

# Anti-cancer selection as a source of developmental and evolutionary constraints

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## Summary

Recently at least two papers<sup>(1,2)</sup> have appeared that look at cancer from an evolutionary perspective. That cancer has a negative effect on fitness needs no argument. However, cancer origination is not an isolated process, but the potential for it is linked in diverse ways to other genetically determined developmental events, complicating the way selection acts on it, and through it on the evolution of development. The two papers take a totally different line. Kavanagh argues that anti-cancer selection has led to developmental constraints. Leroi et al. argue that cancer is a side-effect of recent evolutionary changes that usually will disappear over time through anti-cancer selection. Here we place the papers in a wider perspective, and in so doing discuss various alternative developmental links cancer may have together with their evolutionary implications. *BioEssays* 25:1035–1039, 2003. © 2003 Wiley Periodicals, Inc.

## Anti-cancer selection influences evolution

In most organisms, there is a tight link between cell proliferation, differentiation and survival. A disturbance of the balance between these three processes often leads to cancer. Cancers usually kill post-reproductive individuals and therefore will be selectively neutral, but Leroi et al. rightly emphasise that pediatric cancers will seriously influence fitness. Both papers stress that the tight link between cell proliferation and differentiation implies an important role for anti-cancer selection in shaping evolution. In addition, Kavanagh claims that anti-cancer selection will lead to developmental and evolutionary constraints. This was earlier proposed by Galis<sup>(3,4)</sup> for the specific case of the conservation of the cervical vertebrae in mammals. Kavanagh proposes the following reasons why

anticancer selection may lead to developmental and evolutionary constraints:

- (1) Anti-cancer selection will maintain a switch between proliferation and differentiation. The necessity of keeping such a switch to avoid cancer risks forms an evolutionary constraint.
- (2) The presence of this switch will cause additional developmental and evolutionary constraints, because differences in its timing will cause concerted effects on proliferation and morphogenesis.
- (3) In tightly integrated organisms, the likelihood for the existence of such constraints will be increased. Moreover, any constraints will have cascading effects that will lead to more important evolutionary repercussions.

To prove that anti-cancer selection maintains the switch between division and differentiation, one needs to demonstrate heritable variation for the trait and selection against it. Kavanagh argues that disturbance of the regulation of the trait has very serious effects. This argues only for selection against changes in the regulation of the switch, but not necessarily for selective maintenance of a switch as such, i.e., of the constraint on the inability of differentiated cells to divide. An alternative explanation for the latter switch is provided by Margulis<sup>(5)</sup> and Buss.<sup>(6)</sup> They argue that there is a universal constraint in metazoans and their protist ancestors on cell division and differentiation of ciliated and other cells, because their cells have only one microtubule organizing center (MTOC). The MTOC can either form a centrosome during mitosis, or it can provide functions necessary for differentiation. For example, in neurons, the MTOC forms the axon and dendrites; in sperm cells and cilium-based sensory cells, it forms cilia, and generally it functions in cell communication, cell transport and the generation of asymmetric cell shape. As a result, most cells lose the ability to divide when they differentiate and can only divide again after dedifferentiation. This constraint had presumably already arisen in the unicellular and colonial protistan ancestors of the metazoa and by its very nature should be very resistant to evolutionary change. If indeed the absence of more than one MTOC is at the base of the constraint, it is difficult to argue that the constraint is

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DOI 10.1002/bies.10366

Published online in Wiley InterScience (www.interscience.wiley.com).

maintained because of anti-cancer selection, as no variation for the number of MTOCs has yet been documented, or selection against it.

The second source of constraints mentioned by Kavanagh is the result of the switch's mode of operation. She argues that differences in, for instance, the timing of the switch have effects on proliferation and, therefore, on morphogenesis. A good example is provided by limb development, where changes in the number of cells in the limb bud influence the number of skeletal elements (for instance, Refs. 7,8). Changes in proliferation rate can, therefore, have qualitative effects on morphogenesis. This indeed implies that anti-cancer selection will be a factor in evolution and suggests its potential for generating developmental and evolutionary constraints. However, it does not inescapably follow that the switch leads to long-term constraints on specific evolutionary changes.

