Trends in Cancer

CellPress

Opinion

Evolutionary Ecology of Organs: A Missing Link in Cancer Development?

Frédéric Thomas,[1,7,*] Randolph M. Nesse,[2,3,7] Robert Gatenby,[4,7] Cindy Gidoin,[1] François Renaud,[1] Benjamin Roche,[1,5,7] and Beata Ujvari[6,7]

There is striking variation in the incidence of cancer in human organs. Malignant tumors are common in the colon and breast but rare in the heart and small bowel. The uterus frequently develops benign fibroid tumors but uterine cancers are relatively rare. The organ-specific difference in cancer prevalence has been explained primarily by the relative roles of intrinsic and extrinsic risk factors. In this opinion article, we propose also considering organs as distinct but connected ecosystems whose different vulnerabilities to malignant transformation may be partially explained by how essential each organ is for survival through the age of reproduction. We present and discuss some of the basic concepts and assumptions of this perspective on evolutionary medicine.

Intrinsic versus Extrinsic Cancer Risks: An Incomplete Debate

There is clearly variation in the incidence of cancer in human organs (Figure 1). Malignancies occur with a relatively high frequency in the colon, breast, skin, and prostate, but rarely develop in organs such as the heart and small bowel. The uterus frequently develops fibroids that can become very large but are rarely malignant, while the adrenal gland rarely develops primary cancer, but is the most common site of extrathoracic lung cancer metastases.

Most investigations into this phenomenon have focused on a distinction between intrinsic and extrinsic causes. Tomasetti and Vogelstein [1] recently sparked a debate by suggesting that the total number of stem cell divisions per tissue type could explain two-thirds of the variation in cancer risks (see, for instance [2–4]). Organs with high rates of cellular division are simply more likely to carry cancer-causing mutations, and thus subject to 'bad luck'. In contrast, Wu and colleagues [5] proposed that cancer risk is primarily influenced by extrinsic factors, and that intrinsic risk factors only contribute modestly. For instance, primary lung cancers are common in cigarette smokers and rare in nonsmokers. Similarly, primary liver cancers are common in scarred, cirrhotic livers due to infection, alcoholism, or chronic iron overload and rare in otherwise normal livers.

In this opinion article, we propose an additional factor: vulnerability to cancer differs among organs in part because of their differing contributions to the host's survival and Darwinian fitness. Selection for mechanisms to suppress cancer will be greatest in organs that are relatively small (and can, therefore, be compromised by even small tumors) or are critical for survival and reproduction, such as the heart, brain, and uterus (i.e., keystone organs). Organs that are large or paired, and thus can maintain function even when a relatively large tumor is present, will be less subject to anticancer selection forces. Although specific cancer-suppressing mechanisms

Trends

Despite extensive research, we lack a full explanation for why certain tissues exhibit more susceptibility to cancer than others. An approach focusing on the evolutionary ecology of organs could provide intriguing insights that transcend the dichotomist search for intrinsic versus extrinsic risk factors.

Organs in which malignant cells emerge, survive, and proliferate can be viewed as specialized islands in a living landscape, each with its own distinct ecologies.

All organs serve the organism as a whole, but they differ in how crucial they are to survival and reproduction.

Selection for cancer suppression should be stronger for organs that are more essential for the host's survival and Darwinian fitness.

[1]Centre for Ecological and Evolutionary Research on Cancer (CREEC), UMR CNRS/IRD/UM1 MIVEGEC, Montpellier, France
[2]School of Life Sciences, Arizona State University, Tempe, AZ, USA
[3]Center for Evolution, Medicine, and Public Health, Arizona State University, Tempe, AZ, USA
[4]Department of Radiology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL 33612, USA
[5]UMI IRD/UPMC 209 UMMISCO, Paris, France
[6]Centre for Integrative Ecology, School of Life and Environmental Sciences, Deakin University, Waurn Ponds, Victoria, Australia

