

Position on Black Cohosh Safety

Jeffrey Bland, Ph.D. FACN, CNS
President and Chief Science Officer
Metagenics, Inc.
September 2, 2003

Based on findings from the Women's Health Initiative, the United States Preventive Services Task Force published a recommendation against the routine use of hormone replacement therapy (HRT) for the prevention of chronic conditions in postmenopausal women.¹ This announcement, coupled with the awareness that there appears to be an increased incidence of breast cancer associated with estrogen use,¹ has caused many women to abandon HRT and look for safe and effective non-hormonal solutions for menopausal symptoms.

One of the most popular and well-researched non-hormonal options is black cohosh rhizome (*Actaea racemosa* L., formerly *Cimicifuga racemosa* L.), an herb native to eastern North America. In the year 2001, black cohosh rated fourteenth on the best-sellers list of the U.S. herb market.² Black cohosh has a history of use among Native Americans for female complaints and other conditions related to respiratory, nervous system, and joint function. Nineteenth century eclectic physicians in the U.S. began to investigate and recommend various preparations of black cohosh for a wide range of similar conditions.³ The contemporary use of black cohosh primarily targets menopausal symptom relief, which is owing to German research spanning almost five decades. Today, ethanolic and isopropanolic extracts of black cohosh containing specified levels of triterpene glycosides are the most widely studied for menopausal complaints. Its prevalence of use has justified the need to critically evaluate its safety profile, particularly for women in whom HRT is contraindicated.

Black Cohosh Safety in Women at High Risk of Breast Cancer

In July 2003, the journal *Menopause* published a review article entitled "Critical evaluation of the safety of *Cimicifuga racemosa* in menopause symptom relief."⁴ The lead author was Tieraona Low Dog, Clinical Assistant Professor of Family and Community Medicine at the University of New Mexico Medical Center and an advisor to the National Institutes of Health Center for Complementary and Alternative Medicine. This study reported the results of a comprehensive review on the safety of black cohosh, with a focus on women in whom HRT is contraindicated. For this analysis, the authors reviewed an extensive amount of literature, including all published preclinical and clinical studies on the safety of various forms of black cohosh, the FDA and World Health Organization adverse-event reporting systems, monographs, compendia, foreign literature, and historical anecdotal reports. Results from uncontrolled reports, post-marketing surveillance, and human clinical trials of more than 2,800 patients demonstrate a low incidence of adverse events (5.4%). Of the reported adverse events, 97% were minor and did not result in discontinuation of therapy, and the only severe events were not attributed to black cohosh. The authors concluded that "although the effects of *Cimicifuga* extracts may be dependent on the specific extract preparation, this review clearly supports the safety of specific *Cimicifuga* extracts, particularly isopropanolic preparations, for use in women experiencing menopausal symptoms and as a safe alternative for women in whom estrogen therapy is contraindicated."

An article by Huntley and Ernst, entitled "A systematic review of the safety of black cohosh," also published in *Menopause* in 2003, reported similar findings and concluded that adverse events associated with black cohosh use are mild, transient, and rare.⁵

Mammary Cancer in Genetically Susceptible Mice: How Relevant to Women?

On July 12, 2003, a group of investigators at the Mylan School of Pharmacy at Duquesne University presented results on black cohosh in mice at the American Association for Cancer

Research.⁶ Their work in mice was interpreted in resulting press releases to suggest that black cohosh may accelerate the spread of tumors in women with breast cancer.⁷ Dr. Vicki Davis, lead researcher and assistant professor at the Mylan School of Pharmacy at Duquesne University was noted for saying that “although it is unfortunate to be eliminating another option for women needing therapies to relieve menopausal symptoms, our findings suggest that women who may be at high risk of having an undetected breast tumor and certainly those who do have breast cancer should proceed with great caution—or simply avoid—taking black cohosh until we learn if there are ways to circumvent these adverse effects.”

The observations made by the Duquesne team of investigators are contradictory to many other published studies that indicate black cohosh is safe. We have evaluated the quantity and quality of the published data on the safety of black cohosh in the context of Dr. Davis’s work to determine whether the concerns raised by this investigator are valid. The following represents a summary of our conclusions from this evaluation.

Protocol of the Duquesne Study on Black Cohosh

First, the Duquesne study was presented at a symposium; therefore, the results have not been subjected to a peer-review process and the details of the experimental protocols have not been thoroughly reported. What has been reported is that the study was done with a strain of transgenic mice that have been altered to carry the proto-oncogene HER2-neu. HER2-neu is implicated in some breast cancers in humans, and is known to be an invasive breast cancer capable of metastasizing to other organs. One group of mice was fed a diet that contained an amount of black cohosh equivalent to a woman ingesting 40 mg/day of a standardized black cohosh supplement, which is the normally recommended dose for the management of menopausal symptoms. However, the mice were fed this dosage of black cohosh from the time of sexual maturity (2 months) to their maximum age (~16 months). This would be the equivalent of a woman beginning this dosage in her teens and then continuing to take it throughout her lifetime. (A 13 month old mouse is equivalent in age to a 50 to 60 year old human.)

