Context-dependent selection as the keystone in somatic evolution of cancer

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Abstract

Somatic evolution of cancer involves a series of mutations, and attendant changes, in one or more clones of cells. Unlike a "bad luck" type model, the notion of clonal expansion adds competition-driven selection to the supposedly random process of somatic mutagenesis, with the implicit assumption that any mutation leading to partial loss of regulation of cell proliferation will give a selective advantage to the mutant. However, a number of experiments show that an intermediate pre-cancer mutant has only a conditional selective advantage; given that tissue microenvironmental conditions differ across individual organisms, this selective advantage to a mutant should be widely distributed over the population of organisms. We evaluate three models, namely "bad luck", context-independent, and -dependent selection, in a comparative framework, on their ability to predict patterns in total incidence, age-specific incidence, and their ability to explain Peto's paradox. Results show that context dependence is necessary and sufficient to explain observed epidemiological patterns, and that cancer incidence is largely selection-limited, as opposed to the mutation-centric, "bad luck" view. A wide range of physiological, genetic and behavioural factors influence the tissue micro-environment, and could therefore be the source of this context dependence in somatic evolution of cancer. The identification and targeting of these micro-environmental factors that influence the dynamics of selection offer new possibilities for cancer prevention. Our work also seeks to renew interest in the comparative evaluation framework, whose application has seen a lull in cancer literature, despite the possibilities of rejection it offers for potential theories of carcinogenesis.

1 Epidemiological observations

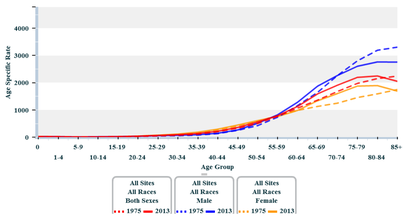

Figure 1: Cancer incidence vs age, from SEER9 (1)

- Late-life decline with age
- Cancer risk saturates with n
- Non-mutagenic carcinogens
- Peto's paradox

2 "Bad luck" model

Equations used:

- $p_{can} = 1-(1-p)^n$
- $p_A = 1-(1-p_{can})^A$

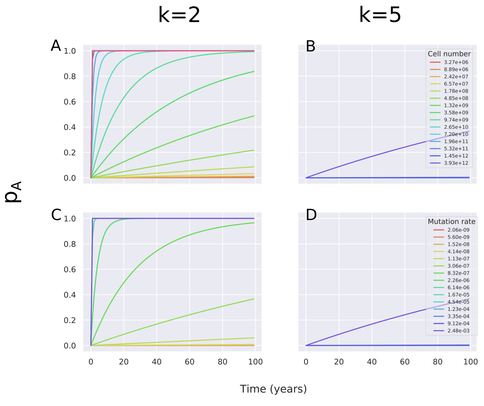

Figure 2: Incidence vs age, with n and p

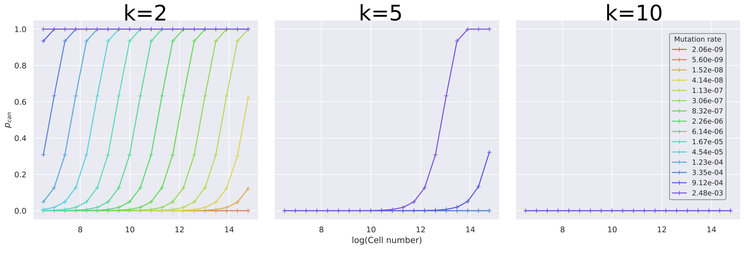

Figure 3: Incidence vs log(n) for different p and k

3 Selection models

- Linear evolution process, leading to mutation accumulation
- Discrere logistic equation for cell growth and competition, with one step growth making one day of lifespan
- Non-mutant growth rate, $g_0 = 0.007$, and a linear progression up to g_k for the kth oncogenic mutation, at which cancer occurs
- $\Delta_g = \frac{g_k - g_0}{k}$ is randomized in the population for context-dependent selection, as $N(\mu, \sigma)$
- $n \in [1.203 * 10^6, 2.649 * 10^{10}]$
- $p \in [3.775 * 10^{-11}, 3.059 * 10^{-7}]$

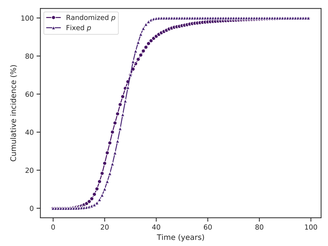

Figure 4: Context-independent model; randomized p vs fixed p. Mean randomized $p \approx$ fixed p.

