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LATE MORBIDITIES OF ANTI-CANCER THERAPY: DOES DNA MATTER?

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Compared to age-matched controls, cancer survivors exhibit reduced physiological reserve and higher rate of frailty, a phenotype predictive of chronic disease and disability. They are also affected with conditions associated with aging such as heart disease and pulmonary dysfunction, as well as secondary malignancies. These effects are generally attributed to the highly intensive and toxic therapy provided. It is conceivable that these devastating late sequelae of anti-cancer therapy are mediated through its genotoxic potential and ability to induce mutagenic response in normal, non-tumorous, cells and tissues. As virtually all conventional anti-cancer drugs are clastogens capable of inducing genome structural variants (GSVs) in affected cells, we hypothesize that the main molecular mechanism of chemotherapy-associated late effects is accumulation of sub-clonal GSVs in normal non-tumor cells, arguably comprising the main damaging burden of chemotherapy-induced mutational load. Using our new, NGS-based method for direct GSV detection in normal tissues we demonstrated that conventional anti-neoplastic drugs are capable of inducing somatic GSVs in both actively proliferating and quiescent cells. We also demonstrated that chemotherapeutic agents applied in doses with similar cytotoxicity have different mutagenic capacity and, hence, can be ranked based on their potential abilities to cause long term complications. Our results clearly indicate that non-cycling differentiated cells can serve as a reservoir of iatrogenically induced somatic mutations. These findings provide an immediate approach for studying the molecular mechanisms of late morbidities in cancer survivors exposed to chemotherapy.