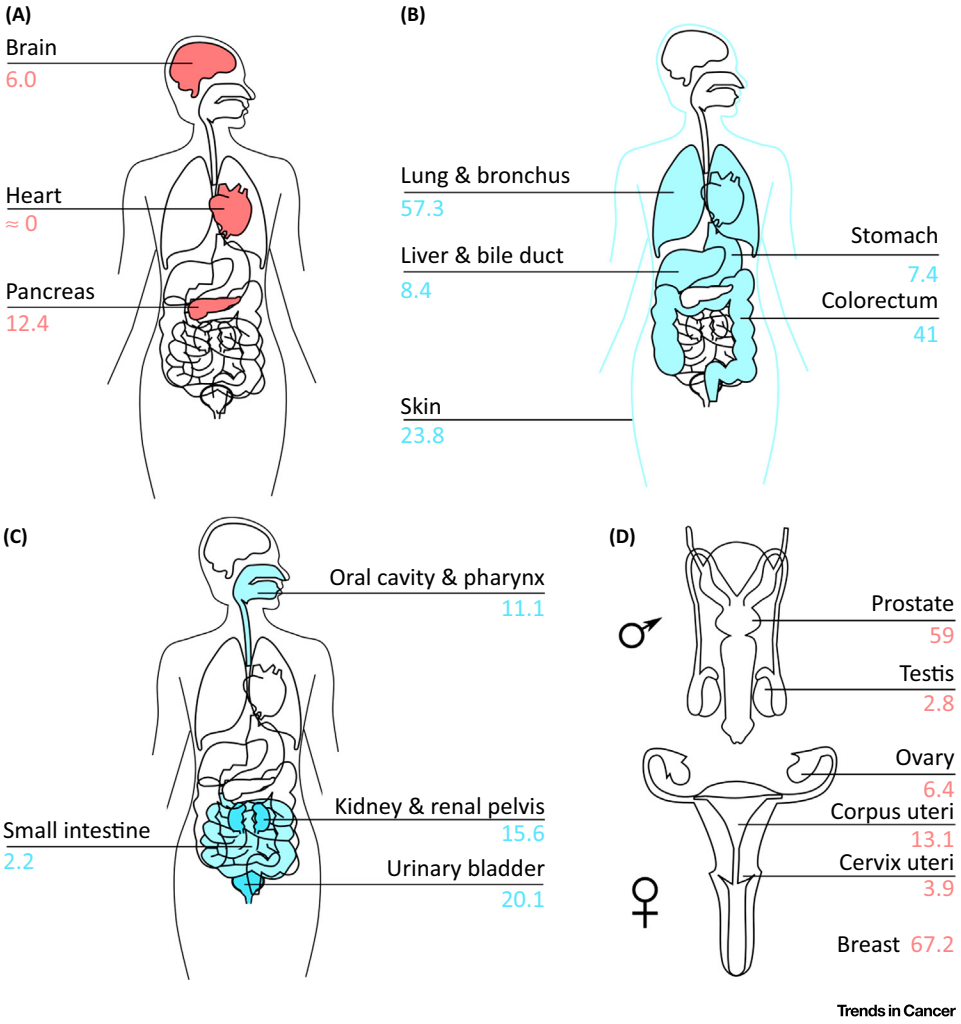

Figure 1. Incidence of Cancer in Different Organs. Malignant cancer incidence in (A) organs essential for survival; (B) organs for which external factors have a strong influence on cancer development; (C) other organs; (D) sex-dependent organs and organs essential for reproduction (except prostate and breast). Incidence rates are per 100,000 and age adjusted. Data from all individuals (without distinction of origin or sex) between 2009 and 2013[i].

can vary, in general they result in reduced vulnerability to tumor formation and/or metastatic invasion by mutant clones arising among cell populations under physiological conditions or following perturbations of the tissue adaptive landscape by infection, trauma, or toxins [6,7].

The Multicellular Body: A Myriad of Distinct Ecosystems

In complex multicellular organisms, cells combine to form tissues, then organs, and, ultimately, arrange in **organ systems** (see Glossary). Entities like tissues and organs have distinct structures and functions, as well as abiotic and biotic ecologies. For instance, abiotic factors (glucose, oxygen gradients, or water; or environmental conditions, such as temperature, pH, or UV light) vary significantly among locations and organs in the body. This is also the case with biotic factors, such as organ-specific microbial communities [8,9].

