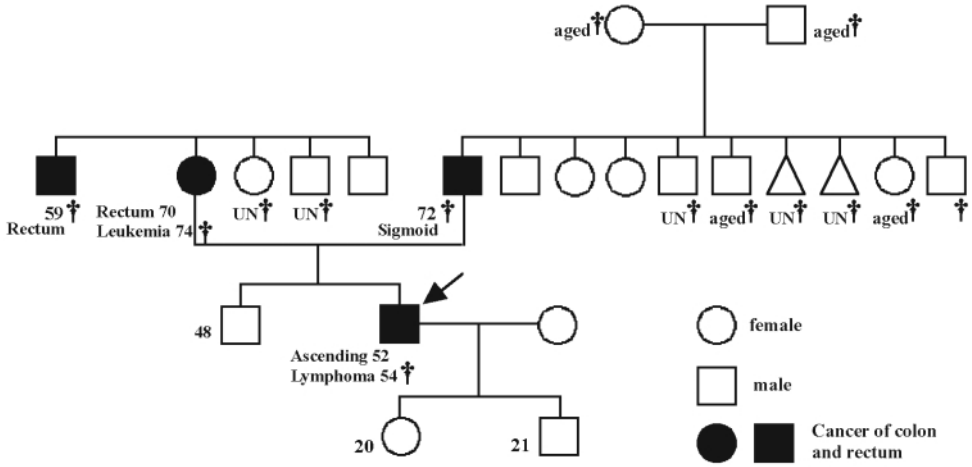
Genetic and clinical study for hereditary nonpolyposis colorectal cancer (HNPCC): toward molecular diagnosis of HNPCC

K. Hirano, Y. Takahashi, M. Mai, T. Minamoto

1. Activities toward molecular diagnosis of hereditary nonpolyposis colorectal cancer

Among the known hereditary cancers, one of the best characterized is the syndrome of hereditary nonpolyposis colorectal cancer (HNPCC), reported to comprise approximately 5-10% of all colorectal cancers. Clinically, this syndrome features multiple instances of colorectal cancer with early onset and a propensity for involvement of the right side of the colon proximal to the splenic flexure. Particularly striking is HNPCC's frequent association with cancers of extracolonic organs—endometrium, ovary, urinary tract, small intestine and stomach. Most HNPCC patients harbor a germ-line mutation in a DNA mismatch repair gene. We have clinically identified HNPCC in 5% of all colorectal cancer patients (459 cases) who underwent surgery in our Institute's hospital. The excitement as a timely topic for basic research has been somewhat diminished, however, one of our ongoing efforts is to establish a program for molecular diagnosis and clinical management of HNPCC patients, addressing ethical, legal, social, and psycho-oncological issues. A preliminary trial of a method for detecting germ-line mutations in *hMSH2* and *hMLH1* is completed here and ready for clinical application.

2. NonHodgkin's Lymphoma in a Patient with colon cancer of HNPCC - Report of A Case



Hematological malignancy has rarely been reported in association with HNPCC. We present here the case of an HNPCC patient in whom nonHodgkin's lymphoma developed after curative resection of colon cancer. Our experience with this rare case encouraged us to determine a possible relationship between the two diseases. A 52-year-old man whose family history was consistent with the criteria of HNPCC had ascending colon cancer. The tumor consisted of adenocarcinoma that was moderately differentiated with mucinous foci. Eight months after surgery, the patient developed nonHodgkin's lymphoma of T-cell origin involving ileum and lungs. Both colon cancer and lymphoma frequently showed micro-satellite DNA instability, sharing alteration in a locus of the chromosome 7 (*D7S501*). A possible association of hematological malignancy with HNPCC reported in the literature, together with a report that *MSH2*-deficient mice are susceptible to malignant lymphoma, strongly supports the finding that this patient's lymphoma was HNPCC-related. In all, this case manifested a distinct clinical course similar to that observed in an animal model that is deficient in DNA mismatch repair machinery, thus providing scientific and clinical implications for understanding the molecular basis of these tumors and for critical management of HNPCC patients, respectively.