**Recurrence dynamics of cancer according to the dormancy paradigm**

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In cancer follow-up, in addition to the evaluation of survival probabilities, there is a fundamental need of assessing recurrence dynamics for optimal disease management. In breast cancer, although the time-dependent effect of the oestrogen receptor (ER) status of the tumour has already been described, so far no factor has proven to disentangle the multi-peak behaviour observed for metastatic recurrences.

We proposed frailty models in the tumor dormancy framework, in order to account for possible unobservable dependence mechanisms in cancer studies where a non-negligible proportion of cancer patients relapses years or decades after surgical removal of the primary tumor. Relapses do not seem to follow a memory-less process, since their timing distribution leads to multimodal hazards. From a biomedical perspective, this behavior is explained by tumor dormancy, i.e., for some patients microscopic tumor foci may remain asymptomatic for a prolonged time interval and, when they escape from dormancy, micrometastatic growth results in a clinical disease appearance. The activation of the growth phase at different metastatic states would explain the occurrence of metastatic recurrences at different times (multimodal hazard). We propose a new frailty model which includes in the risk function a random source of heterogeneity (frailty variable) affecting the components of the hazard function.

Following the inflammatory hypothesis related to the dormancy exit, we aimed at investigating whether adiposity at diagnosis, reflected by increased patient's body mass index (BMI), could be associated with breast cancer recurrence patterns over time after primary cancer therapy. Results demonstrate that the patient's BMI at diagnosis is associated with cancer recurrence dynamics. Patient adiposity should therefore be central to the exploration of late adjuvant treatment modalities. Recent findings proved that anti-inflammatory regimens in the surgery context are associated with a major decrease of the early recurrence peak in overweight and obese patients. The reproducibility of the multimodal hazard for metastatic recurrences is striking across different case series. However, the quality of the follow-up data collection is a relevant issue, even in large multi-center sponsored clinical trials and metanalyses, to assure the resolution of detailed peak effects. Overall, current results in cancer follow-up analysis are calling for new advanced statistical methods suited for the richness of the biological hypotheses associated with tumor dormancy.