Commentary: Induction and selection of variations during cancer development

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In their paper, Vineis and Berwick1 (V&B) suggest a selectionist interpretation of the epidemiological patterns and dynamics of cancer. The incidence of different types of cancer is highly variable around the world and is associated with the specific environmental conditions in different geographic/social regions/conditions rather than with genetic differences between populations. V&B suggest that carcinogenesis-promoting environments (e.g., certain diets, disease treatments, air pollution) may not only induce new mutations that eventually lead to cancer but also create internal cellular environments that lead to the somatic selection of pre-existing genetic variants that were neutral in non-carcinogenic conditions. The existence of such selection is suggested by the rapid change in risk for specific types of cancer when people migrate from high-risk to low-risk areas and vice versa: the risk for migrants comes to match that of the local population. If migrants are exposed to the risk factors as embryos or young children, the change in risk can already be seen in the first generation. V&B give several examples that can readily be interpreted in terms of somatic selection of pre-disposing mutations, although in no case is the role of the environment as a variation-inducing agent excluded. Their goal, indeed, is not to exclude environmentally induced variation but to highlight the complementary, and in their view pivotal, role of somatic selection (and possibly also germ-cell selection), which leads to an increase in the proportion of dividing cells with cancer predisposing variations. Their paper also points to the complex dynamics of gene-environment interactions, which cannot be captured by simple linear mathematical models.

I agree with the emphasis V&B put on the role of somatic selection in cancer and accept that considering the selection of pre-existing somatic genetic variants in altered cellular environments is important for a better understanding of the epidemiology of cancer. However, I believe that the relation between the induction and selection of epigenetic variations and their interaction with genomic changes, which V&B mention in the last part of their paper, is more central than they suggest. In this commentary, I therefore want to develop some of the points raised by V&B in the last sections of their paper. I suggest (i) that many of the primary, predisposing variations may be epigenetic, induced by the new conditions in the somatic cells of the individual, or in the germplasm of the parent generation; (ii) that the genetic assimilation process that V&B describe, in which in the new conditions the effects of some heritable variations lead to their positive selection and to the selection of any additional genetic variants that reinforce and stabilize the selected phenotypes, is most likely if the predisposing variations are stress-induced epigenetic variations; (iii) that stress may lead to a partially regulated epigenetic and genetic reorganization of the genome, through processes that share features with the targeted genomic and chromosomal changes seen during hybridization, polyploidization, and pathogen-induced responses in plants, that were discussed by McClintock.2

Induced epigenetic variations and cancer

It is now well established that epigenetic variations, especially variations in chromatin structure involving altered patterns of methylation (both loss and addition of methyl groups) and histone modifications play a role in various stages of cancer initiation and progression.3–7 Since methylation patterns and histone modifications are responsive to cellular physiological conditions, and induced changes occur in them as part of normal development, changes induced by stressful physiological conditions (especially those occurring during sensitive periods in early development) may play a significant role in cancer and underlie the observed changes in risk for migrants moving from low to high risk regions. Changed conditions could promote both specific and general heritable epigenetic changes in DNA methylation and other components of chromatin. Some of these variations might be somatically selected and lead on to tumorigenesis.

The induction of new heritable epigenetic variations could be initiated not only by an environmental stress that alters gene expression patterns but also by an environmental insult that causes DNA damage: there is evidence that non-specific genetic changes such as single strand breaks caused by irradiation can lead to epigenetic changes that predispose most of the surviving cells to a second event leading to transformation.8,9 A possibly related phenomenon is the bystander effect,10 the ability of cells affected by an agent to convey manifestations of damage to other cells not directly targeted by the agent or necessarily susceptible to it. A signal from damaged cells leads to persistent changes in neighbouring cells, which can involve epigenetic, cell-heritable modifications of chromatin structure.10 The cancer-induction process can thus be initiated either by indirect as well as direct epigenetic modifications, or...
by genetic changes, which in all cases may lead to further alteration of the epigenotype.

The possibility that random and induced epigenetic defects can be transmitted to subsequent generation was first suggested by Holliday, and the relevance of epigenetic inheritance to epidemiological studies was discussed more recently by Jablonka. The results of cancer epidemiological studies, including the kind of data reviewed by V&B, which show the effects of migration on cancer risk, might profit from being considered within an epigenetic framework. If environmentally induced changes and selection affect germine cells as well as somatic cells, then predisposing mutations or induced epimutations are likely to be transmitted to the next generation. Evidence for this can be seen in the transgenerational transmission of carcinogenesis risk in mice exposed to diethylstilbestrol and in the increased mutation ratio in the offspring of mice exposed to irradiation. An indication of the nature of the epigenetic modifications in disease comes from studies showing that a change in diet may alter heritable cancer risk in some genotypes, a process that has been found to be mediated by methylation changes, and from studies showing that intake of androgen suppressors by pregnant rat females leads to heritable epigenetic (methylation) modifications and phenotypic changes in male descendants. If chemical treatment and altered diet cause germline effects in addition to somatic effects, the possibility of transmitting a higher risk of cancer to subsequent generations must be considered. If such germline effects exist, in migrants the risk of familial cancers (and not just sporadic cancers) should also change to match that of the local population, albeit considerably more slowly.

