Abstract

Age has long been known as the primary population ‘risk factor’ for cancer. We suggest that the observed disparities in hormonal cancers by ethnicity, gender, and other indices of social structure and power relationships, imply a differential aging by psychosocial and environmental exposures, in the context of cross-generational epigenetic heritage. A relatively simple model of malignancy regulation illuminates the cellular root of induced aging, and explains the decline in cancer rate with extreme old age via telomere shortening. We find that the multifactorial determinants of the disorder cannot be effectively addressed by ‘small molecule’ interventions at the individual level, but must involve comprehensive prevention strategies that lessen exposure to policies and cultural practices that accelerate senescence in vulnerable or targeted populations.

Key Words: health disparities, hormonal cancer, psychosocial stress, spontaneous symmetry breaking.

1 Introduction

Like Alzheimer’s disease, the principal ‘risk factor’ for cancer is age. Figures 1 and 2 display aggregated cancer incidence by age cohort in the US and in the Miyagi Prefecture of Japan (NIA, 2011; Arbeev et al., 2005).

Cancers of the breast and prostate – ‘hormonal’ cancers – however, show large disparities by ethnicity and economic class in incidence among young adults, stage at presentation, and mortality rate (e.g. Parker et al., 1998; HHS, 1998).

Although certain genetic alleles predispose individuals to higher susceptibility for these cancers (e.g., Gong et al., 2002 for prostate cancer), recent changes of incidence and mortality in time and geography indicate genes alone do not explain the expressed population-level patterns. At present, African-American women under age 35 suffer an approximately twofold higher age-specific rate of breast cancer, compared to white women, and the mortality rate is about three times
of figures 1 and 2, we will explore a model for cancer de-
fect of aging in cancer incidence. Given the powerful patterns
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tation differentials in hormonal cancer incidences and mortality
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Risk behaviors may explain part of the pattern in hormonal
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er (e.g., Ben-Tovin et al., 2002; Wallace et al, 1996). The
driven by frustration, pain, deprivation, humiliation, and dan-
abuse, and violence, are known to be coping mechanisms
is too extensive to fully review here.
Many of the risk behaviors associated with AIDS, drug
abuse, and violence, are known to be coping mechanisms
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Such behaviors, however, may not fully account for popula-
tion differentials in hormonal cancer incidences and mortality
rates, and certainly do not explain the overall dominant ef-
fect of aging in cancer incidence. Given the powerful patterns
of figures 1 and 2, we will explore a model for cancer de-
velopment in which a de-facto aging rate can be driven by
psychosocial and other environmental exposures, with possi-
ble effects across generations via epigenetic mechanisms (e.g.,
Wallace and Wallace, 2010).
We propose, then, an approach that more fully integrates
the biocultural processes that shape the development of hu-
mans, their cancers, and differentials in both their suscepti-
bility and pathways of disease progression. We begin with
Nunney’s (1999) evolutionary history of cancer, as opposed
to more conventional local evolutionary dynamic theories of
tumorigenesis within an organism (e.g., Bertram, 2001). Nun-
ney’s analysis suggests that in larger animals, whose lifespans
are proportional to about the 4/10 power of their cell count,
prevention of cancer in rapidly proliferating tissues becomes
more difficult in proportion to their size. Cancer control re-
quires the development of additional mechanisms and systems
to address tumorigenesis as body size increases – a synergistic
effect of cell number and organism longevity.
As Nunney puts it,
This pattern may represent a real barrier to the
evolution of large, long-lived animals and predicts
that those that do evolve... have recruited additional
controls [over those of smaller animals] to prevent
cancer.
Nunney’s work implies, in particular, that different tissues
may have evolved marked different tumor control strategies.
All of these, however, are likely to be energetically expensive,
permeated with different complex signaling strategies, and
subject to a multiplicity of reactions to signals. For modern
humans, large animals whose principal selective environment
is other humans, this suggests a critical role for the ‘signal’
of psychosocial stress, as mediated by a local ‘sociocultural
network’, i.e., an embedding cognitive social structure linked
to a cultural practice and history.
Contemporary evolutionary anthropology (e.g., Durham,
1991; Richerson and Boyd, 2005) emphasizes that culture,
largely defining what social relations are particularly helpful
or stressful, has become inextricably intertwined with human
biology. The seminal study by Forlenza and Baum (2000)
suggests that psychosocial stress is a very strong signal indeed
and severely affects the stages of mutation control: immune
surveillance, both psychosocial and other environmental exposures, with possi-
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2 ‘Spontaneous symmetry breaking’
with age
The basic mechanism is explored in figure 3, where an initial
cell in a particular tissue undergoes division, from state $S_0$
into two possible final states, $S_n$ for a normal process, and
$S_{can}$ for an abnormal state likely to lead to a cancerous pro-
$D$ between what has been
Figure 3: Developmental paths for a dividing cell lead either to its ‘normal’ form $S_n$, with average distortion from an expected configuration of $D = 0$, or, via a set of pathological tracks, to a cancerous form having $D > 0$, by some appropriate measure. The full and dotted lines represent high probability paths. The filled triangular zone represents the vast majority of low probability ‘nonsense’ developmental pathways.

produced by cell division and what should have been the outcome, via something much a rate distortion argument (e.g., Wallace and Wallace, 2010). The regulatory apparatus acts in a cognitive manner to repair/eliminate cells that deviate from the set of pathways leading to the condition $D = 0$. It seems likely that the exact form of $D$, and the chemical processes that measure it, may be of little importance, via the powerful necessary conditions arguments of the Rate Distortion Theorem (Cover and Thomas, 2006). The mathematical parallel is the way that long sums of stochastic variates converge on the Normal distribution via the Central Limit theorem. In fact, Wallace et al. (2003) give a purely information-theoretic cast to the cancer problem, an approach that we try to simplify here.

