Investigating tumor dormancy with frailty models

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Abstract

A non-negligible percentage of cancer patients relapse after years or decades after surgical removal of the primary tumor. This phenomenon is not following a random memory-less process and its timing is reflected in hazard rates, with respect to both relapse and mortality, showing multimodal shapes. From a biomedical perspective, such a behavior may be 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 and mortality at different times (multimodal hazard). We place this phenomenon in the framework of survival frailty models. We propose a new statistical approach which models the risk function by considering possible effects of Gamma frailty and compound Poisson fraity in acting on components of the hazard function. Thus, the individual hazard rate is the product of a random frailty variable and the sum of basic hazard rates. The basic hazard rates correspond to micrometastatic developments starting from different initial states. The frailty variable represents the heterogeneity between patients with respect to relapse, which might be related to unknown mechanisms that regulate tumor dormancy. The model is applied to analyze the mortality of patients in a large breast cancer dataset. We show how this framework can appropriately model the tumor dormancy phenomenon and possibly improve the understanding of this biological process.

*url: http://www.cussb.unisr.it/