

# Abstract

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## Associations of calcium and vitamin D with E-cadherin and $\beta$ -catenin expression in normal-appearing rectal tissue; markers of adenomatous polyps II (MAP II) case-control study

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**BACKGROUND:** Colorectal cancer is the second leading cause of cancer deaths in the United States. Despite advances in screening methods and treatments, mortality attributed to the disease has declined minimally over the last 30 years.

**OBJECTIVE:** There are no accepted biomarkers of risk for colorectal cancer even though the molecular basis of the disease is becoming clearer. E-cadherin, a calcium-dependent cell-cell adhesion transmembrane glycoprotein, is essential for maintaining cellular organization, morphology, and migration.  $\beta$ -catenin, an important component of the Wnt pathway that serves as a transcriptional coactivator of cellular proliferation, dimerizes with  $\alpha$ -catenin which then binds to E-cadherin. There is mounting evidence for antiproliferative, pro-differentiating, and pro-apoptotic effects of calcium and vitamin D on the gastrointestinal epithelium. Calcium and vitamin D stimulate E-cadherin expression and  $\beta$ -catenin translocation from the nucleus to the cell membrane where it binds with E-cadherin. An influx of intracellular calcium has also been associated with triggering proteolytic cleaving of E-cadherin.

**DESIGN:** In a colonoscopy-based, pilot case-control study of incident, sporadic colorectal adenoma (n = 49 cases, 154 controls) to investigate E-cadherin and  $\beta$ -catenin expression as possible biomarkers of risk for colorectal cancer, biopsies from normal-appearing rectal mucosa from a random selection of cases and controls (E-cadherin: 40 cases, 45 controls;  $\beta$ -catenin: 37 cases, 41 controls) were immunohistochemically processed for E-cadherin and  $\beta$ -catenin. E-cadherin and  $\beta$ -catenin expression was assessed by quantifying their staining intensities with a novel image analysis program.

**RESULTS:** Plots of E-cadherin and  $\beta$ -catenin expression from the base of rectal crypts to the apex revealed nearly identical shapes and intensities for E-cadherin and  $\beta$ -catenin, suggesting a tight association between the two markers. Although mean overall expression of neither E-cadherin nor  $\beta$ -catenin differed significantly between cases and controls (0.5%, [p = 0.96], and 6.9% [p = 0.17], respectively), expression plots stratified by total calcium and vitamin D consumption suggested that expression of both  $\beta$ -catenin and E-cadherin (especially E-cadherin) in persons who were consuming high amounts of calcium and vitamin D were substantially different from those in persons who were consuming low amounts of both nutrients together or high amounts of only one nutrient or the other alone.

**CONCLUSION:** These preliminary data suggest that E-cadherin and  $\beta$ -catenin expression may be modified by calcium and vitamin D intakes. Further investigation into the potential of E-cadherin and  $\beta$ -catenin as modifiable biomarkers of risk for colorectal cancer is warranted.