. A. & Kocher, T. D. (2002). Selective sweeps in the human genome: a starting point for identifying genetic differences between modern humans and chimpanzees. *Molecular Biology and Evolution* **19**, 2342–2345.

Dunn, G. P., Old, L. J. & Schreiber, R. D. (2004). The three Es of cancer immunoediting. *Annual Review of Immunology* **22**, 329–360.

Edmondson, R. J., Monaghan, J. M. & Davies, B. R. (2002). The human ovarian surface epithelium is an androgen responsive tissue. *British Journal of Cancer* **86**, 879–885.

Eick, D. & Hermeking, H. (1996). Viruses as pacemakers in the evolution of defence mechanisms against cancer. *Trends in Genetics* **12**, 4–6.

Ewald, P. W. (1994). Evolution of mutation rate and virulence among human retroviruses. *Philosophical Transactions of the Royal Society of London B* **346**, 333–341.

Ewald, P. W. (2000). *Plague Time: How Stealth Infections Cause Cancers, Heart Disease, and Other Deadly Ailments*. Free Press, New York.

Fares, M. A., Bezemer, D., Moya, A. & Marin, I. (2003). Selection on coding regions determined *Hox7* genes evolution. *Molecular Biology and Evolution* **20**, 2104–2112.

Farhan, H., Wahala, K. & Cross, H. S. (2003). Genistein inhibits vitamin D hydroxylases CYP24 and CYP27B1 expression in prostate cells. *Journal of Steroid Biochemistry and Molecular Biology* **84**, 423–429.

Farrell, W. E. (2005). Epigenetic mechanisms of tumorigenesis. *Hormone and Metabolic Research* **37**, 361–368.

Fay, J. C. & Wu, C.-I. (2003). Sequence divergence, functional constraint, and selection in protein evolution. *Annual Review of Human Genetics* **4**, 213–235.

Feinberg, A. (2000). DNA methylation, genomic imprinting and cancer. *Current Topics in Microbiology* **249**, 87–99.

Ferrara, N. (2000). Vascular endothelial growth factor and the regulation of angiogenesis. *Recent Progress in Hormone Research* **55**, 15–35.

Ferro, P., Catalano, M. G., Dell'Eva, R., Fortunati, N. & Pfeffer, U. (2002). The androgen receptor CAG repeat: a modifier of carcinogenesis? *Molecular and Cellular Endocrinology* **193**, 109–120.

Fleming, M. A., Potter, J. D., Ramirez, C. J., Ostrander, G. K. & Ostrander, E. A. (2003). Understanding missense mutations in the BRCA1 gene: an evolutionary approach. *Proceeding of the National Academy of Sciences U.S.A.* **100**, 1151–1156.

Foulkes, W. D. (2004). BRCA1 functions as a breast stem cell regulator. *Journal of Medical Genetics* **41**, 1–5.

Frank, S. A. (2004*a*). Genetic predisposition to cancer – insights from population genetics. *Nature Reviews Genetics* **5**, 764–772.

Frank, S. A. (2004*b*). Genetic variation in cancer predisposition: mutational decay of a robust genetic control network. *Proceeding of the National Academy of Sciences U.S.A.* **101**, 8061–8065.

Frank, S. A. & Nowak, M. A. (2004). Problems of somatic mutation and cancer. *BioEssays* **26**, 291–299.

Friedman, L. S., Thistlewaite, F. C., Patel, K. J., Yu, V. P., Lee, H., Venkitaraman, A. R., Abel, K. J., Carlton, M. B., Hunter, S. M., Colledge, W. H., Evans, M. J. & Ponder, B. A. (1998). Thymic lymphomas in mice with a truncating mutation in Brca2. *Cancer Research* **58**, 1338–1343.

Galis, F. & Metz, J. A. J. (2003). Anti-cancer selection as a source of developmental and evolutionary constraints. *BioEssays* **25**, 1035–1039.

Galis, F. (1999). Why do almost all mammals have seven cervical vertebrae? Developmental constraints, *Hox* genes, and cancer. *Journal of Experimental Zoology* **285**, 19–26.

Galis, M. & Metz, J. A. J. (2003). Anti-cancer selection as a source of developmental and evolutionary constraints. *BioEssays* **25**, 1035–1039.

Gallin, W. J. (1998). Evolution of the "classical" cadherin family of cell adhesion molecules in vertebrates. *Molecular Biology and Evolution* **15**, 1099–1107.

Garte, S. (1998). The role of ethnicity in cancer susceptibility gene polymorphisms: the example of CYP1A1. *Carcinogenesis* **19**, 1329–1332.

Giguere, Y., Dewailly, E., Brisson, J., Ayotte, P., Laflamme, N., Demers, A., Forest, V. I., Dodin, S., Robert, J. & Rousseau, F. (2001). Short polyglutamine tracts in the androgen receptor are protective against breast cancer in the general population. *Cancer Research* **61**, 5869–5874.

Giovannucci, E. (2003). Nutrition, insulin, insulin-like growth factors, and cancer. *Hormone and Metabolic Research* **35**, 694–704.

Glassey, B. & Civetta, A. (2004). Positive selection at reproductive ADAM genes with potential intercellular binding activity. *Molecular Biology and Evolution* **21**, 851–859.

Gonzalez, F. J. & Nebert, D. W. (1990). Evolution of the P450 gene superfamily: animal-plant 'warfare', molecular drive and human genetic differences in drug oxidation. *Trends in Genetics* **6**, 182–186.

