HISTOPATHOLOGICAL AND GENETIC ASPECTS OF COLORECTAL CANCER

AKADEMISK AVHANDLING
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Abstract

Colorectal cancer (CRC) is the third most common form of cancer in Sweden. The etiology of CRC is considered to be influenced by environmental risk factors on a background of constitutional and acquired genetic variations. It is estimated that inherited susceptibility accounts for approximately 35% of all CRC cases. The well-known high-risk syndromes familial adenomatous polyposis and Lynch syndrome, however, explain less than 5%. The remaining part of the “genetic” group is contributed by risk factors of much smaller magnitude, such as mutations in several low-risk alleles. Genome-wide association studies have identified multiple genetic loci and single nucleotide polymorphisms (SNPs) associated with an increased or decreased risk of CRC. Also, the histopathological profile of CRC shows considerable variation in relation to sex, age, tumor location, family history and mode of presentation, which could speak for different mechanisms of tumor development in different groups of patients.

The aim of paper I was to determine whether 11 newly identified genetic susceptibility loci were associated with tumor morphology, to confirm them as distinct and etiologically different risk factors in colorectal carcinogenesis. To that end, we analyzed 15 histological features in 1572 cases of consecutively operated CRCs during the years 2004-2006. Of the tested loci, five SNPs were significantly associated with morphological parameters such as poor differentiation, mucin production and decreased frequency of Crohn-like peritumoral reaction and desmoplastic response (p=0.004). The results are consistent with pathogenic variants in several loci acting in distinct CRC morphogenic pathways.

The aim of paper II was to provide a systematic histopathological characterization of CRC in the patient material above by comparing the morphology of tumors in men and women, in different age groups, in different anatomical locations, and in sporadic and familial cases, in order to isolate the effects of these four factors. Women had significantly more tumors with a high level of tumor infiltrating lymphocytes compared to men (p=0.002). Patients aged <60 years had less often multiple tumors but more often perineural invasion, infiltrative tumor margin (p<0.0001) and high AJCC-, T- and N-stage tumors (p<0.0001 for AJCC stage III) compared to patients >75 years. The results indicate that younger patients have a more aggressive disease. Most histological features showed a significant difference between left colon and rectum compared to right colon. Tumors in left colon and rectum were smaller and showed less often poor-, mucinous- or medullary differentiation or a circumscribed tumor margin (p<0.0001 for most features). Also, they were generally of a lower AJCC- and T-stage compared to right-sided lesions. The majority of features showed a gradient from right colon to rectum. The findings are in line with tumors in different locations having different genetic and embryological backgrounds as well as developing in different physiological settings. The only difference between the sporadic and familial group was seen in vascular invasion which was more common among the familial cases (p=0.012).

The aim of paper III was to compare the clinicopathological profile of emergency and elective cases of CRC in relation to sex, age groups, location, and family history of CRC. In a multivariate analysis of 976 tumors from Stockholm County emergency cases more often showed multiple tumors, signet-ring cells, desmoplasia, vascular and perineural invasion, infiltrative tumor margin and high AJCC-, T- and N-stage tumors (p<0.0001 for several features). The findings could speak for emergency CRCs being an inherently different group of tumors with a more aggressive biology.

The aim of paper IV was to use the family history of cancer in 1720 patients with CRC together with genotyping and tumor morphology in order to find support for and define new CRC syndromes. There were significantly more cancers (other than CRCs) in the family history of the familial CRC cases compared to the sporadic CRC cases (p<0.001). There were also more bladder, prostate and gastric cancers as well as melanomas. One SNP, previously associated with both CRC and prostate cancer, was confirmed to be more common in families with CRC + prostate cancer. There were some support for different morphological profiles in four of the five tested syndromes with p=0.010 for an association between CRC + gastric cancer and Crohn-like peritumoral reaction.

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