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Breast Cancer and Botanical Medicine

Part I of II-Part Series

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report no financial relationships relevant to this field of study.*

THE FOLLOWING ARTICLE HAS TWO OBJECTIVES: TO PROVIDE CLINI-
cally relevant information on the use of herbs in the treatment of
breast cancer and to provide a context for their use. What follows is a
distillation of some of the more effective botanicals and some sugges-
tions about how to use them in the setting of breast cancer.

Background

Breast cancer is one of the leading causes of cancer-related death
in women.¹ The overall risk for women developing breast cancer is 1
in 8, with the highest risk occurring in women over the age of 60.²
Breast cancer accounts for almost a third of all new cancers that are
diagnosed in the United States and 16% of all cancer-related mortal-
ities in the United States.³ Worldwide, 1 million cases of breast can-
cer are diagnosed annually. The five-year survival rates are almost
100% for stage I disease, but only 20% for stage IV.⁴

Risk Factors

Although there are general predisposing risk factors such as race,
family history, and age, there are many individualized risk factors as
well. As a broad overview, we will categorize cancer risk factors as:
genetic/familial risks and environmental/lifestyle risks.⁵

Genetic/Familial

Genetic factors seem to play a more significant role in the devel-
opment of breast cancer in premenopausal women.⁶ Mutations in the
BRCA 1 and 2 tumor suppressor genes are among the most common
genetic risk factors for developing cancer, with an overall lifetime
risk of 60%-80%.⁷ BRCA mutations are more prevalent among cer-
tain patient populations, such as women of Ashkenazic Jewish
descent. Curiously, increased consumption of coffee may reduce

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breast cancer risk in these women.⁸ Another genetic factor appears to be mutations in tumor suppressor genes, such as p53.

Use of specific medications, or a history of certain illnesses, may also contribute to risk for breast cancer. For example, prior or current use of hormone replacement therapy,⁹ obesity, certain forms of infertility, and fibrocystic breast disease are also known risk factors.

Environment/Lifestyle

Note: For an in-depth review of the various environmental/lifestyle exposures with citations, the reader is referred to: State of the Evidence 2008: The Connection between Breast Cancer and the Environment.¹⁰

Environmental exposures (eg, xenosteroids, organochlorines¹¹ and other chemicals, radiation,¹¹ etc.), lifestyle (eg, smoking, alcohol, etc.), and diet (eg, xenosteroidal compounds, growth hormones¹⁰ carcinogenic byproducts of manufacturing or cooking, food additives, etc.) may also be contributing factors. Clearly there is substantial overlap. For example, recent studies have shown that high consumption of dietary fat does not pose a risk in and of itself.¹² However, certain high fat diets can lead to obesity, which is a risk factor.² Dietary fats can also contain high concentrations of fat soluble contaminants (eg, xenosteroids), which may contribute to cancer pathogenesis. High fat-to-complex carbohydrate ratio diets have also been associated in some studies with dense breast tissue, another known risk factor.¹²

The Strategic Use of Herbs in Breast Cancer

Many useful and novel compounds have been identified within the Chinese Herbal Pharmacopeia with a wide range of effects. Some are directly tumoricidal, where others inhibit aromatase, upregulate p53, induce apoptosis, inhibit cell-cell adhesion pathways, and so forth.

The choice of herbal research targets in breast cancer therapy is often derived from observance of traditional uses. Practitioners of Classical Chinese Medicine (CM) choose herbs based upon a complex synthesis of diagnostic parameters combined with an intricate theoretical model. Essentially, CM views tumors as a physiological response of the body to sequester a pathogen and attempt to keep it from spreading or harming other tissue. Metastasis, therefore, is seen as the loss of the body's ability to contain, eliminate, or repair the pathology (This view is not representative of all Chinese Medicine traditions, but is very pertinent and analogous in many ways to modern discoveries).

Accordingly, three main factors are strategically addressed: 1) the underlying pathology (ie, aberrant cells), 2) the etiological factors involved in that pathology (ie, factors that create the microenvironment facilitating the tumor; these can include toxins, microorganisms, emotions/stressors, etc.), and 3) the body's ability to control the pathogen, prevent metastasis, and maintain homeostasis (ie, immune system, digestive system, etc.).

Addressing the underlying pathology

Note to readers: Please see accompanying chart for references to clinical statements.