Gotoh, O. (1992). Substrate recognition sites in cytochrome P450 family 2 (CYP2) proteins inferred from comparative analyses of amino acid and coding nucleotide sequences. *Journal of Biological Chemistry* **267**, 83–90.

Graham, J. (1992). *Cancer Selection: A New Theory of Evolution*. Aculeus Press, Lexington, KY.

Greaves, M. (2000). *Cancer: The Evolutionary Legacy*. Oxford University Press, Oxford.

Haig, D. (1993). Genetic conflicts in human pregnancy. *Quarterly Review of Biology* **68**, 495–532.

Haig, D. (1996). Gestational drive and the green-bearded placenta. *Proceeding of the National Academy of Sciences U.S.A.* **93**, 6547–6551.

Haig, D. (1999*a*). Altercation of generations: genetic conflicts of pregnancy. *American Journal of Reproductive Immunology* **35**, 226–232.

Haig, D. (1999*b*). Genetic conflicts of pregnancy and childhood. In *Evolution in Health and Disease* (ed. S. C. Stearns), pp. 77–90. Oxford University Press, Oxford.

Haig, D. (2000). The kinship theory of genomic imprinting. *Annual Review of Ecology and Systematics* **31**, 9–32.

Haig, D. (2004). Genomic imprinting and kinship: how good is the evidence? *Annual Review of Genetics* **38**, 553–585.

Haiman, C. A., Brown, M., Hankinson, S. E., Spiegelman, D., Colditz, G. A., Willett, W. C., Kantoff, P. W. & Hunter, D. J. (2002). The androgen receptor CAG repeat polymorphism and risk of breast cancer in the Nurses' Health Study. *Cancer Research* **62**, 1045–1049.

Hamilton, D. W. (1990). Anatomy of mammalian male accessory reproductive organs. In *Marshall's Physiology of Reproduction*, 4th Edn (ed. G. E. Lamming), pp. 691–746. Churchill Livingstone, London.

Hamilton, W. D. (1964). The genetical theory of social behavior I & II. *Journal of Theoretical Biology* **7**, 1–52.

Hampton, T. (2005). Genes that heal body co-opted by breast tumor to promote cancer's spread. *Journal of the American Medical Association* **293**, 1309–1310.

Hanahan, D. & Weinberg, R. A. (2000). The hallmarks of cancer. *Cell* **100**, 57–70.

Healey, C. S., Dunning, A. M., Teare, M. D., Chase, D., Parker, L., Burn, J., Chang-Claude, J., Mannermaa, A., Kataja, V., Huntsman, D. G., Pharoah, P. D., Luben, R. N., Easton, D. F. & Ponder, B. A. (2000). A common variant in BRCA2 is associated with both breast cancer risk and prenatal viability. *Nature Genetics* **26**, 362–364.

Hendrix, M. J. C., Seftor, E. A., Meltzer, P. S., Gardner, L. M. G., Hess, A. R., Kirschmann, D. A., Schatteman, G. C. & Seftor, R. E. B. (2001). Expression and functional significance of VE-cadherin in aggressive human melanoma cells: role in vasculogenic mimicry. *Proceeding of the National Academy of Sciences U.S.A.* **98**, 8018–8023.

Henikoff, S. (2000). Heterochromatin function in complex genomes. *Biochimica et Biophysica Acta* **1470**, 1–8.

Henikoff, S., Ahmad, K. & Malik, H. S. (2001). The centromere paradox: stable inheritance with rapidly evolving DNA. *Science* **293**, 1098–1102.

Hernandez, L., Kozlov, S., Piras, G. & Stewart, C. L. (2003). Paternal and maternal genomes confer opposite effects on proliferation, cell-cycle length, senescence, and tumor formation. *Proceeding of the National Academy of Sciences U.S.A.* **100**, 13344–13349.

Hirohashi, S. & Kanai, Y. (2003). Cell adhesion system and human cancer morphogenesis. *Cancer Science* **94**, 575–581.

Holick, M. F. (2003). Evolution and function of vitamin D. Recent Results in *Cancer Research* **164**, 3–28.

Hurskainen, T. L., Hirohata, S., Seldin, M. F. & Apte, S. S. (1999). ADAM-TS5, ADAM-TS6, and ADAM-TS7, novel members of a new family of zinc metalloproteases. General features and genomic distribution of the ADAM-TS family. *Journal of Biological Chemistry* **274**, 25555–25563.

Hurst, L. D. (1994*a*). Embryonic growth and the evolution of the mammalian Y chromosome. I. The Y as attractor of selfish growth factors. *Heredity* **73**, 223–232.

Hurst, L. D. (1994*b*). Embryonic growth and the evolution of the mammalian Y chromosome. II. Suppression of selfish Y-linked growth factors may explain escape from X-inactivation and rapid evolution of *Sry*. *Heredity* **73**, 233–243.

Hurst, L. & Pál, C. (2001). Evidence for purifying selection acting on silent sites in BRCA1. *Trends in Genetics* **17**, 62–65.

Huttley, G. A., Easteal, S., Southey, M. C., Tesorierio, A., Giles, G. G., McCredie, M. R. E., Hopper, J. L. & Venter, D. J. (2000). Adaptive evolution of the tumour suppressor BRCA1 in humans and chimpanzees. *Nature Genetics* **25**, 410–413.

Ilekis, J. V., Connor, J. P., Prins, G. S., Ferrer, K., Niedeberger, C. & Scoccia, B. (1997). Expression of epidermal growth factor and androgen receptors in ovarian cancer. *Gynecological Oncology* **66**, 250–254.

