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**Genetic polymorphisms in cancer-related pathways in breast and colorectal cancers**

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The aim of this study was to investigate polymorphisms in cancer-related pathways in breast and colorectal cancers (CRCs). Dysregulation of Wnt/β-catenin signaling pathway, apoptotic pathway and tumor suppressors play a major role in breast and colorectal carcinogenesis. In this study, we therefore investigated the effects of polymorphisms in the candidate genes involved in the above mentioned pathways. The investigation was based on the case-control studies using a German breast cancer and a German CRC study population. Candidate single nucleotide polymorphisms (SNPs) or functional SNPs were selected based on the evidence from literature that reported functional effects, *in silico* analysis and from the NCBI SNP database.

Analysis of the Wnt/β-catenin signaling pathway gene polymorphisms in *AXIN2* and *WNT5B* with "breast cancer" risk did not show any significant association. However, *TCF7L2* intronic SNP rs12255372 was significantly associated with breast cancer risk. In an earlier study, *TCF7L2* intronic SNP rs12255372 and microsatellite marker DG10S478 in *TCFL2* has been shown to be associated with type 2 diabetes and rs12255372 has been shown to be perfectly correlated ($r^2 = 0.95$) with the DG10S478. Since the exonic mutations have been ruled out in the earlier study, it can be assumed that the linked repeat polymorphism DG10S478 is causative itself or that DG10S478 and rs12255372 are in strong linkage disequilibrium with a functional variant affecting transcription, splicing or message stability.

Analysis of the Wnt/β-catenin signaling pathway gene polymorphisms in *DKK3*, *FZD6*, *LRP5* and *LRP6* with "CRC" risk did not show any significant association with CRC risk.

However, FRZB (alias sFRP3) Gly324 variant was significantly associated with an increased risk of CRC. In an earlier study, Gly324 variant has been shown to attenuate the ability of FRZB to antagonize Wnt signaling. The observed risk effect of the Gly324 variant is therefore biologically meaningful.

Analysis of the apoptotic gene polymorphisms in *CD44*, *DCC*, *NFκB1*, *TLR4*, *PTPN13*, *PARP2*, *PARP4* and *PARP9* with "breast cancer" risk did not show any significant association. However, a haplotype of DR4 (alias TNFRSF10A) showed a significant association with breast cancer risk. DR4 Thr209Arg and DR4 Glu228Ala by itself did not show any significant association with breast cancer risk. But haplotype analysis of DR4 Thr209Arg and DR4 Glu228Ala revealed 626C-683C (Thr209-Ala228) haplotype to be significantly associated with breast cancer risk. Since the haplotype 626C-683C (Thr209-Ala228) is very rare, it represents a moderate amount of risk regarding familial breast cancer in general. Both the DR4 SNPs investigated reside next to the DR4 ligand TRAIL-binding domain. The observed association indicates that the 626C-683C (Thr209-Ala228) haplotype might be functionally relevant by altering TRAIL binding or that 626C-683C (Thr209-Ala228) might be in linkage disequilibrium with a functional variant residing in *DR4* or in neighbouring genes.

Analysis of the apoptotic gene polymorphisms in *DCC*, *PTPN13* and *NFκB1* did not show any significant association with "CRC". However, DR4 Thr209Arg showed a significant association with a reduced CRC risk for heterozygotes. Stratification by sex and age revealed a significant association of DR4 Thr209Arg with a reduced CRC risk for male heterozygotes and for Arg209 carriers of $\geq$ 65 years of age. Arg209 was also significantly associated with rectal cancer in a protective manner. Regarding DR4 Glu228Ala, this variant showed a significant association with an increased CRC risk for females in an allele dose-dependent manner and the associated risk increased with advanced CRC stages. Similar to the effect observed with breast cancer, haplotype analysis of DR4 Thr209Arg and DR4 Glu228Ala revealed 626C-683C (Thr209-Ala228) haplotype to be associated with CRC risk but only with a borderline significance. Further investigation with a larger study population is necessary to confirm these results.

Another apoptosis related gene *CD44* also showed an association with "CRC". CD44 Thr479Ile showed a significant association with an increased risk for CRC. According to *in silico* analysis, Thr479Ile amino acid substitution was predicted to be possibly damaging as well as affecting the secondary structure of the protein. Therefore, Thr479Ile should be analyzed further using a larger study population to confirm these results.

Analysis of the tumor suppressor gene polymorphisms in *STK11IP* did not show any significant association with breast cancer and CRC risks. Analysis of polymorphism in *PPP1R3A* and *CDX2* did not show any significant association with breast cancer and CRC respectively.

Identification of new predisposing gene variants and gene variant combinations are important for the understanding the etiology of a disease, for risk estimation and might give hints for new drug target. Therefore, our findings might pave the way for a better understanding of the pathogenesis of breast cancer and CRC susceptibility.