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

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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.