Ilyas, M. (2000). Adhesion molecule expression in breast cancer: the phoenix in tumour metastasis? *Journal of Pathology* **190**, 3–5.

Ingles, S. A., Ross, R. K., Yu, M. C., Irvine, R. A., La Pera, G., Hile, R. W. & Coetzee, G. A. (1997). Association of prostate cancer risk with genetic polymorphisms in vitamin D receptor and androgen receptor. *Journal of the National Cancer Institute* **89**, 166–170.

Ingelman-Sundberg, M., Oscarson, M. & McLellan, R. A. (1999). Polymorphic human cytochrome P450 enzymes: an opportunity for individualized drug treatment. *Trends in Pharmacological Sciences* **20**, 342–349.

Jabs, E. W., Tuck-Muller, C. M., Anhalt, G. J., Earnshaw, W., Wise, R. A. & Wigley, F. (1993). Cytogenetic survey in systemic sclerosis: correlation of aneuploidy with the presence of anti-centromere antibodies. *Cytogenetics and Cell Genetics* **63**, 169–175.

Jansa, S. A., Lundrigan, B. L. & Tucker, P. K. (2003). Tests for positive selection on immune and reproductive genes in closely related species of the murine genus *Mus*. *Journal of Molecular Evolution* **56**, 294–307.

Jasienska, G., Ziomkiewicz, A., Ellison, P. T., Lipson, S. F. & Thune, I. (2004). Large breasts and narrow waists indicate high reproductive potential in women. *Proceedings of the Royal Society of London B* **271**, 1213–1217.

Jernström, H., Johannsson, O., Borg, A., Ivarsson, H. & Olsson, H. (1998). BRCA1-positive patients are small for gestational age compared to their unaffected relatives. *European Journal of Cancer* **34**, 368–371.

Jurka, J. A. (2004). Evolutionary impact of human Alu repetitive elements. *Current Opinion in Genetics & Development* **14**, 603–608.

Kalejs, M. & Erenpreisa, J. (2005). Cancer/testis antigens and gametogenesis: a review and "brain-storming" session. *Cancer Cell International* **5**, 4. (epub).

Kállay, E., Adlercreutz, H., Farhan, H., Lechner, D., Bajna, E., Gerdenitsch, W., Campbell, M. & Cross, H. S. (2002). Phytoestrogens regulate vitamin D metabolism in the mouse colon: relevance for colon tumor prevention and therapy. *Journal of Nutrition* **132**, 3490S–3493S.

Kalow, W. (1997). Pharmacogenetics in biological perspective. *Pharmacological Reviews* **49**, 369–379.

Kammerer, S., Roth, R. B., Reneland, R., Marnellos, G., Hoyal, C. R., Markward, N. J., Ebner, F., Kiechle, M., Schwarz-Boeger, U., Griffiths, L. R., Ulbrich, C., Chrobok, K., Forster, G., Praetorius, G. M., Meyer, P., Rehbock, J., Cantor, C. R., Nelson, M. R. & Braun, A. (2004). Large-scale association study identifies ICAM gene region as breast and prostate cancer susceptibility locus. *Cancer Research* **64**, 8906–8910.

Karan, D., Lin, F. C., Bryan, M., Ringel, J., Moniaux, N., Lin, M. F. & Batra, S. K. (2003). Expression of ADAMs (a disintegrin and metalloproteases) and TIMP-3 (tissue inhibitor of metalloproteinase-3) in human prostatic adenocarcinomas. *International Journal of Oncology* **23**, 1365–1371.

Karn, R. C. & Nachman, M. W. (1999). Reduced nucleotide variability at an androgen-binding protein locus (Abpa) inhouse mice: evidence for positive selection. *Molecular Biology and Evolution* **16**, 1192–1197.

Kavanagh, K. D. (2003). Embedded molecular switches, anti-cancer selection, and effects on ontogenetic rates: a hypothesis of developmental constraint on morphogenesis and evolution. *Evolution* **57**, 939–948.

King, N., Hittinger, C. T. & Carroll, S. B. (2003). Evolution of key cell signaling and adhesion protein families predates animal origins. *Science* **301**, 361–363.

Kleene, K. C. (2005). Sexual selection, genetic conflict, selfish genes and the atypical patterns of gene expression in spermatogenic cells. *Development Biology* **277**, 16–26.

Kolomietz, E., Meyn, M. S., Pandita, A. & Squire, J. A. (2002). The role of Alu repeat clusters as mediators of recurrent chromosomal aberrations in tumors. *Genes, Chromosomes & Cancer* **35**, 97–112.

Korhonen, L., Brannvall, K., Skoglosa, Y. & Lindholm, D. (2003). Tumor suppressor gene BRCA-1 is expressed by embryonic and adult neural stem cells and involved in cell proliferation. *Journal of Neuroscience Research* **71**, 769–776.

Kotar, K., Brunet, J.-S., Moller, P., Hugel, L., Warner, E., McLaughlin, J., Wong, N., Narod, S. A. & Foulkes, W. D. (2004). Ratio of female to male offspring of women tested for BRCA1 and BRCA2 mutations. *Journal of Medical Genetics* **41**, e103.

Kouprina, N., Mullokandov, M., Rogozin, I. B., Collins, N. K., Solomon, G., Otstot, J., Risinger, J. I., Koonin, E. V.,

Barrett, J. C. & Larionov, V. (2004). The SPANX gene family of cancer/testis-specific antigens: rapid evolution and amplification in African great apes and hominids. *Proceeding of the National Academy of Sciences U.S.A.* **101**, 3077–3082.

