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Authors
Zell, JA
McLaren, CE
Gerner, EW
et al.

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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

J. A. Zell, C. E. McLaren, E. W. Gerner, F. L. Meyskens

Abstract

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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 $\chi^2$ 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.

No significant financial relationships to disclose.