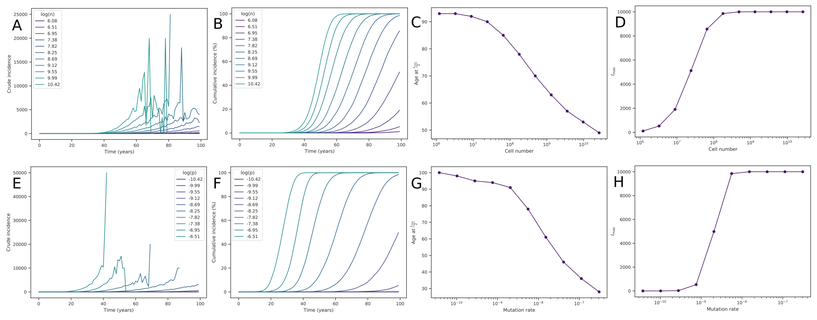

Figure 5: Context-independent selection; crude and cumulative incidence rates vs age, age at half maximum cumulative incidence, and maximum cumulative incidence, over the range of n and p.

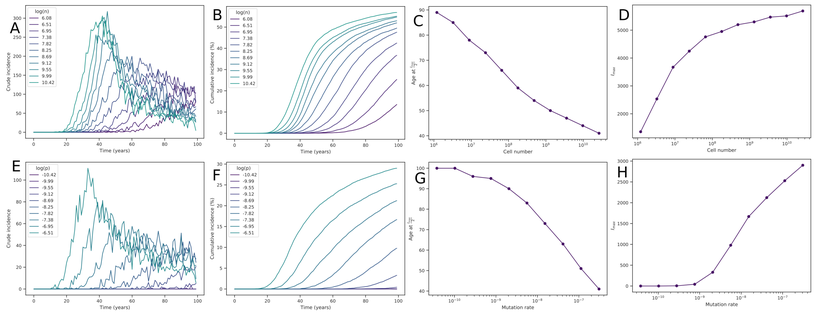

Figure 6: Same incidence parameters as above, for the context-dependent selection case.

3.1 Effect of k

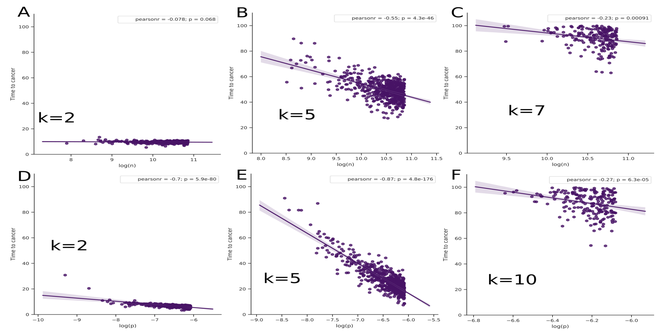

Figure 7: Context-independent selection case; association of time to cancer with n and p is modulated by k.

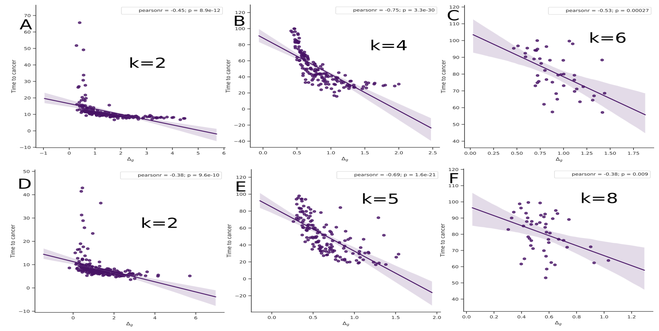

Figure 8: Context-dependent selection case; association of time to cancer with Δ_g is modulated by k.

4 Conclusions

Epidemiological observation	"Bad luck"	Context-independent selection	Context-dependent selection
Total incidence < 30%	100%	100%	<100% possible
Late-life decline	No	No	Yes
Incidence vs n	Threshold	Threshold	Progressive
Non-mutagenic carcinogens	Incompatible	Incompatible	g distribution
Peto's paradox	Extrinsic[1]	Extrinsic[1]	Intrinsic

References

(1) American Cancer Society. "Cancer Facts & Figures 2016". In: Cancer Facts & Figures 2016 (2016), pp. 1–9.

Acknowledgements

The authors acknowledge support from IISER Pune, and valuable feedback from faculty members of the Department of Biology as well as the Watve Lab.