

Estrogen Receptor β Genes Associated with Colorectal Cancer Mortality

January 21, 2013

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Sex hormones are thought to play a role in the development of colorectal cancer. Several sex hormone receptors, including androgen, progesterone, and estrogen receptors, are expressed in the digestive tract. These receptors are proteins that, upon activation by a sex hormone, bind to DNA and regulate important cellular functions. Estrogen receptor β (ER β) in particular is abundantly expressed in the gut. Colon cancer tissue often displays a loss of ER expression, and tumors with a more severe loss of expression are associated with a poorer prognosis. Previous studies have investigated whether certain hormone receptor gene variants are associated with colorectal cancer risk. These studies were, at most, weakly suggestive of a link between certain single nucleotide polymorphisms (SNPs) within sex hormone receptor genes and colorectal cancer risk. However, less is known about how these SNPs may affect colorectal cancer survival.

Michael Passarelli, Dr. Polly Newcomb, and colleagues in the Public Health Sciences Division addressed this question in a large-scale SNP-based study of 729 postmenopausal women diagnosed with colorectal cancer between 1997 and 2002. Participants (ages 50-74 years) were residents of the 13 counties that make up the Seattle-Puget Sound SEER cancer registry. The National Death Index was used to ascertain deaths and causes of death through December 31, 2009. Participants completed an interview, and underwent genotyping to assess whether 99 different sex hormone SNPs were associated with survival. 244 deaths, including 161 due to colorectal cancer, occurred over a median of 6.6 years of follow-up. A subset of SNPs (n=20) were identified for typing in a separate, replication population, which included 1,729 women from the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) to confirm the initial finding.

Minor alleles (less common variants) of 3 SNPs, all in the 5' promoter region of the gene encoding ER β , were associated with better survival, both overall and CRC-specific survival (rs2987983, rs3020443, and rs2978381). For example, women with rs2987983 were 23% less likely to die of colorectal cancer in the initial study (95% CI: 0.60-0.99) and 21% less likely in the replication analysis (95% CI: 0.64-0.98). Other SNPs included in this study, including SNPs of androgen, progesterone, and estrogen receptors, were not associated with survival.

Earlier studies have shown that ER β may influence tumor growth and progression by inducing apoptosis, preventing metastasis, and regulating inflammation. This study adds to the current understanding of ER β regulation by suggesting that certain SNPs in the promoter region of the gene encoding ER β influence the protein's function in clinically relevant ways. Additional research is needed to further elucidate these mechanisms and their role in colorectal cancer progression.

[Passarelli MN, Phipps AI, Potter JD, Makar KW, Coghill AE, Wernli KJ, White E, Chan AT, Hutter CM, Peters U, Newcomb PA](#). 2012. Common single nucleotide polymorphisms in the estrogen receptor β promoter are associated with colorectal cancer survival in postmenopausal women. *Cancer Res*. 2012 Nov 13. [Epub ahead of print]



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A representation of the structure of estrogen receptor beta (ER β)