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Peer Review

Review of: "Mechanisms of Selection on Cancer-Causing Mutations"

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"Mechanisms of Selection on Cancer-Causing Mutations" by Shinde et al. [1] advances an ambitious and thoughtful framework for understanding somatic evolution in cancer through the lens of context-dependent selection. It presents a wide-ranging set of hypotheses linking pleiotropic effects of driver mutations to selective advantages that arise only under specific conditions, including altered tissue microenvironments and lifestyle-associated physiological changes. It is integrative in scope and explicitly formulates testable hypotheses, emphasizing experimentally tractable evolutionary reasoning. In particular, it provides creative and stimulating advocacy for the systematic mapping of altered microenvironmental contexts to classes of driver mutations and calls for timely empirical tests of these ideas. However, several statements in the Introduction and Discussion do not adequately characterize the current state of the field or bear significant conceptual revision: correcting these points would substantially strengthen the manuscript and better position it within contemporary cancer evolutionary biology.

Selection in cancer is not an "upcoming view," but a demonstrated reality

The introductory assertion that "an upcoming view attributes a substantial role to selection acting on potentially cancer-causing mutations" understates the maturity of the field. Far from being an emerging or speculative idea, the role of selection in shaping cancer genomes has been quantitatively demonstrated across multiple tumor types and datasets [2][3][4]. These analyses have quantified selection intensities of somatic variants across cancers, demonstrating that driver mutations exhibit large, gene- and variant-specific selective advantages that cannot be explained by mutation rates alone. Not only major drivers, but the full distributions of selection coefficients have been characterized, including

doi.org/10.32388/LRRYCD

neutral variants and small-effect mutations [5]. These estimates have been leveraged to quantify the mutagenic causation of cancer and quantify the distinct contributions of mutagenic causation of cancer from diverse DNA-damaging environmental exposures [6]. Therefore, the claim that "There is one clear experimental demonstration of selection [10], and a few more are hypothesized [11]" is either deeply incorrect or inadequately contextualized: selection on somatic mutations has been empirically demonstrated in numerous studies using population-genetic, comparative, and statistical evolutionary frameworks applied directly to tumor sequencing data. These results do not merely hypothesize selection; they estimate its magnitude, in some cases with considerable precision and molecular biological and clinical utility [7]. Revising the work of Shinde et al [1] to acknowledge and incorporate this extensive knowledge would clarify that the necessary contribution of future research lies not in establishing the existence of selection, but in proposing biologically grounded hypotheses for how specific microenvironmental contexts modulate selection strength.

Mutation versus selection is a false dichotomy

The manuscript repeatedly frames cancer evolution as being either "mutation-limited" or "selection-limited," culminating in the statement that "cancers are not mutation-limited but are selection-limited." This dichotomy between mutation and selection in their relative roles in causing cancer is rhetorically inviting. However, it is a false dichotomy [8]. Mutation and selection are not alternative explanations for oncogenesis; they are joint components of evolutionary change. Mutation supplies the raw variation upon which selection acts, varying in rate from gene to gene [3] and from site to site [9] over orders of magnitude. Selection also varies over orders of magnitude [2], determining which of those same variants expand, persist, or are eliminated. The outcome of evolution cannot be meaningfully evaluated with either component in isolation. The rate and likelihood of carcinogenesis depend on both the rates at which variants arise and the selective advantages they confer in specific contexts [8][10]. In discussing carcinogens, Shinde et al [1] write that "if the somatic evolution of cancers is not mutation-limited, then why many mutagenic agents are also carcinogenic is a riddle." However, the "mutation-limited" versus "selection-limited" dichotomous premise of this riddle is flawed [8]. Mutagenic carcinogens increase cancer risk precisely because they increase the supply of variants that may later be favored by selection under permissive microenvironmental conditions. Selection does not negate the role of mutation; it conditions its consequences. Framing mutation and selection as coupled rather than competing processes would resolve this apparent paradox and strengthen conceptual coherence.

Genetic context and selective epistasis deserve explicit consideration

Shinde et al [1] provide an extensive and highly laudable treatment of the importance of environmental and microenvironmental context to selection. For instance, their discussion of angiogenesis as a context-dependent selective mechanism is compelling. The argument that angiogenic signaling can confer frequency-dependent advantages aligns well with detailed empirical documentation of angiogenesis facilitation in specific tumor settings [11]: alterations in vascularization directly modulate tumor growth dynamics, providing concrete examples that reinforce the plausibility of proposed mechanisms [12]. However, Shinde et al [1] give comparatively little attention to somatic genetic context—specifically, the growing evidence that selection on one mutation depends critically on the presence or absence of others. Initial research on this topic focused on empirical measures of co-occurrence and mutual exclusivity [13] [14][15][16][17]. Quantitative analyses have now demonstrated widespread selective epistasis in cancer [7][18], where the specific fitness effect of a mutation is contingent on the presence or absence of other driver events. Recent work has shown that oncogenic selection is often conditional on prior mutations, reshaping both the order and magnitude of selective effects during tumor evolution [10][19]. These findings reinforce the authors' broader argument that selection is context-dependent, but extend "context" beyond the microenvironment to include the evolving genomic background of the cell. Incorporating this dimension would enrich the framework proposed here and align it with current evolutionary models of cancer progression.

It must be acknowledged that existing quantitative estimates of driver mutation selection and epistasis represent average selective effects across heterogeneous microenvironmental and physiological contexts. This point bears substantial relevance to the conceptual developments advocated for by Shinde et al [1]: no matter how precise these estimates are, they do not contradict presumably substantial selective effects of microenvironmental context. Rather, these estimates clarify the explanatory challenge: to decompose observed average selection into contributions from distinct environmental, physiological, and genetic contexts [10][20].

Non-mutagenic carcinogens and future directions

With the caveats above, the Shinde et al [1] claim that "whether and how the non-mutagenic carcinogens shape the selective landscape needs to be investigated in detail" is highly apropos and foresightful. This area of research is crucial and underexplored, and requires the application of explicitly evolutionary

frameworks—combining inference of mutation rates and selection strength to yield substantial insights. Accordingly, the central message of Shinde et al [1]—that environmental and microenvironmental context profoundly shapes the strength and direction of selection on somatic variants—is likely correct and highly salient to current research directions. Moving forward, the field will benefit not only from the application of experimental approaches to characterize these contexts but also from the development of new computational methods to quantify selection on driver mutations conditional on specific environmental, physiological, and microenvironmental states, and the application of these methods to increasingly large and increasingly well-annotated tumor sequencing datasets.

Concluding remarks

Shinde et al [1] present a biologically rich set of hypotheses that deserve serious consideration. The core intuition presented—that selection on cancer-causing mutations is context-dependent and deeply influenced by the tissue microenvironment—is sound and important. Refining their work to accurately reflect the existing empirical literature on somatic selection, to avoid framing mutation and selection as opposing explanations, and to integrate genetic context alongside microenvironmental context would substantially strengthen its message. With these clarifications, it may serve as a valuable conceptual bridge between evolutionary theory, cancer biology, and experimental investigation.

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Declarations

Potential competing interests: No potential competing interests to declare.