Krakauer, D. C. & Pagel, M. (1996). Selection by somatic signals: the advertisement of phenotypic state through costly intercellular signals. *Philosophical Transactions of the Royal Society of London* **351**, 647–658.

Kreitman, M. (2000). Methods to detect selection in populations with application to the human. *Annual Review of Genomics and Human Genetics* **1**, 539–559.

Laigaard, J., Christiansen, M., Fröhlich, C., Pedersen, B. N., Ottesen, B. & Wewer, U. M. (2005). The level of ADAM12-S in maternal serum is an early first-trimester marker of fetal trisomy 18. *Prenatal Diagnosis* **25**, 45–46.

Lala, P. K., Lee, B. P., Xu, G. & Chakraborty, C. (2002). Human placental trophoblast as an in vitro model for tumor progression. *Canadian Journal of Physiology and Pharmacology* **80**, 142–149.

Lansdorp, P. M. (1997). Self-renewal of stem cells. *Biology and Blood Marrow Transplant* **3**, 171–178.

Larsson, O., Girnita, A. & Girnita, L. (2005). Role of insulin-like growth factor 1 receptor signalling in cancer. *British Journal of Cancer* **92**, 2097–2101.

LeGrand, E. K. (2001). Genetic conflict and apoptosis. *Perspectives in Biology and Medicine* **44**, 509–521.

Lendeckel, U., Kohl, J., Arndt, M., Carl-McGrath, S., Donat, H. & Röcken, C. (2005). Increased expression of ADAM family members in human breast cancer and breast cancer cell lines. *Journal of Cancer Research and Clinical Oncology* **131**, 41–48.

Leroi, A. M., Koufopanou, V. & Burt, A. (2003). Cancer selection. *Nature Reviews Cancer* **3**, 226–231.

Lewin, B. (2004). *Genes VIII*. Pearson Prentice Hall, Upper Saddle River, New Jersey.

Lewis, D. F. (2004). 57 varieties: the human cytochromes P450. *Pharmacogenomics* **5**, 305–318.

Lewis, D. F., Watson, E. & Lake, B. G. (1998). Evolution of the cytochrome P450 superfamily: sequence alignments and pharmacogenetics. *Mutation Research* **410**, 245–270.

Liang, Q. J., Lu, X. F., Cheng, X. L., Luo, S., He, D. C. & Wang, Y. C. (2004). The active expression of CenpB, a constitutive protein in the centromeres of chromosomes, in breast cancer tissues. *Acta Genetica Sinica* **31**, 236–240.

Loktionov, A. (2004). Common gene polymorphisms, cancer progression and prognosis. *Cancer Letters* **208**, 1–33.

Maiti, S., Doskow, J., Sutton, K., Nhim, R. P., Lawlor, D. A., Levan, K., Lindsey, J. S. & Wilkinson, M. F. (1996). The *Pem* homeobox gene: rapid evolution of the homeodomain, X chromosomal location, and expression in reproductive tissue. *Genomics* **34**, 304–316.

Maley, C. C. & Forrest, S. (2001). Exploring the relationship between neutral and selective mutations in cancer. *Artificial Life* **6**, 325–345.

Malik, H. S. & Henikoff, S. (2001). Adaptive evolution of cid, a centromere-specific histone in *Drosophila*. *Genetics* **157**, 1293–1298.

Malik, H. S. & Henikoff, S. (2002). Conflict begets complexity: the evolution of centromeres. *Current Opinion in Genetics & Development* **12**, 711–718.

Mareel, M. & Van Roy, F. (1998). The human E-cadherin/catenin complex: a potent invasion and tumor suppressor. *Verhandelingen – Koninklijke Academie voor Geneeskunde van België* **60**, 567–598.

Martinez, J., Dugaiczyk, L. J., Zielinski, R. & Dugaiczyk, A. (2001). Human genetic disorders, a phylogenetic perspective. *Journal of Molecular Biology* **308**, 587–596.

Maubert, B., Guilbert, L. J. & Deloron, P. (1997). Cytoadherence of *Plasmodium falciparum* to intercellular adhesion molecule 1 and chondroitin-4-sulfate expressed by the syncytiotrophoblast in the human placenta. *Infection and Immunity* **65**, 1251–1257.

Michels, K. B. (2005). The role of nutrition in cancer development and prevention. *International Journal of Cancer* **114**, 163–165.

Michor, F. (2005). Chromosomal instability and human cancer. *Philosophical Transactions of the Royal Society of London B* **360**, 631–635.

Michor, F., Frank, S. A., May, R. M., Iwasa, Y. & Nowak, M. A. (2003*a*). Somatic selection for and against cancer. *Journal of Theoretical Biology* **225**, 377–382.

Michor, F., Iwasa, Y., Komarova, N. L. & Nowak, M. A. (2003*b*). Local regulation of homeostasis favors chromosomal instability. *Current Biology* **13**, 581–584.

Michor, F., Frank, S. A., May, R. M., Iwasa, Y. & Nowak, M. A. (2004*a*). Somatic selection for and against cancer. *Journal of Theoretical Biology* **225**, 377–382.

Michor, F., Iwasa, Y. & Nowak, M. A. (2004*b*). Dynamics of cancer progression. *Nature Reviews Cancer* **4**, 197–205.

Midgley, R. S., Bell, A. I., McGeoch, D. J. & Rickinson, A. B. (2003). Latent gene sequencing reveals familial relationships among Chinese Epstein-Barr virus strains and evidence for positive selection of A11 epitope changes. *Journal of Virology* **77**, 11517–11530.

Miki, Y. (1998). Retrotransposal integration of mobile genetic elements in human diseases. *Journal of Human Genetics* **43**, 77–84.

