Colorectal Cancer Survival Advantage in \textit{MUTYH}-Associated Polyposis and Lynch Syndrome Families

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The cardinal features of colorectal cancer in patients with the \textit{MUTYH}-associated polyposis syndrome, featured in this editorial, are of very recent discovery and remain under review as new clinical phenotypes for these patients are still being identified. Importantly, its phenotype results from homozygosity of the \textit{MUTYH} gene and, therefore, is inherited in an autosomal recessive pattern.

In a more intensively studied hereditary colorectal cancer syndrome, namely Lynch syndrome, the cardinal features have been shown to result from an autosomal dominantly inherited pattern and includes earlier average age of cancer onset, when compared with the general population (45 years for Lynch syndrome colorectal cancer and 64 years for patients with colorectal cancer in the general population), accelerated carcinogenesis, high risk for metachronous colorectal cancers, specific pathology features for Lynch syndrome colorectal cancers that are more often poorly differentiated and have an excess of
mucoid and signet cell features, a Crohn-like reaction (defined as discrete lymphoid aggregates, some with germinal centers, and surrounding stellate fibrosis commonly found around colorectal adenocarcinomas in the absence of clinical or pathological evidence of previous Crohn disease), an excess of infiltrating lymphocytes within the tumor, and, importantly, an increased survival for patients with Lynch syndrome colorectal cancer. With these considerations, the *sine qua non* for its diagnosis is the presence of a germline mutation in a mismatch repair gene (most commonly *MLH1*, *MSH2*, or *MSH6*) segregating in the family (1–3).

As far as we can determine, the first publication dealing with improved survival in a hereditary form of cancer, in this case endometrial and colorectal cancers, in what was then called the cancer family syndrome, was by Lynch et al. (4) in 1978. Survival advantage in familial breast cancer and in hereditary nonpolyposis colorectal cancer was also described by Lynch et al. (5) in 1981. This report was followed in 1996 by that of Sankila et al. (6) who found a survival advantage among patients with colorectal cancer who had *MLH1* germline mutations.

In 1998, Watson et al. (7) discussed a survival advantage in Lynch syndrome. In this retrospective cohort study, 274 patients with Lynch syndrome from 98 Lynch syndrome families were compared with a control group of 820 consecutive unselected hospital-based patients with colorectal cancer, all of whom were staged according to the TNM system. Median follow-up among living patients was greater than 10 years among patients with Lynch syndrome and 8.5 years among patients in the unselected control series. Cox regression was used to compare survival in stage-stratified analyses of time from diagnosis to death. Patients with Lynch syndrome had lower-stage disease than control patients (*P* < .001) and fewer had distant metastases at diagnosis (*P* < .001). The stage-stratified survival analysis showed that the patients with Lynch syndrome had a statistically significant overall survival advantage, regardless of adjustment for their younger age (when patients with Lynch syndrome were compared with unselected control patients, a conservative estimate of the hazard ratio was 0.67, *P* < .001). The lower stage at diagnosis of patients with Lynch syndrome, compared with the unselected control patients with colorectal cancer, was attributed to the fewer distant metastases at diagnosis observed among patients with Lynch syndrome and their longer survival in subset analyses restricted to patients with tumors of the same stage. Finally, the estimated death rate for patients with Lynch syndrome, when adjusted for stage and age differences, was at most two-thirds of the rate for the unselected control patients.

The survival benefit for colorectal cancer is not restricted to patients with Lynch syndrome. Specifically, in this study, Nielsen et al. (8) have studied survival among patients with *MUTYH*-associated polyposis, which has been characterized by a lifetime risk of colorectal cancer that is as high as 100%, and found that they also have a survival advantage. The authors appropriately reason that the molecular genetic features driving colorectal cancer in this recessively inherited syndrome (ie, homozygosity for *MUTYH* mutations) likely may be influencing tumor behavior and patient survival. To test this hypothesis, survival was investigated between patients with *MUTYH*-associated polyposis and carefully matched control patients with colorectal cancer from the general population. The results were highly statistically significant in that the 5-year survival for patients with *MUTYH*-associated polyposis colorectal cancer “...was 78% (95% confidence interval [CI] = 70% to 84%) and for control patients was 63% (95% CI = 56% to 69%)(log rank test *P* < .001)” (8). When the case patients and control patients were carefully matched with appropriate adjustment for differences in age, stage, sex, subsite, country, as well as year of diagnosis, survival remained better for patients with *MUTYH*-associated polyposis. Therefore, it is unlikely that any major environmental influences would be sufficient to account for this increase in survival.

What does this survival advantage mean in these hereditary colorectal cancer settings? The statistically significant improved survival of patients with *MUTYH*-associated polyposis colorectal cancer and patients with Lynch syndrome colorectal cancer who have mutations in mismatch repair genes might be driven, in part, by their respective underlying molecular pathogenic events. Is there a survival advantage for other hereditary colorectal cancer syndromes, such as Peutz-Jeghers syndrome? The answer is not known, but research is clearly indicated.

We hypothesize that the cancer-causing mutations in *MUTYH* and in the mismatch repair genes that predispose to Lynch syndrome are also the causal factors for their respective survival advantages. The initial two-hit theory of colon carcinogenesis is now understood to be much more elaborate, with multiple hits, rate-limiting steps, and genomic instability (9). Within this complex progression maze, might we be able to find paths to different outcomes? The ultimate understanding of what drives the development of an individual tumor may enable us to materially improve the care and, in turn, prognosis of cancer patients. Furthermore, the ultimate understanding of the pathogenetic pathways elicited by these respective mutations may serve as models for studying both survival and increased virulence of hereditary and sporadic colorectal cancers. The genotype and its accompanying cancer phenotype may harbor strong implications for individualizing cancer care. Indeed, Vasan’s group (10) has shown previously that, among patients with *MUTYH*-associated polyposis, genome differences are reflected in phenotypic differences.

Finally, the family history, coupled with its genotypic and phenotypic heterogeneity, remains paramount in unraveling the mechanism of colon neoplasia and its vexing patterns of survival. Recognition of the distinct molecular pathways, as mentioned above, by which colorectal cancers arise from various genetic mutations, will materially refine our approach to improved surveillance and treatment of patients with hereditary colorectal cancer.

**References**


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