The first factor involves directly addressing the aberrant cells in the tumor and their mechanisms of promoting abnormal cell growth (eg, estrogen receptors in an ER + tumor). In this respect, certain herbs may act synergistically with chemotherapy, radiation, and estrogen antagonists. Due to the novel actions of many herbs, it is also possible to utilize herbs where conventional therapies are not indicated, or as an option in cases where it is unclear whether conventional therapies will be more helpful or harmful.

Herbs used in this arena have various targets. Some seem to directly suppress tumor growth, induce apoptosis, or induce DNA repair mechanisms, where bioherbs seem to inhibit angiogenesis, cell adhesion pathways, metastasis, or block estrogen receptors. Several of the more useful herbs in this category include: *Curcumae longae* (eg, cell adhesion pathway inhibition), *Salvia miltiorrhiza* (eg, inhibits both estrogen receptor positive and negative tumors), *Boswellia serrata* (eg, metastasis inhibition), *Ganoderma lucidum* (eg, decreases estrogen receptor signaling and downregulates ER alpha expression), *Tanacetum parthenium* (eg, induces apoptosis), *Scutellaria baicalensis* (eg, inhibits multi-drug resistance and promotes DNA repair), and *Scutellaria barbata* (eg, selectively cytotoxic to breast cancer cells leaving normal mammary tissue unharmed). ❖

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Table 1				
Breast Cancer and Botanic**				
Herb Name	Categories	Specific Effects	Dosage	Cx
<i>Astragalus membranaceus</i>	I, E	Enhances NK cell activity, increases interferon production, anti-viral properties. ¹ Paradoxically enhances effect and reduces toxicity of certain chemotherapeutic regimes, ² improves gut mucosa ³	Aqueous Extract (AE): 9-30 grams per day. Ethanol Extract (EE): 1:1 20 mL per day	
* <i>Poria cocos</i>	P,I,E	Induces apoptosis of MCF-7 breast cancer cells in-vitro. ⁴ Increases digestive capacity, anti-proliferative, induces cell differentiation ⁴	AE: 10-15 g/day	
<i>Eleutherococcus senticosus</i>	I,E	Mitigates side effects and increases tolerance of chemotherapy, ⁵ increases interferon, antiviral, anti-tumor activity ^{6,7}	AE: 9-27 g/day 10:1 dried extract standardized to 150-300 mg/day of eleutherosides B and E	One report on interference with blood digoxin levels, likely due to a contaminant in the herb. ³²
* <i>Ganoderma lucidum</i>	P,I,E	Significantly inhibits proliferation of breast cancer cells (MCF-7 and MDA-MB-231) without cytotoxic effects on normal breast tissue. Immune support and modulation, Anti-angiogenic, ⁸ decreases estrogen receptor and nuclear factor kappa beta (NF-kB) signaling in certain breast cancer cell lines, downregulates expression of ER alpha, ⁹ synergistic with Herceptin (trastuzumab) in suppression of Her-2/ neu oncogene. ¹⁰	AE: 3-15 g/day	Experimental data suggest water extracts may potentially aggregate blood in vitro, leading to cautions about interactions with anti-coagulants. The herb has shown no effect on coagulation parameters in humans ³²
* <i>Curcuma longae</i> (curcumin)	P, E	Significantly reduces tumor volume in MDA-MB-231 breast cancer cells. Reduces mutant p53 RNA, K67, increases apoptosis, reduces proliferation, ¹¹ inhibits angiogenesis through inhibition of VEGF, b-FGF, ¹² sensitizes cancer cells to gamma radiation, ¹³ impairs cell-cell adhesion pathways, ^{13(b)} and has an effect on many other biological targets in carcinogenesis	AE: 9-12 g/day Standardized to 400-600 mg curcumin-up to 1800 mg per day	Curcumin may, under some circumstances decrease the efficacy of Doxorubicin, but it is unlikely. ³² Traditionally contraindicated in pregnancy ³³