Importantly, tissues and organs provide specific microenvironments not only for microbes, but also for malignant cells that emerge, survive, and proliferate locally. Thus, organs in multicellular organisms can be viewed as specialized islands in a living landscape, with their own distinct

[7]These authors contributed equally to this work.

*Correspondence: frederic.thomas2@ird.fr (F. Thomas).

ecology characterized by structure, function, abiotic conditions, biotic community (microbes, malignant cells), **carrying capacity**, spatial distribution of resources, heterogeneity, network with other organs, and by exposure to acute and chronic external perturbations [8,9]. In this context, the fitness of the host depends on the function of each organ, and the survival and proliferation of each normal cell are fundamentally determined by the host. In contrast, the fitness of each cancer cell is not fully controlled by the host. Instead, tumor cell fitness depends on the rate of replication within a local tissue environment.

The Multicellular Body: Several Organs but One Evolutionary Function

All organs serve the organism as a whole, but their contributions to survival and reproduction are unequal and, as a result, they are subject to variations in the intensity of evolutionary forces. For instance, human fitness may be more affected by perturbations in the heart and brain than in the gallbladder or liver. Similarly, paired organs (lungs or kidney) can retain function even when one of the organs is damaged or rendered less functional by tumor growth. Reproductive organs are not essential for survival *per se*, but are crucial for reproduction and hence for fitness.

The assumption that evolutionary selection will optimize all organs to maximize health and longevity is common but has been questioned [10]. An alternative evolutionary perspective [11] emphasizes trade-offs and constraints when selection maximizes reproductive success at the expense of survivorship and longevity. As a result, organs that can undergo significant loss of function without altering the probability of reproduction may ironically be 'more' vulnerable to lethal pathologies such as cancer.

Evolutionary Ecology of Organs and Cancer Dynamics

Akin to microparasitic organisms, malignant cells depend on the tissue environment for sustenance, proliferation, and survival; and tumor development, progression, and metastasis are strongly dependent on the local conditions [12]. Several recent studies have clearly shown that ecological interactions such as competition, mutualism, and antagonism are likely to shape somatic evolution of cancer cells [13,14]. However, only few studies have placed these interactions within a spatial context, transposing **landscape ecology** to oncology [15–17].

Organ Ecology

Different organ ecologies can, at least partially, explain variations in cancer risks. For example, the relative rarity of heart and brain cancers can potentially be attributed to the low cellular turnover in these organs, and therefore to the low opportunities for oncogenic mutations [1]. We hypothesize that turnover rates may also be low in these organs because they are crucial to survival. For example, while the cell turnover rate of heart endothelial and mesenchymal cells is approximately 15% and 4% per year, respectively [18], and the annual striatal neuronal turnover is approximately 2.7% in the brain [19], the intestinal epithelium completely self-renews approximately every 5 days [20].

Interestingly, these traits might also render these crucial organs less capable of repair following injury, although traumatic damage to crucial organs would have been so consistently fatal in ancestral environments that selection for repair would be weak in any case [20].

Mutation rates may also be greatly affected by exposure to mutagens. This is common, for instance, in tissues such as the skin, or the respiratory and digestive epithelia, which are in direct contact with the external environment [21]. Therefore, melanoma can result from exposure to UV radiation, lung cancer from exposure to external carcinogens (e.g., pollution), and colon cancer from food-borne carcinogens such as polycyclic hydrocarbons. Organs that are regularly exposed to oncogenic infectious agents are also expected to be vulnerable to cancers; and hepatocellular carcinomas (the most common primary liver cancer), stomach cancers, and

Glossary

Carrying capacity: maximum number of individuals of a given species that an area's resources can sustain indefinitely without significantly depleting or degrading those resources.

Landscape ecology: discipline that studies why and how living organisms are distributed in the environment in the ways that they are. Landscape ecology is broadly interdisciplinary (e.g., hydrology, community ecology, forestry, wildlife biology, geology).

Organ systems: the human body is made up of several organ systems that all work together as a unit to make sure the body keeps functioning. There are ten major organ systems in the body, each of which plays a different role in helping the body work: (i) circulatory system, (ii) digestive system, (iii) endocrine system, (iv) integumentary system, (v) muscular system, (vi) nervous system, (vii) reproductive system, (viii) respiratory system, (ix) skeletal system, and (x) urinary system.

