

More begets more: patient heterogeneity and prior cancer burden as an independent risk factor in Lynch syndrome

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Keywords

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Abstract

Background Most Lynch syndrome (LS) patients now survive their first and second cancers, most always colorectal (CRC) and/or endometrial cancer (EC). The hazard posed by the prior cancer burden is recognized clinically as an informal risk factor, but has not been quantified previously. Only age, sex and gene are currently used for risk evaluation.

Methods A cohort of 8,493 LS patients from the Prospective Lynch Syndrome Database with 70,856 observation years in colonoscopy surveillance was examined. A total of 1,934 cancers occurred during follow-up. Hazards were modelled using a multivariate Cox model with frailty to account for within-patient correlation.

Results After adjustment for sex, gene, age and prior burden of CRC and/or EC, the model of hazard for other cancers confirmed prior other cancer as a strong risk factor (hazard ratio 1.28 [1.15, 1.48] per prior cancer). The effect size was similar for prior CRC and/or EC (HR 1.21 [1.11 – 1.32] per prior cancer). Despite equal risk of lifetime cancer, the hazard for cancer in rare organs in *path_MSH2* carriers was high compared to *path_MLH1* carriers (HR 1.61 [1.38, 1.88]). Analysis of frailty distribution revealed two distinct patient subgroups: low-risk group, comprising 80% of patients, and a high-hazard group constituting 20%.

Conclusion Cumulative burden of prior cancers is a strong risk factor for subsequent cancer in Lynch syndrome. Age, sex and LS gene only explain 60% of patient heterogeneity. More individualized strategies are needed to identify high-risk patients.