Table 1

...continued from previous page**

Herb Name	Categories	Specific Effects	Dosage	Cx
* <i>Scutellaria baicalensis</i>	P,E	Strongly inhibits breast cancer cell growth (MCF-7). Inhibition of multi-drug resistance, ¹⁴ anti-microbial activity, ¹⁵ anti-oxidant activities related to DNA repair, ¹⁶ hepatoprotective ¹⁷	AE: 3-10 g/day	
* <i>Salvia miltiorrhiza</i>	P,E	Inhibits both ER+ and ER- breast tumors. Neo-tanshin-lactone (component of SM) showed inhibition against two ER+ breast cancer cell lines, more selective than tamoxifen. Effect shown against an ER- Her2 expressing cell line ¹⁸ Synergistic with SBAI for even stronger inhibitory effects on breast tumors.	AE: 5-10 g/day	May potentiate anti-coagulant or anti-platelet drugs. May falsely elevate serum digoxin levels ³³
<i>Boswellia serrata</i>	P	Anti-inflammatory AKBA (Acetyl-11-keto-beta-boswellic acid) inhibits 5-lipoxygenase pathway (5-LOX), ²⁰ inhibits angiogenesis, VEGF, EGF ²¹ Case report of BoS reversing breast cancer brain metastasis.	AE: 3-10 grams 30% AKBA 600 mg	Traditionally Contraindicated in pregnancy, may cause GI distress ³³
* <i>Tanacetum parthenium</i>	P	Anti-inflammatory. Parthenolide induces apoptosis, ²² inhibits proliferation of several different cancer cell lines including MCF-7 breast cancer cells ²³ increases the cytotoxicity of paclitaxel ²⁴	EE: 1:5 25% (0.2% parthenolide) 5 mL per day	Tanacetum exhibits platelet inhibiting properties, which theoretically may increase the effect of other antiplatelet medications. There is no substantiation to this in the literature
* <i>Scutellaria barbata</i>	P,E	Inhibits intracellular aromatase production. Broad spectrum anti-cancer agent that is selectively cytotoxic to breast cancer cells (leaving normal mammary tissue unharmed), likely through ROS induced DNA damage leading to necrotic cell death. ²⁵ Currently in phase II clinical trials at the Ohio State University Medical Center (OSUMC).	AE: 10-30 g/day	
* <i>Andrographis paniculata</i>	P,E	In vitro and in vivo anti-tumor activity in breast cancer models. Anti-microbial, ²⁶ immune enhancement through NK cell modulation, and increases immune-dependent cytotoxicity. ²⁷ Andrographolide directly cytotoxic to cancer cell lines. ²⁸ Anti-oxidant, anti-inflammatory, ²⁹ inhibits Bcl-2 expression and increases apoptosis, ³⁰ anti-angiogenic ³¹	AE: 6-15 g/day	Traditionally used with caution during pregnancy ³³
<i>Magnolia officinalis</i>	P,E	Antidepressant effects. ³⁴ Inhibits growth and induces apoptosis. Anti-angiogenic. Inhibits ER+ and ER- breast cancer cell lines, as well as drug-resistant breast cancer cell lines such as adriamycin- and tamoxifen-resistant lines. ³⁵ Synergistically enhance the effect of lapatinib (Tykerb), ³⁵ adriomycin ³⁷ and rapamycin. ³⁵ Increases Capace dependent apoptosis. ³⁵ Inhibits Phospholipase D and Ras. ³⁶ Decreases Epidermal Growth Factor (Her2). ³⁵	AE: 3-9g/day <i>Note: some functions are maximized in lipid soluble fractions</i>	1) Do not use with Reovirus therapy due to actions on Ras. 2) Has laxitive effects.

• Specific against breast cancers

P = Pathology;

E = Etiology;

I = Integrity of host

** References 1-38 for *Table 1* will be included in Part II of this II-Part Series (published in next month's issue).

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Use of CAM for Menopause

ABSTRACT & COMMENTARY

By Donal P. O'Mathuna, PhD

Dr. O'Mathuna is a lecturer in Health Care Ethics, School of Nursing, Dublin City University, Ireland; he reports no financial relationships relevant to this field of study.

Source: Bair YA, et al. Use of complementary and alternative medicine during the menopause transition: longitudinal results from the Study of Women's Health Across the Nation. *Menopause.* 2008;15:32-43.

THIS STUDY EXAMINED WHETHER USE OF COMPLEMENTARY and alternative (CAM) therapies during the menopause transition varied by ethnicity.

Design: The Study of Women's Health Across the Nation is a prospective cohort study following a group of 3,302 women from five racial/ethnic groups at seven clinical sites nationwide. Using longitudinal data encompassing six years of follow-up, we examined trends in use of five categories of CAM (nutritional, physical, psychological, herbal, and folk) by menopause status and ethnicity. To account for potential secular trends in CAM use or availability, we also evaluated the trends in CAM use over calendar time.

