Mammary Cancer Chemoprevention with the Polyphenols Genistein and Resveratrol

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Despite recent advances in therapeutic treatments, breast cancer remains a devastating disease and a leading killer among female cancers. There is, and should be, a strong effort to work toward the prevention of this disease. It is well accepted that environmental factors, especially diet and lifestyle, play critical roles in determining one's risk for breast cancer. Two dietary polyphenols that have received much attention for their health benefits, including anti-cancer properties, are the soy isoflavone genistein and resveratrol, a phytoalexin found in red grapes and red wine. We have hypothesized that these two polyphenols given alone or in combination could suppress mammary cancer. Initially, we determined that genistein and resveratrol given from birth onward at 250 mg/kg and 1000 mg/kg AIN-76A diet, respectively can suppress dimethylbenz(a)anthracene (60 mg DMBA/kg body weight at day 50)- induced mammary carcinogenesis in female Sprague Dawley rats. Next, we treated rats from birth throughout life with one of five treatments: 1) Control (AIN-76A diet only), 2) 333 mg resveratrol/kg diet, 3) 83 mg genistein/kg diet, 4) 333 mg resveratrol + 25 mg genistein/kg diet, or 5) 100 mg resveratrol + 83 mg genistein/kg diet (30/group). A significant reduction in mammary tumor multiplicity and a significant increase in tumor latency were observed in all four polyphenol treatments. Interestingly, adding a low dose (25 mg/kg diet) of genistein to the resveratrol treatment, we observed a further reduction in tumor multiplicity. As to the mechanisms of chemoprevention, analysis of mammary whole mounts revealed that genistein enhanced gland differentiation and reduced cell proliferation. Resveratrol significantly decreased epithelial cell proliferation and increased apoptosis in mammary terminal ductal structures, the most susceptible mammary structure to carcinogenesis. Microarray analysis at 50 days postpartum revealed 386 and 470 genes that were differentially regulated between the resveratrol- and genistein-treated rats (respectively) versus control rats at a p value ≤ 0.01. Many of these genes provide possible mechanisms to our findings on altered mammary gland differentiation, cell proliferation, apoptosis, and a reduction in carcinogenesis. Resveratrol treatment modulated many survival and apoptosis-related genes including Akt, several cyclin-dependant kinases, and Bad. Genistein in the diet affected several growth factor receptors including growth hormone receptor, IGF-2 receptor, and PPAR delta and other genes such as p53 and Bcl-2. The polyphenols genistein and resveratrol, alone and in combination, suppressed mammary tumorigenesis by modulating mammary gland differentiation and epithelial cell proliferation/apoptosis. More elucidation of these mechanisms should allow the use of these polyphenols in clinical trials and to prevent breast cancer. (Supported by NIH-NCI-P20-CA93753, DAMD17-00-1-0119, and DOD-BC043793)