Miller, D. C., Zheng, S. L., Dunn, R. L., Sarma, A. V., Montie, J. E., Lange, E. M., Meyers, D. A., Xu, J. & Cooney, K. A. (2003*a*). Germ-line mutations of the macrophage scavenger receptor 1 gene: association with prostate cancer risk in African-American men. *Cancer Research* **63**, 3486–3489.

Miller, G. J., Miller, H. L., van Bokhoven, A., Lambert, J. R., Werahera, P. N., Schirripa, O., Lucia, M. S. & Nordeen, S. K. (2003*b*). Aberrant HOXC expression accompanies the malignant phenotype in human prostate. *Cancer Research* **63**, 5879–5888.

Modugno, F. (2004). Ovarian cancer and polymorphisms in the androgen and progesterone receptor genes: a HuGE review. *American Journal of Epidemiology* **159**, 319–335.

Møller, A. P. & Pagel, M. (1998). Developmental stability and signalling among cells. *Journal of Theoretical Biology* **193**, 497–506.

Mossman, H. W. (1987). *Vertebrate Fetal Membranes*. Rutgers University Press, New Brunswick, U.S.A.

Naora, H., Yang, Y. Q., Montz, F. J., Seidman, J. D., Kurman, R. J. & Roden, R. B. (2001). A serologically identified tumor antigen encoded by a homeobox gene promotes growth of ovarian epithelial cells. *Proceeding of the National Academy of Sciences U.S.A.* **98**, 4060–4065.

Nebert, D. W. (1997). Polymorphisms in drug-metabolizing enzymes: what is their clinical relevance and why do they exist? *American Journal of Human Genetics* **60**, 265–271.

Negishi, M., Iwasaki, M., Juvonen, R. O., Sueyoshi, T., Darden, T. A. & Pedersen, L. G. (1996). Structural flexibility and functional versatility of cytochrome P450 and rapid evolution. *Mutation Research* **350**, 43–50.

Nelson, J. W. & Nusse, R. (2004). Convergence of Wnt, B-Catenin, and cadherin pathways. *Science* **303**, 1483–1487.

Nielsen, R., Bustamante, C., Clark, A. G., Glanowski, S., Sackton, T. B., Hubisz, M. J., Fledel-Alon, A., Tanenbaum, D. M., Civello, D., White, T. J., Sninsky, J. J., Adams, M. D. & Cargill, M. (2005). A scan for positively selected genes in the genomes of humans and chimpanzees. *PLoS Biology* **6**, e170.

Nollet, F., Kools, P. & van Roy, F. (2000). Phylogenetic analysis of the cadherin superfamily allows identification of six major subfamilies besides several solitary members. *Journal of Molecular Biology* **299**, 551–572.

Nunney, L. (1999). Lineage selection and the evolution of multistage carcinogenesis. *Proceedings of the Royal Society of London B* **266**, 493–498.

Nunney, L. (2003). The population genetics of multistage carcinogenesis. *Proceedings of the Royal Society of London B* **270**, 1183–1191.

Ohlsson, R., Kanduri, C., Whitehead, J., Pfeifer, S., Lobanenkov, V. & Feinberg, A. P. (2003). Epigenetic variability and the evolution of human cancer. *Advances in Cancer Research* **88**, 145–168.

Okada, Y. (2000). Tumor cell-matrix interaction: pericellular matrix degradation and metastasis. *Verhandlungen der Deutschen Gesellschaft für Pathologie* **84**, 33–42.

Old, L. J. (2001). Cancer/testis (CT) antigens – a new link between gametogensis and cancer. *Cancer Immunity* **1**, 1–7.

Olson, G. E., Winfrey, V. P., Matrisian, P. E., NagDas, S. K. & Hoffman, L. H. (1998). Blastocyst-dependent upregulation of metalloproteinase/disintegrin MDC9 expression in rabbit endometrium. *Cell and Tissue Research* **293**, 489–498.

O'Neill, R. J., Eldridge, M. D. & Metcalfe, C. J. (2004). Centromere dynamics and chromosome evolution in marsupials. *Journal of Heredity* **95**, 375–381.

Oyama, R. (2001). The relationship between the level of expression of intercellular adhesion molecule-1 in placenta and onset of preeclampsia. *Journal of Obstetrics and Gynaecology Research* **27**, 147–154.

Pandini, G., Mineo, R., Frasca, F., Roberts, C. T. Jr., Marcelli, M., Vigneri, R. & Belfiore, A. (2005). Androgens up-regulate the insulin-like growth factor-I receptor in prostate cancer cells. *Cancer Research* **65**, 1849–1857.

Pavlicek, A., Noskov, V. N., Kouprina, N., Barrett, J. C., Jurka, J. & Larionov, V. (2004). Evolution of the tumor suppressor BRCA1 locus in primates: implications for cancer predisposition. *Human Molecular Genetics* **13**, 2737–2751.

Pawlowski, B. (1999). Permanent breasts as a side effect of subcutaneous fat tissue increase in human evolution. *Homo* **50**, 149–162.

Pearson, R. D. (1981). Tumorigenesis: the subterfuge of selection. *Acta Biotheoretica* **30**, 171–176.

Pearson, R. D. (1982). Cellular heterochrony and neoplasia. *Medical Hypotheses* **8**, 231–235.

Pitman, J. L., Lin, T. P., Kleeman, J. E., Erickson, G. F. & MacLeod, C. L. (1998). Normal reproductive and macrophage function in Pem homeobox gene-deficient mice. *Developmental Biology* **202**, 196–214.