Results: Approximately 80% of all participants had used some form of CAM at some time during the six-year study period. White and Japanese women had the highest rates of use (60%), followed by Chinese (46%), African-American (40%), and Hispanic (20%) women. Overall use of CAM therapy remained relatively stable over the study period. In general, CAM use did not seem to be strongly associated with change in menopause transition status. Use of CAM among white women did not change with transition status. Among Chinese and African-American participants, we observed an increase in CAM use as women transitioned to perimenopause and a decrease in CAM use with transition to postmenopause. Among Hispanic and Japanese women, we observed a decrease in use of CAM in early perimenopause, followed by an increase as women entered late perimenopause and a decrease as they progressed to postmenopause. Patterns of use for the five individual types of CAM varied. White women had relatively

stable use of all CAM therapies through the transition. Japanese women decreased use of nutritional and psychological remedies and increased use of physical remedies as they transitioned into late perimenopause. Among African-American women, use of psychological remedies increased as they progressed through menopause.

Conclusions: Although CAM use did vary in some ethnic groups in relation to advancing menopause status, there was no evidence of influence of calendar time on CAM use. Patterns of CAM use during menopause are likely to be driven by personal experience, menopausal health, and access to therapies. Women's personal preferences should be taken into consideration by healthcare providers for medical decision making during menopause and throughout the aging process.

■ COMMENTARY

Women are the primary consumers of complementary and alternative medicine (CAM), and of healthcare in general. Historically, menopausal symptoms have been one of the most common indications for which herbal remedies were pursued.¹ Interest in CAM for menopausal symptoms was heightened after studies in 2002 reported higher incidences of certain adverse events after long-term use of hormone replacement therapy (HRT).²

However, even prior to those reports, many women considered CAM preferable to HRT. A survey of almost 1,000 US women aged 45 to 65 found that 76.1% had used at least one alternative therapy and 22.1% had used CAM to treat menopausal symptoms.³ Almost two-thirds of these women believed a natural approach to managing menopause was better than HRT. Herbal and homeopathic remedies made up the particular form of alternative therapy most popular with these women (13.1% of all women), followed by relaxation techniques (9.1%), and then soy products (7.4%).

The study by Bair et al sought to provide information on changes in CAM use during the menopause transition and also to look at any variation in use dependant on ethnicity. The data for this report derive from the Study of Women's Health Across the Nation (SWAN) study. At each of seven clinical sites around the United States, cohorts of white women and one other ethnic minority group were recruited. Four African-American cohorts were recruited. However, the Hispanic, Japanese, and Chinese Groups were each recruited in one city only and, thus, do not represent a nationwide sample.

When recruited, the 3,302 women were aged between 42 and 52 years and were either pre- or early perimenopausal at baseline. Women were excluded if, at baseline, they had experienced a hysterectomy or bilateral oophorectomy, were pregnant, or were using oral contraceptives or menopausal hormone therapy. As Bair et al noted, these criteria and other factors (such as the participants

of all ethnic groups being more educated and affluent than the general population) limit the generalizability of the findings of this study.

Participants undertook several self-administered and interviewer-administered surveys at baseline and annually for six years (1996 to 2003). Use of CAM was evaluated using a five-item survey. Participants were asked each year whether or not they had used any of the following five groups of CAM in the previous 12 months:

- Herbs and herbal remedies, including homeopathy and teas;
- Special diets or vitamins and dietary supplements;
- Psychological therapies, such as meditation or relaxation techniques;
- Physical methods, such as acupuncture, massage or acupressure; and/or
- Folk medicine or traditional Chinese medicine.

Data on the fifth category was not reported here because so few participants reported using this category. The use of such broad categories makes it difficult to interpret the implications of this study. Hence, it is not surprising that 80% of participants reported using CAM at some point during the study. However, this does not adequately distinguish between people using an approach that might not be perceived as CAM (such as vitamins or massage) and those committed to practices widely acknowledged as being part of CAM (such as herbs or acupuncture).

Similarly, the level of use of CAM is not captured in this report. It is not completely clear how participants were to respond to the CAM survey, but it appears that they answered either yes or no to using the therapies. As the researchers acknowledge, more specific questions would have elicited "a more detailed and accurate assessment of women's actual practices," which would have given a more meaningful description of what is happening in practice. Further analyses are currently under way.

