Carmen Lilla
Dr. sc. hum.

Genetic polymorphisms in Phase II-metabolizing enzymes and susceptibility to colorectal cancer

Geboren am 19.08.1977 in Friedberg/Bayern
Staatsexamen der Fachrichtung Pharmazie am 19.06.2002 an der Ludwig-Maximilians-Universität München

Promotionsfach: Deutsches Krebsforschungszentrum
Doktormutter: Prof. Dr. sc. hum. Jenny Chang-Claude

Colorectal cancer is the second most common cancer among both males and females in Germany. The vast majority of cancers are thought to be attributable to the complex interplay of environmental factors and genetic predisposition. Tobacco smoking as well as cooking meat at high temperatures gives rise to a plethora of procarcinogens, such as heterocyclic aromatic amines or polycyclic aromatic hydrocarbons, that may be activated to their ultimate carcinogenic forms *in vivo*. Thus, genetically determined differences in the metabolism of xenobiotics may influence individual susceptibility to disease. To further understand the complex pathways leading to colorectal cancer, the influence of genetic polymorphisms in Phase II-metabolizing enzymes on colorectal cancer risk associated with tobacco smoke and meat consumption was investigated.

A population-based case-control study of colorectal cancer was conducted in Southern Germany. Patients with incident invasive colorectal cancer and controls matched according to gender, age and residence were recruited between January 2003 and June 2004. A total of 507 patients and 604 controls provided both detailed risk factor information during a personal interview and a biological sample. The interview included a detailed assessment of lifetime exposure to both active and passive smoking. DNA was isolated from either blood or mouthwash samples and genotyped for common polymorphisms in the N-acetyltransferase (*NAT*) 1 and 2 genes, glutathione-S-transferase (*GST*) M1 and T1 genes and the sulfotransferase (*SULT*) 1A1 gene. Genotyping was performed using a multiplex PCR method and capillary based real-time PCR followed by melting curve analysis. Multivariate conditional regression analysis was carried out to estimate the association between genotypes, environmental exposures and colorectal cancer risk, accounting for previous endoscopic screening, use of non-steroidal anti-inflammatory drugs, family history of colorectal cancer, alcohol consumption, body mass index and education level.

Active smoking at a high intensity and for a long duration was associated with a moderately increased risk of colorectal cancer. More precisely, accumulation of 30 or more pack-years increased the risk of colorectal cancer by 50% compared to non-smokers. In addition, very frequent consumption of red or processed meat conferred an increased risk when compared to individuals consuming meat less than once per week (OR 1.7, 95% CI 0.9-3.0 and OR 1.6, 1.0-2.4, respectively). Overall, exposure to environmental tobacco smoke, also referred to as passive smoking, was not associated with an elevated risk of colorectal cancer in the present study. None of the genetic polymorphisms under investigation was an independent risk factor for colorectal cancer. However, the findings point towards a modifying effect of certain genotypes. Risk associated with frequent red meat consumption

was more pronounced among NAT2 fast acetylators than among NAT2 slow acetylators (ORs were 2.1, 95% CI 0.8-6.0 and 1.7, 0.8-3.7, respectively). The joint analysis of *NAT1* and *NAT2* genotypes strengthened the notion of increased susceptibility to meat-related carcinogens among individuals with greater acetylation capacity (OR 2.5, 95% CI 1.1-6.0 for 'NAT intermediate/fast acetylators' vs. OR 1.3, 0.6-1.5 for 'NAT slow acetylators'), but the test for interaction did not reach statistical significance (p=0.15). *SULT1A1*1/*1* genotype may also contribute to individual susceptibility to carcinogens present in red meat (p for interaction 0.10). Exposure to environmental tobacco smoke in adulthood conferred a 2-fold increased risk among NAT2 fast acetylators but was not associated with colorectal cancer risk among NAT2 slow acetylators. In the joint analysis of *NAT1* and *NAT2* genotypes, high exposure to active smoking appeared to be a stronger risk factor for NAT slow acetylators than for NAT intermediate or fast acetylators (OR for 31+ pack-years 1.9, 95% CI 1.0-3.7 and OR 1.3, 0.7-2.4, respectively). In accordance with previous studies, *GSTM1* or *GSTT1* null genotypes did not predispose to colorectal cancer associated with smoking or red meat consumption.

The findings of increased susceptibility to meat-related carcinogens among NAT fast acetylators support the hypothesis that bioactivation of heterocyclic aromatic amines by NATs may play a role in colorectal carcinogenesis. It appears that *NAT1* and *NAT2* genotypes contribute jointly to individual susceptibility. The observation that an association between passive smoking and colorectal cancer risk was only apparent among NAT2 fast acetylators may indicate that passive smoking is only a risk factor among more susceptible individuals.

Due to limitations in sample size, the present study had adequate power to detect only strong gene-environment interactions (OR for interaction>2.0). The study did not have sufficient power to allow for subgroup analyses by gender or cancer site, emphasizing the need for large molecular epidemiological studies. Further studies may help to determine the relevant carcinogens in complex mixtures, such as tobacco smoke, and render possible the identification of high-risk groups in the population, which may provide a basis for tailored prevention and therapy of colorectal cancer in the future.

In conclusion, the study strengthens the evidence that tobacco smoking and frequent consumption of red and processed meat increase the risk of colorectal cancer. Some individuals may be more susceptible to environmental carcinogens due to genetically determined differences in Phase II-metabolism.