The model we invoke is analogous to a spontaneous symmetry breaking in Landau’s sense (Landau and Lifshitz, 2007; Pettini, 2007): With increasing age, the regulatory apparatus corrodes, becoming progressively less effective in containing cancerous proliferation. This is taken as equivalent to raising the temperature of a physical system so that increasing numbers of symmetries of a Hamiltonian become accessible.

By analogy, then, the probability of the distortion measure $D_i, P[D_i]$, becomes

$$P[D_i] = \frac{\exp[-D_i/kT]}{\sum_j \exp[-D_j/kT]}$$

(1)

Figure 4: Dynamics of the probability of cancerous proliferation as a function of age for two de-facto aging rate parameters, $k$. The basic idea is that, for humans, $k$ depends on individual exposures to environmental or psychosocial stresses over the life course, as affected by possible epigenetic heritage across generations. As the regulatory machinery ages out, cancer probability rises according to a roughly sigmoidal curve.

where $k$ is a socially-determined scaling constant, $T$ is temporal age, and $D_j$ any measure of average distortion from the normal cellular configuration for the cell configuration $j$.

For the two-state system of figure 3 this gives

$$P[Cancer] = \frac{\exp[-D_{can}/kT]}{1 + \exp[-D_{can}/kT]},$$

(2)

a sigmoidal relation.

For an arbitrary fixed value of $D_{can} > 0$ and increasing age, figure 4 shows the dynamics of cancer expression for the two scaling conditions, $k = 1, 2$ that represent different possible rates of physiological aging with time. Both curves top out at 1/2, but this would represent an extreme condition. Nonetheless, the general principle seems evident.

Explaining the downturn at very old age in figures 1 and 2 requires a second step in the model. Following, somewhat, the
arguments of Eisenberg (2011), telomeres – repetitive DNA sequences found at the ends of linear chromosomes – play a role in regulating cellular proliferation, and shorten with increasing age in proliferating human tissues. The rate of age-related shortening of telomeres is highest early in life, and decreases with age. Shortened telomeres are thought to limit the proliferation of cells and are associated with increased morbidity and mortality. Figure 5, adapted from Eisenberg (2011), shows telomere length vs. age, as abstracted from a variety of studies. 

Arbeev et al. (2005) argue, in effect, that \( k \) in equation (2) is itself a declining function of time \( T \), having, in their approach, the general form

\[
k = k_0 \exp[-k_1 T].
\]

(3)

Nesting equation (3) in equation (2) produces the general pattern of figure 6, declining at sufficiently old age.

We have, then, produced a relatively simple two-stage conceptual model that reproduces the essential features of figures 1 and 2. The critical parameters \( k_0 \) and \( k_1 \) represent aging rates determined by psychosocial and other environmental stressors in the context of possible cross-generational epigenetic inheritance.

Figure 5: Adapted from figure 1 of Eisenberg (2011). Shortening of telomere length with age in humans. Negative numbers are weeks before birth, and positive numbers years after birth. The rate of decline itself declines, leading in the direction of the arguments of Arbeev et al., (2005).

Figure 6: Substituting equation (3) into equation (2) – representing the general form of telomere shortening in figure 5 – produces a rate model that does indeed begin to decline at the oldest ages. We conjecture that the synergism of psychosocial and environmental stressors, in conjunction with epigenetic heritage across generations, determines \( k_0 \) and \( k_1 \).
3 Discussion and conclusions

An earlier paper examined ‘racial’ disparities among hormonal cancers in the US, extending the theory of immune cognition to include an elaborate tumor control mechanism constituting the principal selection pressure acting on pathologically mutating cell clones (Wallace et al., 2003). The interplay between them occurs, from that perspective, in the context of an embedding, highly structured, system of culturally-specific psychosocial stress. A classic rate distortion argument found that the larger system of stressors was able to literally write an image of itself onto the disease process, in terms of enhanced ‘risk behavior’, accelerated mutation rate, and depressed mutation control. The dynamics of that model were analogous to punctuated equilibrium in simple evolutionary systems, accounting for the often staged nature of disease progression at the individual level. That work found ‘social exposures’ to be far more than incidental cofactors in human cancer etiology, but rather an essential part of the ‘basic biology’ of the disorder. The aphorism that ‘culture is as much a part of human biology as the enamel on our teeth’ seems literally true at a fundamental cellular level. That study, however, ran to 22 equations, involving fairly elaborate mathematical machinery.

Here we have reconsidered the problem, examining in particular the large-scale ‘age spectrum’ of the disorder, as in figures 1 and 2. A relatively simple two-stage nested model accounts in a qualitative manner for the overall cancer/age pattern, in which de-facto aging is determined by the synergism of simple temporal age with patterns of psychosocial and environmental stress, most likely compounded by cross-generational epigenetic inheritance (e.g., Wallace and Wallace, 2010) that must affect both rates of telomere shortening and the corrosion of tissue-specific tumor regulatory systems.

This view reinforces our earlier conclusions that the multifactorial – ‘psychosocialneuroimmuno’ – nature of the disorder will not, ultimately, be addressed by ‘small molecule’ interventions at the individual level, but must involve comprehensive prevention strategies that lessen exposure to policies and practices that accelerate physiological aging among vulnerable or targeted populations. Wallace and Fullilove (2008) show in some detail how serial forced displacement of African-American populations, in the context of an ongoing American Apartheid (Massey and Denton, 1998), contributed materially to the failure of AIDS control in the USA. Our analysis suggests the argument might well be extended to patterns of hormonal and other cancers.

4 References


