

Gene-related cancer spectrum in families with Lynch Syndrome

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Summary

This study analysed all cancers reported in a cohort of Lynch syndrome families with a known mutation to assess the relative risk of each cancer type and explored tumour spectrums in families with mutations in different genes.

Introduction to study

Lynch syndrome (HNPCC) is an inherited condition which causes a number of different cancers. It is diagnosed by family history and the detection of a mismatch repair mutation. The lifetime risk of colon and endometrial cancers is very high. There is also an increased risk of a number of other cancer types although the relative risks of these have not yet been confirmed.

HNPCC families were recruited and subdivided dependent upon the gene involved (MSH2, MLH1 and MSH6). For each particular tumour type the odds ratio and familial relative risk was calculated. 64 families were studied who carried MSH2 mutations and an equal number with mutations in MLH1. Only 4 families with a mutation in the MSH6 gene were analysed since mutations in this gene are possibly less frequent and are less commonly diagnosed. There was an even split between total number of tumours recorded in patients from the MSH2 and MLH1 groups (338 for MSH2 and 362 for MLH1).

Colorectal Cancer

- As expected, colorectal cancer was the most common tumour type present in all families.
- Individuals with 3 or more colorectal cancers were far more common in MSH2 families than MLH1. In addition, the MSH2 families where at least one person had 3 or more colorectal cancers had a significantly different tumour spectrum to other MSH2 mutation families.
- 10 individuals were diagnosed with colorectal cancer before the age of 25, mainly in MLH1 families.
- The average age of onset of first colorectal cancer was much lower in MSH2 and MLH1 families (45 years and 44 years respectively) than MSH6 (59 years).
- There was no evidence of clustering of the age of diagnosis of colon cancer in families. It is therefore currently impossible to predict the age of onset in individuals. These data support the current practice of offering screening over the age of 25 in known or at risk MLH1 and MSH2 mutation families.

Endometrial Cancer

- Endometrial cancer was common to all 3 mutation groups although twice as common in MSH2 families.

Pancreatic Cancer

- 22 cases of pancreatic cancer were detected which were fairly evenly split between MSH2 and MLH1 families. The odds ratio was greatly increased in individuals under the age of 60.

Renal and ureterial cancer

- Some of the most significant data were found in cancers of the urological tract. There were 37 cases of renal cancer, and 13 urothelial cancers, mostly in MSH2 families, which was many times more common than expected.
- In MSH2 families where there was strong and highly significant clustering for renal cancer the specific mutation present was analysed. No features have yet been identified that distinguish the mutations present from those in other MSH2 families.

Small intestine and stomach cancer

- The odds ratio for cancer of the small intestine was greatly increased over that seen in the general population and stomach cancer also had a substantially increased odds ratio.

Breast cancer

- There was no evidence for high relative risk and clustering of breast cancer in Lynch syndrome families. There was only a slight increase in incidence when compared to the general population.
- This indicates that specialised breast cancer screening in MSH2 and MLH1 families may be unnecessary.

Overall conclusions

The study confirmed the prominence of colorectal and endometrial cancer in Lynch syndrome families. It also identified and confirmed a number of extra colonic cancers with high odds ratios compared to the general population. A broader spectrum of cancers was present in MSH2 mutation carriers compared to MLH1 mutation carriers.

Both colonic and extra-colonic cancers are diagnosed at an older age in MSH6 families. This late diagnosis with MSH6 mutations may result in families not being investigated for Lynch syndrome because their tumour spectrums do not fall into the normal pattern for analysis. These findings also suggest that cancer surveillance for MSH6 mutation families could be started later due to the delayed onset of disease.

Certain types of cancers were found to cluster within families. It may be that this is due to particular mutations although no evidence supporting this was identified in the study and further research is necessary.