Price, D. K., Franks, M. E. & Figg, W. D. (2004). Genetic variations in the vitamin D receptor, androgen receptor and enzymes that regulate androgen metabolism. *The Journal of Urology* **171**, S45–S49.

Rao, M. K., Maiti, S., Ananthaswany, H. N. & Wilkinson, M. F. (2002). A highly active homeobox gene promotor regulated by Ets and Sp1 family members in normal granulosa cells and diverse tumor cell types. *Journal of Biological Chemistry* **277**, 26036–26045.

Rebbeck, T. R., Kantoff, P. W., Krithivas, K., Neuhausen, S., Blackwood, M. A., Godwin, A. K., Daly, M. B., Narod, S. A., Garber, J. E., Lynch, H. T., Weber, B. L. & Brown, M. (1999). Modification of BRCA1-associated breast cancer risk by the polymorphic androgen-receptor CAG repeat. *American Journal of Human Genetics* **64**, 1371–1377.

Reynolds, N. & Cooke, H. J. (2005). Role of the DAZ genes in male fertility. *Reproductive Biomedicine Online* **10**, 72–80.

Rice, W. (1996). Sexually antagonistic male adaptation triggered by experimental arrest of female evolution. *Nature* **381**, 232–234.

Rice, W. R. & Holland, B. (1997). The enemies within: intergenomic conflict, interlocus contest evolution (ICE), and the intraspecific Red Queen. *Behavioral Ecology and Sociobiology* **41**, 1–10.

Rice, W. R. & Chippindale, A. K. (2001). Intersexual ontogenetic conflict. *Journal of Evolutionary Biology* **14**, 685–693.

Risch, H. A. (1998). Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone. *Journal of the National Cancer Institute* **90**, 1774–1776.

Salemi, M., Desmyter, J. & Vandamme, A. M. (2000). Tempo and mode of human and simian T-lymphotropic virus (HTLV/STLV) evolution revealed by analyses of full-genome sequences. *Molecular Biology and Evolution* **17**, 374–386.

Sawyer, S. L., Emerman, M. & Malik, H. S. (2004). Ancient adaptive evolution of the primate antiviral DNA-editing enzyme APOBEC3G. *PLos Biology* **2**, e275.

Scanlan, M. J., Simpson, A. J. G. & Old, L. J. (2004). The cancer/testis genes: review, standarization, and commentary. *Cancer Immunity* **4**, 1–15.

Scanlan, M. J., Gordon, C. M., Williamson, B., Lee, S. Y., Chen, Y. T., Stockert, E., Jungbluth, A., Ritter, G., Jäger, D., Jäger, E., Knuth, A. & Old, L. J. (2002). Identification of cancer/testis genes by database mining and mRNA expression analysis. *International Journal of Cancer* **98**, 485–492.

Shi, Z., Xu, W., Loechel, F., Wewer, U. M. & Murphy, L. J. (2000). ADAM 12, a disintegrin metalloprotease, interacts with insulin-like growth factor-binding protein-3. *Journal of Biological Chemistry* **275**, 18574–18580.

Schwab, E. D. & Pienta, K. J. (1997). Modeling signal transduction in normal and cancer cells using complex adaptive systems. *Medical Hypotheses* **48**, 111–123.

Shah, J. V., Botvinick, E., Bonday, Z., Furnari, F., Berns, M. & Cleveland, D. W. (2004). Dynamics of centromere and kinetochore proteins; implications for checkpoint signaling and silencing. *Current Biology* **14**, 942–952.

Shibata, D. (2002). Molecular tumour clocks and colorectal cancer: seeing the unseen. *Pathology* **34**, 534–540.

Silva, E. G., Tornos, C., Fritsche, H. A. Jr., el-Naggar, A., Gray, K., Ordonez, N. G., Luna, M. & Gershenson, D. (1997). The induction of benign epithelial neoplasms of the ovaries of guinea pigs by testosterone stimulation: a potential animal model. *Modern Pathology* **10**, 879–883.

Slatkin, M. (2000). Allele age and a test for selection on rare alleles. *Philosophical Transactions of the Royal Society of London B* **355**, 1663–1668.

Slatkin, M. & Rannala, B. (2000). Estimating allele age. *Annual Review of Genomics and Human Genetics* **1**, 225–249.

Slev, P. R. & Potts, W. K. (2002). Disease consequences of pathogen adaptation. *Current Opinions in Immunology* **14**, 609–614.

Smith, N. G. & Hurst, L. D. (1998). Molecular evolution of an imprinted gene: repeatability of patterns of evolution within the mammalian insulin-like growth factor type II receptor. *Genetics* **150**, 823–833.

Stajich, J. E. & Hahn, M. W. (2005). Disentangling the effects of demography and selection in human history. *Molecular Biology and Evolution* **22**, 63–73.

Sterling, K. M., Jr. & Cutroneo, K. R. (2004). Constitutive and inducible expression of cytochromes P4501A (CYP1A1 and CYP1A2) in normal prostate and prostate cancer cells. *Journal of Cellular Biochemistry* **91**, 423–429.

Summers, K. & Crespi, B. (2005). Cadherins in maternal-fetal interactions: red queen with a green beard? *Proceedings of the Royal Society of London B* **272**, 643–649.

Summers, K., da Silva, J. & Farwell, M. A. (2002). Intragenomic conflict and cancer. *Medical Hypotheses* **59**, 170–179.

Sun, S., Ting, C.-T. & Wu, C.-I. (2004). The normal function of a speciation gene, Odysseus, and its hybrid male sterility effect. *Science* **305**, 81–83.

