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Genetic polymorphisms in selenoprotein P gene affect colorectal, prostate and breast cancer risk

Catherine Méplan[1,2] and John Hesketh[1,2]
[1]*Institute for Cell and Molecular Biosciences and* [2]*Human Nutrition Research Centre, Newcastle University, Newcastle-upon-Tyne, NE2 4HH, UK*

Selenium (Se) is incorporated into various selenoproteins which mediate its biological roles. Selenoproteins play a major role in oxidative and ER stress response and mitochondrial function. Homeostatic dysregulation of these mechanisms is implicated in many age-related disorders including cancer. Suboptimal selenium status, as found in Europe, has been associated with increased cancer incidence. Selenoprotein expression and activity depends on bioavailability of Se. Selenoprotein P (SePP) is the major plasma transporter of Se and it delivers hepatic selenium to tissues to support the synthesis of other selenoproteins. Two single nucleotide polymorphisms (SNP) that affect SePP plasma isoform pattern and expression of other selenoproteins were identified in the SEPP1 gene (rs3877899, rs7579)[(1,2)], suggesting that these SNPs affected Se bioavailability for the synthesis of other selenoproteins. Rs7579 induces a G/A base change in the 3′ untranslated region of *SEPP1* mRNA in a region close to a regulatory element required for SePP synthesis and rs3877899 induces an amino acid change at position 234 from Alanine to Threonine. To determine the impact of these SNPS on cancer risk, we compared their effects on colorectal, prostate and breast cancer risk using data from three European case-control cohorts. There was an association between rs7579 genotype in *SEPP1* and prostate and colorectal cancer risk in males, with men homozygous for the rare allele (AA) having an increased risk of developing prostate cancer (OR, 1.72; 95% CI, 0.99–2.98) and colorectal cancer (OR, 1.67; 95% CI, 1.07–2.60)[(3,4)]. In addition, in a recent collaboration we found that females homozygous for the rare allele (AA) for rs3877899 showed a dramatically reduced risk of developing breast cancer. A non-significant reduction of prostate cancer risk was also observed in homozygous AA for rs3877899 (OR, 0.66; 95% CI, 0.31–1.39). However in another population, a genetic interaction was found between rs3877899 and a SNP in the *SOD2*, encoding for the mitochondrial superoxide dismutase, with an increased prostate cancer risk in male smokers homozygous AA who were *SOD2*-Val16 homozygotes[(5)]. Taken together our studies suggest that genotype for these two *SEPP1* variants affects cancer risk.

Further studies of larger cohorts and incorporating both genotype and Se status are needed to confirm these effects. Since selenoproteins are essential to many stress responses, and their expression is regulated by dietary Se intake, they represent prime targets for modulating an individual's susceptibility to stressors by changes in diet. Factors, such as *SEPP1* genetic polymorphisms, which influence Se bioavailability, could impact on the capacity of an individual to respond to stressors thus affecting cancer risk.

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