Systems ecology: encompasses the complexity of ecosystems with emergent properties, and analyses how human interventions influence the interactions and transactions of ecological and biological systems.

cervical cancers are substantially attributable to hepatitis B and C viruses, *Helicobacter pylori* bacteria, and human papillomavirus, respectively [22]. Within this theoretical framework, and in accordance with observations [18], organs subject to injury and infection have a higher cellular turnover to allow repair of tissue damage. While this may increase the probability of cancer, it may also allow rapid elimination of mutant cells. Furthermore, these organs are relatively large, and fatal dysfunction would require the growth of large tumors over a long period.

Evolution of Organ-Specific Resistance to Cancer Growth

Recently, Noble *et al.* [2], using the Tomasetti and Vogelstein dataset, suggested that variation in cancer risk across human organs is analogous to 'Peto's paradox': an observed lack of correlation between cancer risk and body mass (and life span) across the animal kingdom. They conclude that variation in risk of human cancer types is analogous to the paradoxical lack of variation in cancer incidence among animal species and may likewise be understood as a result of evolution by natural selection. Tissues with high levels of turnover (e.g., the lining of the small intestine) may have evolved especially powerful anticancer mechanisms. In parallel, Davies *et al.* [23] suggested that organ-specific cancer rates correlate negatively with an organ's evolutionary antiquity (estimated indirectly by considering the organs' presence in extant vertebrate groups and the time at which those groups first appeared in the fossil record). Although this relationship may just be coincidental, it suggests the possibility that recently evolved differentiation states may be intrinsically more vulnerable to neoplastic change because selection has had less time to reduce neoplastic tendencies. These interesting proposals can be extended to the analysis of how different oncogenic manifestations (from precancerous lesions to metastatic cancers) interact with how vital the organ is to survival and fitness. Indeed, the malignant transformation of normal cells following mutations is probably not lethal in most cases unless it occurs in a small vital organ. Solid tumors become threatening when the angiogenic switch allows tumor growth, and/or when metastases spread to other more vital organs. In this context, one would expect that cells in small vital organs are especially resistant to malignant transformation, and/or especially vulnerable to apoptosis when they become malignant. In contrast, larger less essential organs are likely to be relatively less able to prevent malignant transformation, but should have been shaped to resist invasion by metastatic cancer cells. In evolutionary terms, noninvasive tumors in nonessential organs may persist because natural selection is too weak to eliminate them (i.e., the fitness costs of eliminating them could be too high and/or the fitness benefits too small). For instance, certain cancers, such as prostate cancer, grow too slowly to impact fitness (i.e., detrimental health effects appear only at ages when natural selection is weak). Thus, there could be little selection to inhibit the early stages of late-life cancers that do not significantly decrease fitness. Further, mechanisms that suppress small neoplastic growth may have costly trade-offs by inhibiting wound healing, immune function, or developmental processes that require active cell proliferation [24]. Finally, the energetic costs of adaptations that could eliminate a tumor might exceed the benefits, especially because the costs are imposed at ages when natural selection is most intense [25]. Autopsy-based studies in humans or other animals that died of causes other than cancer indicate that most individuals develop *in situ* tumors in many organs with aging (see [12,26]). Further studies are needed that correlate age-specific rate of precancerous tumor lesions in each organ with the number of cells in that specific organ, number of stem cells, rate of new cell formation, importance of the organ to survival, and the importance of the organ to reproduction.