In the mice treated with black cohosh, the incidence of new tumor development did not significantly increase over the control group. However, in black cohosh-treated mice that did develop mammary tumors, investigators observed an increase in metastasis (21.7% for the black cohosh treated group versus 10.9% for the control group). It was these results that led Dr. Davis to conclude, “The recommended doses of black cohosh may promote progression of metastatic disease in women with early stage breast cancer.”

Putting the Duquesne Black Cohosh Study into Perspective

At least 10 peer-reviewed studies assessing the safety of black cohosh for the management of menopausal symptoms in women have been published—including the two articles previously mentioned. In a recent article published in the *Annals of Internal Medicine*, scientists concluded that “black cohosh...show[s] promise for the treatment of menopausal symptoms...”⁸

In vitro research has shown that black cohosh does not function like a traditional estrogen, but rather has estrogen antagonistic activity.⁹ This finding has been supported by a number of other studies in which black cohosh has been shown to function through non-estrogen mediated mechanisms.^{10,11} Although some studies have suggested that black cohosh may promote selective estrogen activities, similar to soy isoflavones,¹² several recent reports with purified estrogen receptors suggest that black cohosh does not bind to estrogen receptors.^{13,14} The combined results of these studies indicate that the risk of estrogen-mediated effects in women who use black cohosh for the management of menopausal symptoms is significantly lower than HRT.

The Duquesne study warrants further evaluation. However, given that black cohosh is used for a relatively short time, as compared to the duration of the dosing in the Duquesne study, and the weight of evidence is in favor of its safety, a judgment that black cohosh should not be recommended to menopausal women seems premature. Furthermore, there are many confounding differences between influences in mice and humans.

Conclusion

In evaluation of the present published literature on the safety of black cohosh used by women for the management of menopausal symptoms, the weight of evidence speaks in favor of its safety, particularly for the isopropanolic black cohosh preparations which have been widely studied. In a recent presentation, given by Dr. Vicki Davis at the American Association for Cancer Research, possible safety concerns regarding the use of black cohosh in menopausal women who may be at risk of having breast cancer were discussed. These concerns were based upon the results of a study on a mouse model for breast cancer, in which long-term black cohosh administration was shown to not influence incidence of breast cancers, but possibly increase metastatic events. This research needs to be further evaluated for reproducibility and applicability to menopausal women. Due to the large amount of published literature on black cohosh and its history of safe use, it seems premature to conclude that black cohosh supplementation poses a risk of breast cancer development. Furthermore, it would be unfortunate to eliminate another option for women seeking to relieve menopausal symptoms who may be concerned about breast cancer risk. However, if a woman has a known risk of breast cancer, we advise her to seek the advice of a healthcare practitioner prior to taking any nutritional supplements.

References

1. U.S. Preventive Services Task Force. Postmenopausal hormone replacement therapy for primary prevention of chronic conditions: recommendations and rationale. *Ann Intern Med* 2002;137(10):834-39.
2. Blumenthal M. Market report: herb sales down 15 percent in mainstream market. *Herbalgram* 2001;51:69.
3. Beuscher N. *Cimicifuga racemosa* L. —Black Cohosh. *Qtr Rev Nat Med* 1996;19-27.
4. Dog TL, Powell KL, Weisman SM. Critical evaluation of the safety of *Cimicifuga racemosa* in menopause symptom relief. *Menopause* 2003;10(4):299-313.
5. Huntley A, Ernst E. A systematic review of the safety of black cohosh. *Menopause* 2003;10(1):58-64.
6. Davis VL, Jayo MJ, Hardy ML, et al. Effects of black cohosh on mammary tumor development and progression in MMTV-neu transgenic mice. *Proc Amer Assoc Cancer Res (1st ed.)* 2003;44:R910.
7. New findings suggest black cohosh increases spread of breast cancer. Retrieved on July 16, 2003, from <http://www.nutraingredients.com/news/news.asp?id=7369>.
8. Kronenberg F, Fugh-Berman A. Complementary and alternative medicine for menopausal symptoms: A review of randomized, controlled trials. *Ann Intern Med* 2002;137(10):805-13.
9. Bodinet C, Freudenstein J. Influence of *Cimicifuga racemosa* on the proliferation of estrogen receptor-positive human breast cancer cells. *Breast Cancer Res Treat* 2002;76(1):1-10.
10. Liske E, Hanggi W, Henneicke-von Zepelin HH, et al. Physiological investigation of a unique extract of black cohosh (*Cimicifugae racemosae rhizoma*): a 6-month clinical study demonstrates no systemic estrogenic effect. *J Womens Health Gend Based Med* 2002;11(2):163-74.
11. Düker EM, Kopanski L, Jarry H, et al. Effects of extracts from *Cimicifuga racemosa* on gonadotropin release in menopausal women and ovariectomized rats. *Planta Med* 1991;57:420-24.
12. Wuttke W, Jarry H, Becker T, et al. Phytoestrogens: endocrine disrupters or replacement for hormone replacement therapy? *Maturitas* 2003;44(1 Suppl):S9-S20.
13. Mahady GB. Is black cohosh estrogenic? *Nutr Rev* 2003;61:183-186.
14. Jarry H, Metten M, Spengler B, et al. In vitro effects of the *Cimicifuga racemosa* extract BNO 1055. *Maturitas* 2003;44(1 Suppl):S31-S38.