### **Cancer as a by-product of recent evolutionary changes**

Leroi et al. make plausible claims that there is an increased cancer risk coupled to certain morphological and life-history changes (see also Ref. 9), especially those that involve an increase in proliferation rate and metabolic rate. They suggest, for instance, that the high prevalence of CNS tumours in humans, may be related to the recent fast evolution of a very large brain size, threefold that of chimpanzees. Animal husbandry and pet keeping also provide us with many examples that show how strong artificial selection for rapid growth and large size carry a high associated cancer-risk. The extremely high cancer rates in large breeds of dogs such as Great Danes, Newfoundlands and St. Bernards (up to 180-fold increases in osteosarcoma incidence compared to smaller breeds, Refs. 10,11) are probably related to the intense selection on growth rate and size. Leroi et al. argue that anti-cancer selection will eventually lead to a lower incidence of cancer and, therefore, cancer will not negatively affect fitness of traits for long evolutionary times. They hypothesise, therefore, that anti-cancer selection will mainly drive the evolution of features of cellular behaviour and regulation. Indeed, many different protective mechanisms at the cellular level have evolved against cancer in different taxonomic groups. Leroi et al. further argue that different selection pressures in different taxonomic groups will lead to different anticancer adaptations and, possibly, different cancer incidence as well. They illustrate several differences in anticancer adaptations between mice and men. These differences may have important implications for the use of mice as models for man in cancer research.

From Leroi et al.'s perspective, the continued occurrence of cancer in animals results from the continuation of evolutionary change over time. Cancer risk should, thus, be low in taxonomic groups that have undergone long-term evolutionary stasis. This is a testable prediction. In Leroi et al.'s view, specific cancer-risks will only stay high over longer evolu-

tionary periods when the system is exposed to perpetual evolutionary change. As an example, they mention cancer of the immune system (leukemia, lymphoma), a system that supposedly continually evolves in response to a co-evolutionary arms race against pathogens. Cancers of the immune system are the most prevalent paediatric cancers.<sup>(12)</sup>

In addition, there are at least two more reasons why selection may not always succeed in lowering cancer risks, which we will discuss below. Another issue that we will discuss is that, on a longer time-scale, anti-cancer selection may prevent the evolution of specific traits, when the initial benefit of a trait does not exceed the initial cost of the associated increase in cancer risk.

### **Anticancer risks that selection cannot remove**

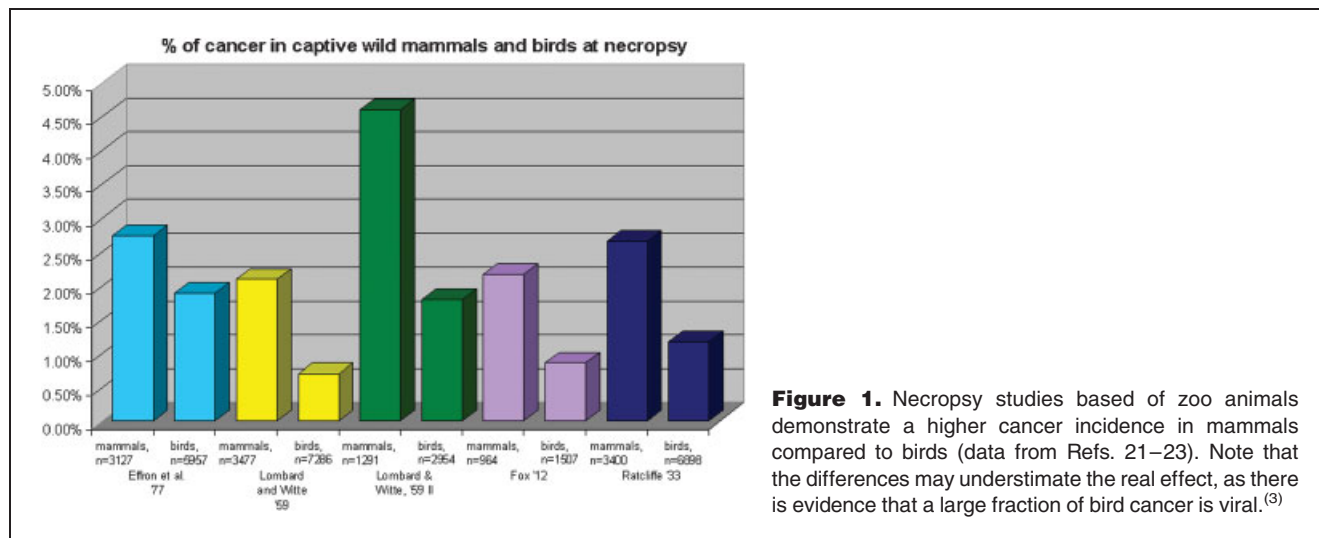
There are several reasons why cancer risks cannot always be reduced by natural selection. Therefore, some evolutionary changes will probably continue to be associated to elevated cancer risks. These reasons are: (1) continued evolutionary change of a system (see above), (2) decreases in genomic stability, and (3) intragenomic selection.