If fatal malignancies derive mainly from *in situ* malignancies that progress, preventing the formation or persistence of these 'seeds' should decrease cancer mortality rates. Several studies have demonstrated that eliminating precancerous cells/lesions can prevent cancer. For example, ablating Barrett's esophagus (a change in the lining of the esophagus tissue) may lower the risk of later developing esophageal adenocarcinoma [27], as does administration of agents that decrease inflammation [28]. Similarly, removing polyps decreases future colorectal

cancer occurrence by 75–90% [29], and eliminating precancerous cells on the cervix reduces subsequent risks of developing cervical cancer [30]. Applying such preventive strategies as early as possible, even before birth, would theoretically reduce levels of *in situ* tumors and thus reduce cancers in elderly individuals (see [31,32]). However, the costs of evolutionary trade-offs render envisioning the body of multicellular organisms free of precancerous cells unrealistic. Nevertheless, technological advancements could potentially fill certain loopholes of multicellular control to prevent cancer. For example, engaging the immune system in the systematic elimination of precancerous lesions via prophylactic cancer vaccination is among the most promising research directions to date (e.g. [33,34]). Yet, even this approach comes with compromises: it is well established that inflammation, a key element of active immune response, contributes significantly to neoplasm growth. It is also possible that the energy required by the frequent, if not permanent, activation of immune system would be too costly and detrimental to health. High inflammation itself increases risks of cancer (e.g. [35]). Even augmenting the body's own tumor-suppressor mechanisms could unbalance system homeostasis and result in unintended consequences, such as collateral tissue damage, autoimmune inflammatory complications, and other nonspecific side effects.

Metastatic Cascade

In animal ecology, the local availability of resources not only impacts population size, but also drives local and long-distance population dispersal [36]. For instance, many animals disperse to avoid intraspecific competition, especially from kin [37]. Evolutionary models also suggest that organisms should move only when the costs of remaining in place outweigh the potential costs of leaving the habitat [36]. Cancer cells within organs face a similar trade-off [14,38,39]. When local conditions are harsh or when resources are spatially or temporally heterogeneous, somatic selection favors metastatic cancer phenotypes, that is, the so-called mesenchymal transition ([40], but see [41]).

As recently highlighted by Cunningham *et al.* [42], the metastatic process is highly inefficient, with less than 1% of circulating tumor cells (of millions shed per day) progressing into macroscopic tumors. It is now widely recognized that metastasis depends on the interaction between malignant cells and the microenvironment of the distant organ site (i.e., its ecology). Thus, only tumor cells that already are sufficiently adapted or that can evolve adaptations to the local growth constraints of the 'foreign' landscape of distant organs can form metastases. Cunningham *et al.* [42] therefore argued that treatment strategies against metastatic cells should consider not only the primary site, but also the newly colonized site, because the predicted convergence of phenotypes within organ-adaptive landscapes could propose organ-specific therapies.

Concluding Remarks

Organ-specific evolutionary ecological variations are likely to influence cancer cell population dynamics, including emergence, proliferation, movement, or interactions, among others. Clearly, more empirical research is needed to identify and to decipher the range of variables that define organ ecology (see Outstanding Questions).

Our theoretical concept proposes that natural selection has shaped increased protection against cancer for small, essential, unpaired organs compared with larger, less essential, and often paired organs. This should provide a crucial ecological framework for preventing tumor initiation, growth, and metastasis. We predict that after the effects of stem cell numbers, rates of cell division, and exposure to toxins and infection are taken into consideration, the ecology of different organs will account for considerable differences in vulnerability to cancer. A formal test of our hypothesis will require assembling all of these data for a variety of organs. This kind of evolutionary ecological analysis of variations in different organs may prove of great value in cancer prevention and treatment.

Outstanding Questions

How do organ-specific evolutionary ecological variations influence oncogenesis (from precancerous lesions to metastatic cancers)?

How can we best exploit this conceptual framework for cancer prevention and treatment?

Does this concept from evolutionary medicine research apply more broadly than just to cancer?

However, an alternative explanation could be that large organs (e.g., the liver) have an intrinsic high cancer risk and therefore had to evolve to be large and redundant enough to cope with primary tumors. Independent of the direction of causality, the correlation between organ size and cancer prevalence remains relevant. Further mathematical models, focusing on the evolution of organs and incorporating autonomous and nonautonomous factors controlling organ size (e.g., cell size, type and number, competition for limiting growth or survival factors, tissue/organ environment, and the propensity of oncogenesis) may be able to pinpoint the direction of selective forces.

