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**File: ■ Grapes (*Vitis vinifera*, Vitaceae)  
■ Colorectal Cancer  
■ Wnt Signaling**

**HC 081522-538**

**Date: February 15, 2016**

**RE: Daily Grape Consumption Decreases Gene Expression Associated with Cell Signaling and Proliferation in Colon Cells of Healthy, Adult Subjects**

Holcombe RF, Martinez M, Planutis K, Planutiene M. Effects of a grape-supplemented diet on proliferation and Wnt signaling in the colonic mucosa are greatest for those over age 50 and with high arginine consumption. *Nutr J.* June 2015;14:62. doi: 10.1186/s12937-015-0050-z.

Numerous studies have shown that the risk of developing colorectal cancer (CRC) decreases with increased consumption of fruits and vegetables. Grapes (*Vitis vinifera*, Vitaceae) contain resveratrol, which has been shown to alter cellular gene expression. In particular, resveratrol has been shown to suppress Wnt signaling in colon cancer cells and inhibit intestinal tumor cell growth in several cell and animal models. Studies in healthy, human subjects also have shown that Wnt signaling is downregulated with resveratrol intake. However, there is some debate over the bioavailability of resveratrol in grapes and the effect of grapes on biomarkers of CRC. The goal of this randomized study was to measure the effect of daily grape intake on Wnt signaling and Ki67 protein concentration in colonic mucosa.

Thirty nondiabetic, healthy subjects were enrolled in this 4-week study at the University of California, Irvine. Subjects were randomly divided into 1 of 3 groups who consumed either 1/3 lb, 2/3 lb, or 1 lb (0.15 kg, 0.30 kg, or 0.45 kg, respectively) of grapes per day. Subjects were given a digital kitchen scale and a voucher redeemable at a local grocery store for red, seedless grapes. For the first 2 weeks of the study, subjects were placed on a low-resveratrol diet and consumed no grapes. During the second 2 weeks of the study, subjects consumed the daily allocation of grapes. Subjects recorded their daily food intake for 24 hours for 3 days during each of the 2-week periods. Sigmoidoscopies and rectal mucosal biopsies were conducted on day 15 and day 30. Quantitative real-time polymerase chain reaction (PCR) analyses were performed on the biopsies to measure changes in messenger RNA (mRNA) expression associated with cell proliferation and Wnt signaling. Markers included cyclin D1, AXIN2, cMYC, and CD133. The percentage of cells expressing the proliferation protein, Ki67, also was measured in the biopsies. Data were analyzed with 1-way analysis of variance, Wilcoxon matched-pairs signed-rank tests, unpaired t-tests, and linear regression.

The average age of the subjects was  $43.28 \pm 2.28$ . Nine men and 21 women completed the study. No differences were found among the groups in the parameters measured, so data from the groups were analyzed together. Most subjects lost weight during the grape consumption phase of the study, and this weight loss was significant ( $P < 0.005$ ). Cyclin D1, CD133 expression, and Ki67 levels decreased significantly in the biopsies pre-grape to post-grape ( $P < 0.01$ ,  $P = 0.02$ , and  $P < 0.005$ , respectively). This change in expression was completely dependent on age. Subjects under the age of 50 had no significant change in these markers, whereas subjects over the age of 50 had large, significant decreases. Data were also analyzed by arginine consumption level because higher arginine intake has been associated with an increased risk of developing CRC. Twenty-one subjects had arginine intake levels below the average of 4-5 g/d, whereas 9 subjects had arginine intake levels above average. In the pre-grape phase of the study, cyclin D1, AXIN2, cMYC, and CD133 were all significantly higher in subjects with above average arginine intake ( $P < 0.05$ ,  $P < 0.01$ ,  $P < 0.005$ , and  $P < 0.05$ , respectively). In addition, there was a large decrease in cyclin D1 with grape consumption in subjects with high arginine intake.

Daily grape consumption resulted in decreased gene expression associated with Wnt signaling and cell proliferation in colonic mucosa cells. The effects of grape consumption were found to be most profound in older subjects. In other studies, older subjects have been found to have increased colorectal inflammation and a decreased regenerative capacity of the colonic mucosa than younger subjects. These changes with age may be related to the increased incidence of CRC in individuals over the age of 50. The authors hypothesize that grape consumption may help reduce the risk of CRC in older individuals. Expression of cell proliferation was also significantly higher in subjects who had a higher than average arginine intake, and grape consumption helped reduce the expression of cyclin D1. No relationship was found between the amount of grapes consumed daily and signaling and proliferation markers. This may have been due to the very small sample size in each group.

—*Cheryl McCutchan, PhD*

Referenced article can be accessed at <http://www.nutritionj.com/content/14/1/62>.

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