#### *Decreases in genomic stability*

Traits can lead to an increased cancer risk when their adaptive advantage is coupled to a decrease in genomic stability. This is probably another explanation for the high incidence of cancers of the immune system. Genomic stability is decreased by the physiological rearrangement mechanism that generates antigen receptor diversity within individuals.<sup>(13)</sup> The loss of genomic integrity that results from splicing and rearrangements of chromosomal segments is expected to increase the occurrence of translocations between chromosomes and other chromosomal rearrangements and, thus, of cancer.

#### *Intra-genomic selection*

Evolutionary changes that result from intra-genomic selection, rather than from selection at the level of the individual, also may lead to increased cancer risks that cannot easily be selected away.<sup>(14)</sup> The effects of genomic imprinting (parent-specific gene expression) are probably a good example of how genomic selection can lead to an increased cancer risk.<sup>(14,15)</sup> Typically, one allele at an imprinted locus is transcriptionally silent, with all gene products being produced from the other allele (mono-allelic expression). Imprinted genes are frequently involved in cell proliferation, and changes in activity of these genes are, therefore, often involved in cancer. Cancer risk is expected to be increased by imprinting, because mutational loss of function of only one allele is sufficient to eliminate gene function (one hit instead of two hits for bi-allelic gene expression) and because loss of imprinting of an allele changes the proliferation rate as well. Imprinting seems to be absent in birds.<sup>(16)</sup> D. Haig (personal commu-



**Figure 1.** Necropsy studies based of zoo animals demonstrate a higher cancer incidence in mammals compared to birds (data from Refs. 21–23). Note that the differences may underestimate the real effect, as there is evidence that a large fraction of bird cancer is viral.<sup>(3)</sup>

nication) has, therefore, proposed that the absence of imprinting in birds may be involved in the lower cancer incidence in birds compared to mammals (Fig. 1).

*High prevalence of cancers of the lymphoid system*

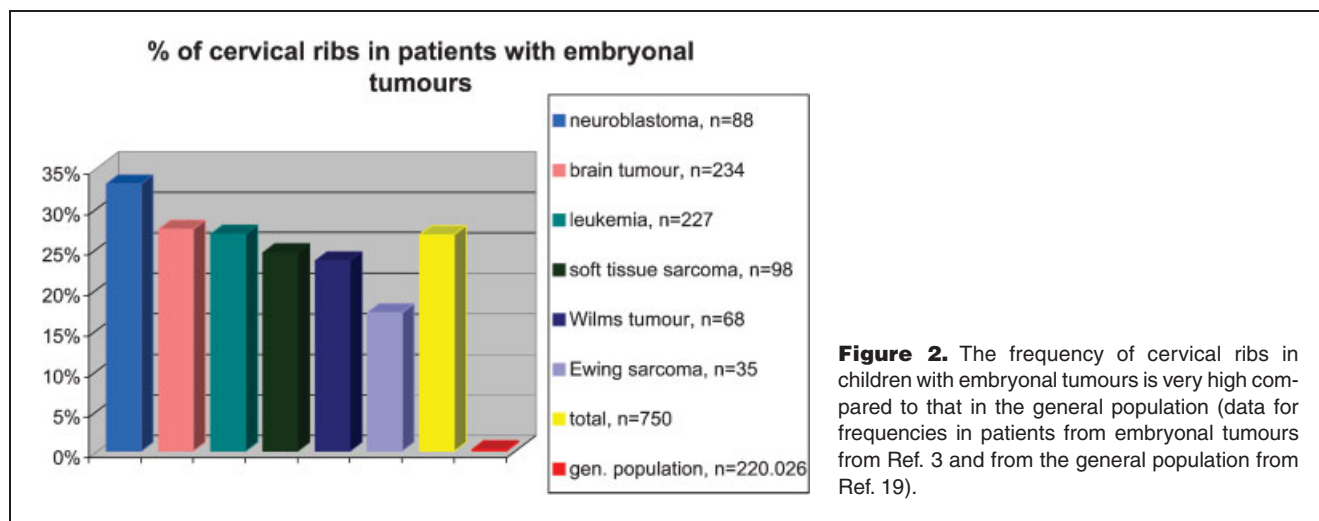
All three described causes are probably involved in the high prevalence of cancers of the lymphoid system: continued evolutionary change, genomic instability and genomic imprinting. The latter because imprinting of the *Igf-2* gene appears to be involved in the development of leukemia<sup>(17,18)</sup> and lymphoma, as well as of most other pediatric cancers.<sup>(14,15)</sup>

