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## Effects of black cohosh on mammary tumor development and progression in MMTV-neu transgenic mice

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Although, hormone replacement therapies are effective for treating the symptoms associated with menopause, the fear of increased risk of breast cancer has induced many women to look for alternative therapies. Recent studies have heightened this fear, leading to recommendations for women to abandon the use of estrogen-progestin replacement therapies and chose alternative therapies, such as black cohosh, for symptom relief. Many women who take botanical therapies like black cohosh, infer they are safe since they are natural products and have unencumbered availability on drug store shelves. However, in truth, there is very little information on safety of black cohosh, especially regarding cancer risk. Since black cohosh may influence estrogen-dependent responses, it could have the potential to modify the development of hormonally dependent cancers, such as breast cancer. Therefore, in this study, we investigated whether black cohosh alters the risk of developing mammary cancer using the MMTV-neu transgenic mouse model. In this model, the female mice develop primary and metastatic mammary tumors through the spontaneous activation of the proto-oncogene neu (erbB2, HER2), the most common oncogene in breast cancer. Black cohosh was provided via the diet to mimic the oral route of delivery in women (dosage was 40 mg/1800 calories of diet; comparable to women receiving 40 mg/day). The sexually mature females were fed the black cohosh diet from 2 months of age until the maximum age of 16 months. Black cohosh did not alter the latency or incidence of mammary tumors compared to MMTV-neu females maintained on the control diet. The lack of effect on mammary tumor development suggests that black cohosh would not beneficially or adversely modify a woman's risk of developing breast cancer. In contrast to its lack of effect on primary mammary tumor development, black cohosh negatively influenced progression to metastatic disease. In black cohosh-treated females, the percentage of mice with detectable lung tumors at necropsy was increased compared to those on the control diet (27.1%, n=96, versus 10.9%, n=110, of females with primary mammary tumors). In addition, the number of lung tumors/female was increased after long-term exposure to black cohosh. Since most lung metastases in this model are detected by histology versus by gross inspection at necropsy, the ongoing analysis of metastatic lesions by histopathology may help us determine whether black cohosh is accelerating the development of metastatic disease or is increasing its incidence. The results of this study suggest that black cohosh is not a safe alternative menopausal therapy for breast cancer patients and may also be undesirable for women that could have undetected breast tumors. Supported by the Susan G. Komen Breast Cancer Foundation

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