Suter, N. M., Malone, K. E., Daling, J. R., Doody, D. R. & Ostrander, E. A. (2003). Androgen receptor (CAG)n and (GGC)n polymorphisms and breast cancer risk in a population-based case-control study of young women. *Cancer Epidemiology, Biomarkers and Prevention* **12**, 127–135.

Sutton, K. A. & Wilkinson, M. F. (1997). Rapid evolution of a homeodomain: evidence for positive selection. *Journal of Molecular Evolution* **45**, 579–588.

Swanson, W. J., Nielsen, R. & Yang, Q. F. (2003). Pervasive adaptive evolution in mammalian fertilization proteins. *Molecular Biology and Evolution* **20**, 18–20.

Talbert, P. B., Bryson, T. D. & Henikoff, S. (2004). Adaptive evolution of centromere proteins in plants and animals. *Journal of Biology* **3**, 18.

Taplin, M.-E. & Balk, S. P. (2004). Androgen receptor: a key molecule in the progression of prostate cancer to hormone independence. *Journal of Cellular Biochemistry* **91**, 483–490.

Teare, M. D., Cox, A., Shorto, J., Anderson, C., Bishop, D. T. & Cannings, C. (2004). Heterozygote excess is repeatedly observed in females at the BRCA2 locus N372H. *Journal of Medical Genetics* **41**, 523–528.

Teng, Y. N., Lin, Y. M., Lin, Y. H., Tsao, S. Y., Hsu, C. C., Lin, S. J., Tsai, W. C. & Kuo, P. L. (2002). Association of a single-nucleotide polymorphism of the deleted-in-azoospermia-like gene with susceptibility to spermatogenic failure. *Journal of Clinical Endocrinology and Metabolism* **87**, 5258–5264.

Thaler, D. S. (1999). Hereditary stability and variation in evolution and development. *Evolution & Development* **1**, 113–122.

Thomas, M. A., Weston, B., Moltu, J., Wu, W., Nekrutenko, A. & Tonellato, P. J. (2003). Evolutionary dynamics of oncogenes and tumor suppressor genes: higher intensities of purifying selection than other genes. *Molecular Biology and Evolution* **20**, 964–968.

Ting, C.-T., Tsaur, S.-C., Wu, M.-L. & Wu, C. I. (1998). A rapidly evolving homeobox at the site of a hybrid sterillity gene. *Science* **282**, 1501–1504.

Torgerson, D. G., Kulathinal, R. J. & Singh, R. S. (2002). Mammalian sperm proteins are rapidly evolving: evidence of positive selection in functionally diverse genes. *Molecular Biology and Evolution* **19**, 1973–1980.

Tricoli, J. V. & Bracken, R. B. (1993). *ZFY* gene expression and retention in human prostate adenocarcinoma *Genes Chromosomes and Cancer* **6**, 65–72.

Tricoli, J. V., Yao, J. L., D'Souza, S. A. & Bracken, R. B. (1993). Detection of sex-region Y (*SRY*) transcripts in human prostate adenocarcinoma and benign prostatic hypertrophy *Genes Chromosomes and Cancer* **8**, 28–33.

Trivers, R. L. (1974). Parent-offspring conflict. *American Zoologist* **14**, 249–264.

Tsaur, S. C. & Wu, C. I. (1997). Positive selection and the molecular evolution of a gene of male reproduction, Acp26Aa of *Drosophila*. *Molecular Biology and Evolution* **14**, 544–549.

Tucker, P. K. & Lundrigan, B. L. (1993). Rapid evolution of the sex determining locus in Old World mice and rats. *Nature* **364**, 715–717.

Tucker, P. K., Adkins, R. M. & Rest, J. S. (2003). Differential rates of evolution for the *ZFY*-related zinc finger genes, *Zfy*, *Zfx*, and *Zfa* in the mouse genus *Mus*. *Molecular Biology and Evolution* **20**, 999–1005.

Tycko, B. & Morison, I. M. (2002). Physiological functions of imprinted genes. *Journal of Cell Physiology* **192**, 245–258.

Uria, J. A. & Lopez-Otin, C. (2000). Matrilysin-2, a new matrix metalloproteinase expressed in human tumors and showing the minimal domain organization required for secretion, latency and activity. *Cancer Research* **60**, 4745–4751.

Vacquier, V. D. (1998). Evolution of gamete recognition proteins. *Science* **281**, 1995–1998.

Vaux, D. L., Haecker, G. & Strasser, A. (1994). Evolution of gamete recognition proteins. *Cell* **76**, 777–779.

Van de Peer, Y., Taylor, J. S., Braasch, I. & Meyer, A. (2001). The ghost of selection past: rates of evolution and functional divergence of anciently duplicated genes. *Journal of Molecular Evolution* **53**, 436–446.

Wang, X. & Zhang, J. (2004). Rapid evolution of mammalian X-linked testis-expressed homeobox genes. *Genetics* **167**, 879–888.

Wastl, U. M., Rossmanith, W., Lang, M. A., Camus-Randon, A. M., Grasl-Kraupp, B., Bursch, W. & Schulte-Hermann, R. (1998). Expression of cytochrome P450 2A5 in preneoplastic and neoplastic mouse liver lesions. *Molecular Carcinogenesis* **22**, 229–234.

Waters, D. J., Shen, S. & Glickman, L. T. (2000). Life expectancy, antagonistic pleiotropy, and the testis of dogs and men. *The Prostate* **43**, 272–277.

