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Ornithine decarboxylase (*Odc*)-1 gene polymorphism effects on baseline tissue polyamine levels and adenoma recurrence in a randomized phase III adenoma prevention trial of DFMO + sulindac versus placebo

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Abstract

1502

Background: The *Odc* G315A single nucleotide polymorphism (SNP) affects *Odc* transcription and favorably modifies aspirin's effect on colorectal adenoma risk. Treatment with the polyamine-inhibitory regimen difluoromethylornithine (DFMO) and sulindac has been shown to markedly decrease adenoma recurrence compared to placebo. Here we investigate modifying effects of the *Odc* G315A SNP on baseline tissue polyamine content and polyp recurrence after treatment with DFMO + sulindac or placebo. **Methods:** Data from the randomized phase III DFMO (500mg daily) + sulindac (150mg daily) colorectal adenoma prevention trial were analyzed. *Odc* genotyping was performed on patient-derived genomic DNA samples using allele-specific TaqMan probes. Baseline rectal tissue polyamine content was determined via HPLC. Clinicopathologic data were compared after stratification by genotype. Fisher's exact test or χ^2 tests for independence were used for comparisons of categorical variables. Two-tailed t-tests or Kruskal-Wallis nonparametric analysis of variance were used for numerical comparisons between groups. **Results:** Data were available for 122 of 375 study patients. *Odc* genotype distribution was 54% GG, 5% AA, 41% GA. Patients with any *Odc* A- allele (AA/GA) were similar in age, gender, race, and prior aspirin use across treatment arms, as were *Odc* GG patients. *Odc* GG vs AA/GA patients had significantly higher median baseline rectal tissue putrescine (0.52 vs 0.31 nmol/mg protein, P=0.046) and spermidine (2.10 vs 1.65 nmol/mg protein, P=0.011) content. Among *Odc* AA/GA patients, 7/26 patients (27%) had recurrent adenoma in the DFMO + sulindac arm vs 14/30 patients (47%) in the placebo arm (P=0.13, absolute risk difference=20%). Among *Odc* GG patients, 6/39 patients (15%) had recurrent adenoma in the DFMO + sulindac arm compared with 14/27 (52%) placebo patients (P=0.002, absolute risk difference=37%). **Conclusions:** DFMO + sulindac treatment lowers the incidence of recurrent adenomata among adenoma patients, with pronounced effects observed among *Odc* homozygous GG patients. This may be related to baseline tissue polyamine differences across these genetically-defined groups.

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