Nonetheless, this report does highlight that a significant number of women are using CAM during the transition through menopause. Of interest is the finding that such use was not strongly associated with transition status. However, ethnic variations were noted, which should be kept in mind when discussing CAM use with patients. ❖

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2. identify risks and interactions associated with alternative therapies;
3. discuss alternative medicine options with patients;
4. offer guidance to patients based on latest science and clinical studies regarding alternative and complementary therapies.

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CME Questions

26. Adaptogens are herbs that have a regulatory effect on the body to help it "adapt" to various stressors.
- a. True
 - b. False
27. Which of the following may contribute to risk for breast cancer?
- a. prior or current use of hormone replacement therapy
 - b. obesity
 - c. certain forms of infertility
 - d. fibrocystic breast disease
 - e. All of the above
28. Mutations in the BRCA 1 and 2 tumor suppressor genes are among the most common genetic risk factors for developing cancer. What is the overall lifetime risk?
- a. 20%-40%
 - b. 40%-60%
 - c. 60%-80%
 - d. 80%-100%

Answers: 26. (a); 27. (e); 28. (c)

News Briefs

Many female cancer patients turn to CAM therapies

A new report from the American Cancer Society (ACS) in Atlanta, GA, shows that more than half of cancer patients are using complementary and alternative medicine (CAM), with CAM methods being more popular among breast and ovarian cancer survivors.

This study looked at the prevalence and the medical and demographic associations of CAM use among cancer survivors surveyed 10 to 24 months after receiving the diagnosis. The study had a sample size of 4,139 survivors of 1 of 10 adult cancers. The patients were selected from stratified random samples provided by statewide cancer registries and surveyed by mail and telephone. The researchers then used three logistic regression models to examine associations between

medical and demographic factors and CAM use among survivors of sex-specific and non-sex-specific cancers.

Nineteen CAM therapies were included in the survey. Of these, the most frequently reported were prayer/spiritual practice (61.4%), relaxation (44.3%), faith/spiritual healing (42.4%), nutritional supplements/vitamins (40.1%), meditation (15%), religious counseling (11.3%), massage (11.2%), and support groups (9.7%). The least reported were hypnosis (0.4%), biofeedback therapy (1.0%), and acupuncture/acupressure (1.2%). The cancer survivors more likely to use CAM therapies were female, younger, white, higher income, and more educated.

The study was published online Aug. 4 on the website of the journal *Cancer*. It will also be included in the Sept. 1st print issue of the journal.

Cancer survivors with “unmet needs” more likely to use CAM therapies

Cancer survivors who say they have multiple types of unmet needs within their cancer treatment and support system are more likely to use complementary and alternative medicine (CAM) to help with their cancer problems, according to a study published in the June 2008 issue of the *Journal of Cancer Survivorship: Research and Practice*.

The researchers in this study wanted to determine the relationship between patients' perceived unmet needs and their use of CAM therapies to help with cancer problems during and after treatment. The researchers mailed a cross-sectional survey, which was completed by 614 cancer survivors identified through the Pennsylvania Cancer Registry 3.5 to 4 years from initial diagnosis. They then examined the relationships among the unmet needs and CAM use, along with clinical and socio-demographic factors.

The researchers found that respondents who identified any unmet needs were 63% more likely to report CAM use than those without those needs (58% vs. 36%). Unmet needs remained the only independent predictor of CAM use in a multivariate logistic regression model that included age, sex, marital status, education, previous chemotherapy, and radiotherapy. Adjusted for covariates, unmet needs in the areas of emotional, physical, nutritional, financial, informational, treatment-related, employment-related, and daily living activities were all related to CAM use, whereas unmet needs in transportation, home care, medical staff, family, and spirituality, were not related to CAM use. Patients who experienced multiple types of unmet needs were also more likely to use multiple types of CAM.

CAM conference on scientific discovery and health set for May

Complementary and alternative (CAM) health professionals may be interested in attending the North

American Research Conference on Complementary & Integrative Medicine: Collaboration to Promote Scientific Discovery and Health conference, scheduled for May 12-16, 2009, in Minneapolis, MN.

The conference is sponsored by the Consortium of Academic Health Centers for Integrative Medicine and will showcase original scientific complementary, alternative and integrative medical research through keynote and plenary presentations, oral and poster presentations, and scientific sessions. The directors of this conference want to provide a single event that attracts a “critical mass of cutting-edge, peer-reviewed science and discussion in the broad field of complementary and integrative medical research.” Abstracts will be accepted through Sept. 30, 2008. For more information visit <http://www.imconsortium-conference.org>. ♦

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