Furthermore, our primary aim is to provide a simple concept (focusing on single organ evolution and ecology) that will initiate scientific debates and the development of theoretical and empirical approaches. Clearly, the topic would greatly benefit from a more holistic approach, for example, a **systems ecology** approach that applies systems theory to the correlation between the ecosystems of organs (i.e., the individual) and oncogenesis. For example, different organs are exposed to a mix of extrinsic and intrinsic exposures (e.g., possible influences of viruses and hormone fluctuations), as well as having intricate interconnected relationships. Emergent properties of simple entities (organs) may form a more complex behavior as a collective entity that can influence the functioning of the entire system. For example, a primary tumor may not have a significant effect in the organ of origin (e.g., breast cancer), but may have a fitness reducing effect when it metastasizes to a different organ (e.g., bones, lung, liver [43]). Metastasis to distant vital organs is determined by several factors, including the cellular origin, intrinsic tumor properties, circulation patterns, and tissue affinities [44]. Therefore, selection influencing tumor resistance may not only be driven by the potential emergence of selfish malignant cells, but also by the metastatic propensity of cells in a given organ, as well as by the interconnectivity of the different organs. Further studies will be necessary to investigate how the synergistic effects and complex behavior of properties (e.g., organs) within the ecosystem of an organism could lead to selection acting on the organ level in response to oncogenesis.

Acknowledgments

This article is dedicated to the memory of our friend Audrey Rioust, 24 years old, who died from cancer the same day the article was accepted. This work was supported by the ANR (Blanc project EVOCAN), the CNRS (INEE), and an International Associated Laboratory Project France/Australia.

Resources

[i] http://seer.cancer.gov/

References

1. Tomasetti, C. and Vogelstein, B. (2015) Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science* 347, 78–81
2. Noble, R. *et al.* (2015) Peto's paradox and human cancers. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 370, 20150104
3. Garattini, E. and Tavani, A. (2015) Is "bad luck" an important determinant of cancer incidence and does this concept apply to kidney tumors? *Nephron* 129, 219–222
4. Weinberg, C. and Zaykin, D. (2015) Is bad luck the main cause of cancer? *J. Natl. Cancer Inst.* 8, 107
5. Wu, S. *et al.* (2015) Substantial contribution of extrinsic risk factors to cancer development. *Nature* 529, 43–47
6. Roche, B. *et al.* (2015) Bad luck and cancer: does evolution spin the wheel of fortune? *BioEssays* 37, 586–587
7. Thomas, F. *et al.* (2016) Intrinsic versus extrinsic cancer risks: the debate continues. *Trends Cancer* 2, 68–69
8. Engwerda, C.R. and Kaye, P.M. (2000) Organ-specific immune responses associated with infectious disease. *Immunol. Today* 21, 73–78
9. Costello, E.K. *et al.* (2009) Bacterial community variation in human body habitats across space and time. *Science* 326, 1694–1697
10. Brüne, M. and Hochberg, Z. (2013) Evolutionary medicine—the quest for a better understanding of health, disease and prevention. *BMC Med.* 11, 116
11. Nesse, R.M. and Williams, G.C. (1994) *Why We Get Sick: The New Science of Darwinian Medicine,* Vintage Books
12. Bissell, M.J. and Hines, W.C. (2011) Why don't we get more cancer?. A proposed role of the microenvironment in restraining cancer progression. *Nat. Med.* 17, 320–329
13. Crespi, B. and Summers, K. (2005) Evolutionary biology of cancer. *Trends Ecol. Evol.* 20, 545–552
14. Marusyk, A. and Polyak, K. (2010) Tumor heterogeneity: causes and consequences. *Biochim. Biophys. Acta* 1805, 105–117
15. Daoust, S.P. *et al.* (2013) From forest and agro-ecosystems to the microecosystems of the human body: what can landscape ecology tell us about tumor growth, metastasis, and treatment options? *Evol. Appl.* 6, 82–91
16. Alfarouk, K.O. *et al.* (2013) Riparian ecosystems in human cancers. *Evol. Appl.* 6, 46–53
17. Lloyd, M.C. *et al.* (2015) Pathology to enhance precision medicine in oncology: lessons from landscape ecology. *Adv. Anat. Pathol.* 22, 267–272