**Anticancer selection as a source of developmental and evolutionary constraints**

*High cancer risks and evolutionary constraints*

If the selective advantage of a trait is outweighed by the

disadvantage of the initially associated cancer risk, evolution of the trait will generally not occur. This hypothesis was proposed as explanation for the strong evolutionary constraint on changes in the number of cervical vertebrae in mammals.<sup>(3,4)</sup> Changes in the number of cervical vertebrae are associated with a highly increased susceptibility to pediatric cancers, congenital abnormalities and still births in humans (Fig. 2). Children in which the 7<sup>th</sup> cervical vertebra is transformed into a thoracic one by the addition of a so-called cervical rib have an excessively high chance to develop embryonal tumours (12%, a 120-fold increase compared to the general population, see also Ref. 19). One of us has recently found support for the association between cancer and cervical ribs in obductions of fetuses and infants (unpublished data). The hypothesis is in agreement with the absence of the evolutionary constraint and a much lower cancer incidence in birds, reptiles and amphibians<sup>(20–26)</sup> (see Fig. 1 for a



**Figure 2.** The frequency of cervical ribs in children with embryonal tumours is very high compared to that in the general population (data for frequencies in patients from embryonal tumours from Ref. 3 and from the general population from Ref. 19).

comparison of birds and mammals). Furthermore, manatees, exceptions within mammals with only 6 cervical vertebrae, have an excessively low cancer incidence. In 2000 necropsies in Florida (where in 800 cases the death was not caused by humans), not a single case of cancer was detected (C.A. Beck, personal communication). Sloths, which stand out among the mammals as sharing with the manatees an extremely low metabolic rate,<sup>(27–30)</sup> are the only other mammals having a different number of cervical vertebrae. Unfortunately, we have not been able to obtain information about cancer incidence in sloths. The existence of a relation between metabolic rate and oxidative DNA damage, and, thus, to cancer<sup>(31)</sup> suggests, combined with their very low metabolic rate, that their susceptibility to cancer may be low.

### *Association between cancer and congenital abnormalities*

The fact that cancer appears to be a side-effect of many different mutations for cervical ribs, emphasizes the tight link between morphogenesis and cancer-risk in this specific case. The strong association between pediatric cancers and a wide variety of congenital abnormalities<sup>(19,32–35)</sup> supports the tightness of the link in general. Not all congenital abnormalities involve dysfunctional organs; e.g. changes in the number of digits and nipples are variations on the normal vertebrate bodyplan, just like variations in the number of vertebrae. It is, therefore, well possible that anticancer selection plays a role in the maintenance of other strong evolutionary constraints as well, like the one on polydactyly, as discussed in Refs. 36,37.

### *Developmental and evolutionary constraints*

If cancer is an inevitable by-product of specific evolutionary changes, the inevitability of cancer risks represents a developmental constraint.<sup>(38)</sup> If the initial risk is sufficiently high, anti-cancer selection will lead to an evolutionary constraint. Further study of the associations of cancer with other variations of the body plan may teach us more about the importance of internal selection as a source of evolutionary and developmental constraints. The tight link between cancer and congenital abnormalities suggests that as a cause of internal selection cancer will probably not act alone, but in combination with the adverse effects due to congenital abnormalities.

Recently, many articles have appeared on the possibility and implications of developmental constraints.<sup>(39–41)</sup> Hard data are urgently required to estimate the importance of internal selection as a cause of apparent developmental constraints. The high prevalence of cancer and its ubiquity in the animal kingdom potentially make it a good system for analysing the importance of developmental constraints and internal selection in guiding evolution. Hopefully the renewed attention on cancer in an evolutionary perspective will attract

the attention of evolutionary developmental biologists willing to explore the full potential of this system.

### **Acknowledgments**

We would like to thank Jacques van Alphen, Ron Amundson, Ricardo Azevedo, Patricia Beldade, Paul Brakefield, Dave Carrier, Tom van Dooren, Russ Lande, Armand Leroi, Ineke van der Sar and Gunter Wagner for stimulating discussions, and Joris van Alphen for help with the figures.

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