SURVEY OF CANCERS AND GENOTYPE-PHENOTYPE CORRELATIONS IN THE HNPCC PATIENT POPULATION AT U.T. M.D. ANDERSON CANCER CENTER

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Hereditary Non-Polyposis Colorectal Cancer (HNPCC) is characterized by early age onset of colorectal cancer with right-sided predominance, and an increased incidence of synchronous and metachronous neoplasms, as well as extracolonic cancers. It is caused by germline mutations in a mismatch repair (MMR) gene, usually hMLH1, hMSH2, hMSH6, and hPMS2. As most of the published data on HNPCC comes from homogeneous European populations with centralized cancer registries, the purpose of this study was to examine the prevalence of cancers and evaluate genotype-phenotype correlations in patients suspected to have HNPCC from a heterogeneous North American patient population. A retrospective chart review of patients suspected to have HNPCC evaluated at M.D. Anderson Cancer Center from February 1, 1996 to December 31, 2006 was performed. Patients were classified into 3 study groups according to their MMR gene status. Seventy-one patients had a MMR gene mutation (MUT + group), 12 had a variant of unknown significance (VUS group), and 40 had no mutation clinically identified but did have informative microsatellite Instability and immunohistochemistry tumor studies (MUT - group). hMSH2 mutations and VUS were present in 50 MUT+ patients and 6 VUS patients, respectively; while hMLH1 mutations and VUS were present in 18 MUT+ patients and 5 VUS patients, respectively. hMSH6 mutations and VUS were present in 3 MUT+ patients and 1 VUS patient, respectively. Males were diagnosed with their first colorectal cancer at an earlier age than females (p=0.0436). Patients in the MUT+ group had the longest time interval to sentinel cancer diagnosis and longest time to first colorectal cancer diagnosis among the 3 study populations (p=0.0054; p=0.0003). Extracolonic cancers were more common in patients with hMSH2 mutations. A VUS (G683R) in hMSH2 was seen exclusively in 4 African American patients. The results of this investigation suggest that our study populations exemplified both phenotypic similarities and differences compared to what is currently reported in the HNPCC literature. Further studies evaluating large, heterogeneous North American patient populations, especially African Americans, and mutation specific genotype-phenotype correlations are warranted.