18. Bergmann, O. *et al.* (2015) Dynamics of cell generation and turnover in the human heart. *Cell* 161, 1566–1575
19. Ernst, A. *et al.* (2014) Neurogenesis in the striatum of the adult human brain. *Cell* 156, 1072–1083
20. Blanpain, C. *et al.* (2007) Epithelial stem cells: turning over new leaves. *Cell* 128, 445–458
21. Ducasse, H. *et al.* (2015) Cancer: an emergent property of disturbed resource-rich environments? Ecology meets personalized medicine. *Evol. Appl.* 8, 527–540
22. de Martel, C. and Franceschi, S. (2009) Infections and cancer: established associations and new hypotheses. *Crit. Rev. Oncol. Hematol.* 70, 183–194
23. Davies, J. (2004) Inverse correlation between an organ's cancer rate and its evolutionary antiquity. *Organogenesis* 1, 60–63
24. Aktipis, C.A. and Nesse, R.M. (2013) Evolutionary foundations for cancer biology. *Evol. Appl.* 6, 144–159
25. Hochberg, M.E. *et al.* (2013) Preventive evolutionary medicine of cancers. *Evol. Appl.* 6, 134–143
26. Folkman, J. and Kalluri, R. (2004) Cancer without disease. *Nature* 427, 787
27. Shaheen, N.J. *et al.* (2009) Radiofrequency ablation in Barrett's esophagus with dysplasia. *N. Engl. J. Med.* 360, 2277–2288
28. Abdel-Latif, M.M. *et al.* (2009) Inflammation and esophageal carcinogenesis. *Curr. Opin. Pharmacol.* 9, 396–404
29. Winawer, S.J. *et al.* (1993) Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N. Engl. J. Med.* 329, 1977–1981
30. World Health Organization (2006) *Comprehensive Cervical Cancer Control: A Guide to Essential Practice,* World Health Organization
31. Frank, S.A. (2007) *Dynamics of Cancer: Incidence, Inheritance, and Evolution,* Princeton University Press
32. Frank, S.A. (2010) Evolution in health and medicine Sackler colloquium: somatic evolutionary genomics: mutations during development cause highly variable genetic mosaicism with risk of cancer and neurodegeneration. *Proc. Natl. Acad. Sci. U. S. A.* 107, 1725–1730
33. Yaddanapudi, K. *et al.* (2012) Vaccination with embryonic stem cells protects against lung cancer: is a broad-spectrum prophylactic vaccine against cancer possible? *PLoS ONE* 7, e42289
34. Johnston, S.A. (2013) Cancer goal: vaccine is cause for optimism. *Nature* 493, 304
35. Cressler, C.E. *et al.* (2015) Evolution of hosts paying manifold costs of defence. *Proc. Biol. Sci.* 282, 20150065
36. North, A. *et al.* (2011) Evolutionary responses of dispersal distance to landscape structure and habitat loss. *Evolution* 65, 1739–1751
37. Fahrig, L. (2007) Non-optimal animal movement in human-altered landscapes. *Funct. Ecol.* 21, 1003–1015
38. Polyak, K. *et al.* (2009) Co-evolution of tumor cells and their microenvironment. *Trends Genet.* 25, 30–38
39. Lee, H.O. *et al.* (2011) Evolution of tumor invasiveness: the adaptive tumor microenvironment landscape model. *Cancer Res.* 71, 6327–6337
40. Anderson, A.R. *et al.* (2006) Tumor morphology and phenotypic evolution driven by selective pressure from the microenvironment. *Cell* 127, 905–915
41. Arnal, A. *et al.* (2015) Evolutionary perspective of cancer: myth, metaphors, and reality. *Evol. Appl.* 8, 541–544
42. Cunningham, J.J. *et al.* (2015) Divergent and convergent evolution in metastases suggest treatment strategies based on specific metastatic sites. *Evol. Med. Public Health* 2015, 76–87
43. Weigelt, B. *et al.* (2005) Breast cancer metastasis: markers and models. *Nat. Rev. Cancer* 5, 591–602
44. Nguyen, D.X. *et al.* (2009) Metastasis: from dissemination to organ-specific colonization. *Nat. Rev. Cancer* 9, 274–284