Genetic assimilation in somatic cells during cancer development

V&B suggest that a process of genetic assimilation is involved in the environment-dependent change in cancer risk. They propose that there is genetic variability among somatic cells, with most mutations being silent in normal conditions. When conditions change and become stressful (e.g. during hyperinsulinaemia or exposure to androgen suppressors), some pre-existing mutations become visible to selection. Any subsequent cell-heritable change that reinforces and stabilizes the selective advantage rendered by the primary variation will be further selected, leading to the further development of cancer. I think that such a process is more likely if one assumes that the primary variations are epigenetic, and that they are induced by the environment. The work of Fraga et al. on identical twins has shown that although identical twins begin life genetically and epigenetically identical, there is considerable divergence in their methylation and chromatin structure patterns when the environments in which they live differ, and the older they are the more divergent they become. In view of these and many similar data on epigenetic variability and its correlation with variable conditions, it seems likely that changed condition will not only alter the selective significance of pre-existing mutations and epimutations but will also induce new epimutations in non-mutated cells, some of which will give a selective advantage to the cell. In stressful conditions that promote cancer, the induction of epigenetic changes may not be confined to one or few changes in the pattern of activity of specific genes, but may be more global, involving, for example, changes in patterns of methylation in whole sets of repetitive sequences. The global changes may act as mutators, predisposing the cells that survive despite their occurrence to further genomic changes, some of which might lead to greater cell-fitness. Jablonka and Lamb have suggested that some of the cases of genetic assimilation described by Waddington may have been initiated by the selection of induced and random germine epimutations, which altered gene activity and hence selective conditions, and may also have directly biased genetic mutations by creating new mutational hotspots. A similar process might occur in somatic cells during cancer development, especially if we assume, as V&B suggest, that the primary (randomly generated or environmentally induced) heritable variations are positively selected in the new conditions.

The reorganization of the epigenome under (carcinogenic) stress

V&B point to the mutator phenotype of cancer cells and propose that when normal cells enter into nutritional, chemical, or physical conditions that are stressful, their DNA repair systems becomes impaired and they accumulate non-repaired, non-specific, mutations. They believe that the mechanisms underlying the mutability of cancer cells may be similar to those of nutritionally stressed bacterial cells in which the rate of mutation is increased under stress. However, as they note, unlike stressed bacterial cells, mammalian cells going through a carcinogenic process often show macroscopic changes in chromosomes and genome organization. I suggest, therefore, that a more appropriate model for understanding carcinogenic alterations may be the response of plant cells to genomic stress (due to hybridization, ploidy changes, and pathogen attack). Plant cells respond to genomic stresses (and to some nutritional stresses too) by reorganizing their genome: this involves chromosomal rearrangements, deletions and insertions of various repeated sequences, and massive changes in DNA methylation and histone modification patterns, which may be associated with the activation of transposable elements. Moreover, such genomic changes in plants are not random but are targeted with more or less specificity (depending on the genos studied) to certain chromosomal regions and to certain classes of repetitive sequences. There is an interesting parallel between the response of stressed plant cells and cancer cells: cancer development often involves changes in chromosome structure as well as multiple changes in DNA sequences and global changes in chromatin, and recent data suggest that in cancerous cells these changes too are targeted to certain chromosomal regions and certain classes of repeated sequences. It is, therefore, possible that cells exposed to the physiological stresses that lead to cancer respond by recruiting some of the same evolved coping mechanisms that are used during the response of plants to the stresses imposed by hybridization and polyploidization. If so, studying the mechanisms involved in the response to recurrent genomic stress in plants (e.g. suppression and activation of the RNAi system, alterations in the activities of DNA methylases and of...
histone modifying enzymes) may shed light on the late stages in the evolution of cancer cells during tumorigenesis, and suggest ways of controlling these processes through the manipulation of these shared, evolved mechanisms.

As V&B have shown, thinking about cancer from an evolutionary point of view is rewarding and may offer new interpretations of epidemiological data. However, as Darwin explained in On the Origin of Species, changed conditions affect not only the selection but also the induction of heritable variations.

Acknowledgement
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References
11 Holliday R. The possibility of epigenetic transmission of defects induced by teratogens. Mutat Res 1998;422:203–05.

Commentary: Carcinogenesis as Darwinian evolution? Do the math!
Robert A Gatenby

The transition from normal tissue to invasive cancer is a multistep, multipath process in which increasingly malignant cellular populations emerge over time generally coincident with accumulating genetic mutations. This is often described as “somatic evolution” because it appears formally analogous to Darwinian processes in nature. While this conceptual model is well accepted, the interactions of phenotypic properties with environmental selection forces that determine individual fitness...