HNPCC, molecular and clinical dilemmas

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Onvergeeflijk is het, dat de mensen dromen hebben
en ze niet waarmaken!
En toch, hoop vervliegt elke dag en overal
In elke kamer. Ieder bed.
Op mijn reizen heb ik dit duidelijk gezien:
Iedere ontmoeting, elk gesprek brengt mensen verder af
van wat zij willen.
Zij vertrouwen niet op wat zij zijn,
maar op hoe zij worden gezien.

Arthur Japin

Voor mijn ouders

In herinnering aan Ondiene en aan mijn patiënten die stierven aan kanker

Contents

Aims and outline of the thesis

Hereditary Non-Polyposis Colorectal Cancer (HNPCC) is the main inherited predisposition to colorectal cancer. Major features of HNPCC are colorectal and endometrial cancers. Tumours of the ovaries, stomach, small bowel, biliary tract, urinary tract, skin and brain occur at lower frequencies. Mutations in at least 4 different mismatch repair (MMR) genes are responsible for HNPCC, namely *MSH2* and *MLH1* in the majority of cases and, more rarely, *MSH6* and *PMS2*. In previous studies, *MSH2* and *MLH1* mutations were found in 45-64% of the families with HNPCC[73].

In **Chapter 2**, we questioned whether unresolved HNPCC families were due to a lack of sensitivity of *MSH2* and *MLH1* mutation detection techniques, or to mutations of *MSH6* or other genes. To this aim, we thoroughly investigated a cohort of 59 US HNPCC families, clinically selected by Prof. Henry Lynch, for the presence of point mutations and genomic rearrangements in the *MSH2*, *MLH1* and *MSH6* genes. We identified a North American founder mutation, a deletion of *MSH2* exons 1-6, common to 12% of the cohort. The birthplace of the eldest ancestor carrying this founder mutation could be traced back to 18th century Germany. Additionally we detected a10-Mb paracentric inversion inactivating the *MSH2* gene.

The clinical cancer phenotype associated with mutations of *MSH6* is less well defined when compared to *MLH1* and *MSH2*. In **Chapter 3.1** and **3.2**, we analysed a large Dutch pedigree and a cohort of 20 *MSH6* mutation positive families to calculate the cumulative age-specific risks of colorectal cancer and endometrial cancer, and compared the outcomes with the cancer risks in *MSH2* and *MLH1* mutation carriers. Based on the findings, we formulated *MSH6*-tailored screenings and preventative options.

The detection of a germline mutation in *MSH2*, *MLH1* or *MSH6* in an individual enables predictive genetic testing of at-risk relatives. In **Chapter 3.3**, we analysed the demand for genetic testing of members of 18 Dutch families with a known mutation in *MSH2*, *MLH1* or *MSH6*. Regular colonoscopy reduces the overall mortality by 65% in members of families with HNPCC [117]. It is therefore of utmost importance that mutation carriers adhere to surveillance protocols. We evaluated (**Chapter 3.4**) the impact of genetic testing on the adherence to cancer surveillance protocols. Simultaneously, we investigated the satisfaction with cancer screening and genetic testing procedures in 70 proven mutation carriers at the long term.

The studies described in this thesis contribute to the understanding of the molecular genetic aetiology of HNPCC, and add to evidence-based clinical care for HNPCC families.