Weber, W. W. (1995). Influence of heredity on human sensitivity to environmental chemicals. *Environmental and Molecular Mutagenesis* **25**, 102–114.

Weinstein, B. S. & Ciszek, D. (2002). The reserve-capacity hypothesis: evolutionary origins and modern implications of the trade-off between tumor-suppression and tissue-repair. *Experimental Gerontology* **37**, 615–627.

Westbrook, V. A., Schoppee, P. D., Diekman, A. B., Klotz, K. L., Allietta, M., Hogan, K. T., Slingluff, C. L., Patterson, J. W., Frierson, H. F., Irvin, W. P. Jr., Flickinger, C. J., Coppola, M. A. & Herr, J. C. (2004). Genomic organization, incidence and localization of the SPAN-X family of cancer-testis antigens in melanoma tumors and cell lines. *Clinical Cancer Research* **10**, 101–112.

Wheelock, M. J. & Damsky, C. H. (1997). Human cytotrophoblasts adopt a vascular phenotype as they differentiate. A strategy for successful endovascular invasion? *Journal of Clinical Investigation* **99**, 2139–2151.

Wheelock, M. J. & Johnson, K. R. (2003). Cadherins as modulators of cellular phenotype. *Annual Review of Cell and Developmental Biology* **19**, 207–235.

Whitfield, L. S., Lovell-Badge, R. & Goodfellow, P. N. (1993). Rapid sequence evolution of the mammalian sex-determining gene *SRY*. *Nature* **364**, 713–715.

Wildman, D. E., Uddin, M., Liu, G., Grossman, L. I. & Goodman, M. (2003). Implications of natural selection in shaping 99.4% nonsynonymous DNA identity between humans and chimpanzees: enlarging genus *Homo*. *Proceeding of the National Academy of Sciences U.S.A.* **100**, 7181–7188.

Wissenbach, U., Niemeyer, B., Himmerkus, N., Fixemer, T., Bonkhoff, H. & Flockerzi, V. (2004). TRPV6 and prostate cancer: cancer growth beyond the prostate correlates with increased TRPV6 Ca2+ channel expression. *Biochemical and Biophysical Research Communications* **322**, 1359–1363.

Wooding, S. P., Watkins, W. S., Bamshad, M. J., Dunn, D. M., Weiss, R. B. & Jorde, L. B. (2002). DNA sequence variation in a 3.7-kb noncoding sequence 5′ of the CYP1A2 gene: implications for human population history and natural selection. *American Journal of Human Genetics* **71**, 528–542.

Wyckoff, G. J., Wang, W. & Wu, C. I. (2000). Rapid evolution of male reproductive genes in the descent of man. *Nature* **403**, 304–309.

Xiao, J., Garcia-Lloret, M., Winkler-Lowen, B., Miller, R., Simpson, K. & Guilbert, L. J. (1997). ICAM-1-mediated adhesion of peripheral blood monocytes to the maternal surface of placental syncytiotrophoblasts: implications for placental villitis. *American Journal of Pathology* **150**, 1845–1860.

Xu, X., Wagner, K.-U., Larson, D., Weaver, Z., Li, C., Ried, T., Hennighausen, L., Wynshaw-Boris, A. & Deng, C.-X. (1999). Conditional mutation in *Brca1* in mammary epithelial cells results in blunted ductal morphogenesis and tumour formation. *Nature Genetics* **22**, 37–43.

Yang, Z. & Bielawski, J. P. (2000). Statistical methods for detecting molecular adaptation. *Trends in Ecology and Evolution* **15**, 496–503.

Yang, Z. & Nielsen, R. (2002). Codon-substitution models for detecting molecular adaptation at individual sites along specific lineages. *Molecular Biology and Evolution* **19**, 908–917.

Yeager, M. & Hughes, A. L. (1999). Evolution of the mammalian MHC: natural selection, recombination, and convergent evolution. *Immunological Reviews* **167**, 45–58.

Yoshida, K., Yoshitomo-Nakagawa, K., Seki, N., Sasaki, M. & Sugano, S. (1998). Cloning, expression analysis, and chromosomal localization of BH-protocadherin (PCDH7), a novel member of the cadherin superfamily. *Genomics* **49**, 458–461.

Zendman, A. J. W., Ruiter, D. J. & Muijen, G. (2003). Cancer/testis-associated genes: identification, expression profile, and putative function. *Journal of Cellular Physiology* **194**, 272–288.

Zhang, J. & Rosenberg, H. F. (2002). Diversifying selection of the tumor-growth promoter angiogenin in primate evolution. *Molecular Biology and Evolution* **19**, 438–445.

Zhang, J. & Zhang, Y. (2003). Pseudogenization of the tumor-growth promotor angiogenin in a leaf-eating monkey. *Gene* **308**, 95–101.

Zhou, Y., Fisher, S. J., Janatpour, M., Genbacev, O., Dejana, E., Wheelock, M. & Damsky, C. H. (1997). Human cytotrophoblasts adopt a vascular phenotype as they differentiate. A strategy for successful endovascular invasion? *Journal of Clinical Investigation* **99**, 2139–2151.

Zhu, Y., Spitz, M. R., Amos, C. I., Lin, J., Schabath, M. B. & Wu, X. (2004). An evolutionary perspective on single-nucleotide polymorphism screening in molecular cancer epidemiology. *Cancer Research* **64**, 2251–2257.

Zygmunt, M., Herr, F., Munstedt, K., Lang, U. & Liang, O. D. (2003). Angiogenesis and vasculogenesis in pregnancy. *European Journal of Obstetrics, Gynecology and Reproductive Biology* **110**, S10–S18.