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Breast Cancer: The Benefits of Exercise

By Roanne Segal, MD, FRCPC

THE FIVE-YEAR, OVERALL SURVIVAL RATE FOR BREAST CANCER IS about 85%; the majority of women will live for a significant length of time after diagnosis.[1] Women routinely receive some combination of surgery, chemotherapy, and hormonal and radiation therapy over a prolonged period of time, increasing the incidence of side effects or sequelae.

Side effects generally can be divided into two categories: 1) physical and functional, including fatigue, cardiovascular deconditioning, changes in weight or lean body mass, and muscle weakness, and 2) emotional changes, including depression, anxiety, stress, poor body image, and low self-esteem. Other health problems, including osteoporosis and lymphedema, can have a significant impact on quality of life. This review will summarize the research evaluating exercise as a self-care modality for women at risk for, or living with, breast cancer.

Physical Activity and Risk of Breast Cancer

Over the last decade there has been mounting evidence suggesting an inverse relationship between physical activity and estrogen-dependent cancers. While the exact relationship remains unclear, it generally is accepted that physical activity may affect serum estrogen levels, and several large epidemiological studies have demonstrated an inverse relationship between breast cancer and physical activity.[2-5]

Thune et al evaluated the influence of physical activity, both at work and during leisure time, on the risk of breast cancer in a cohort of 25,624 pre- and postmenopausal women.[4] Data on parity, dietary factors, and body mass index (BMI) were collected and were reassessed after 3-5 years, to estimate the effect of sustained vs. short-term physical activity. During a median follow-up of 13.7 years, 351 incident cases of breast cancer (100 in premenopausal women and 251 in postmenopausal women) were identified.

After adjustments for age, BMI, height, parity, and country of residence, greater leisure-time activity was associated with a reduced risk of breast cancer, (relative risk [RR] 0.63, 95% confidence interval [CI] 0.42-0.95), among women who exercised regularly, as compared with sedentary women (P = 0.04). In regularly exercising women, risk reduction was greater in premenopausal than in postmenopausal women, and greater in women younger than 45 years of age than in older women (RR 0.38; 95% CI 0.19-0.79). In stratified analyses, the risk of breast cancer was lowest in lean women (BMI < 22.8) who exercised at least four hours per week (RR 0.28, 95% CI 0.19-0.70). This risk also was reduced with higher levels of activity at work.[4]

More recently, Friedenreich et al performed a case-control study of 1,233 breast cancer cases and 1,237 controls between 1995 and 1997 to examine the effect of lifetime physical activity patterns on breast cancer risk.[5] Lifetime physical activity was estimated using a questionnaire that assessed occupational, household, and recreational activity. The intensity of physical activity was estimated as light, moderate, or heavy. Definitions were provided for each intensity level, and a specific metabolic equivalent (MET) value then was assigned.

Their results demonstrated important differences between pre- and postmenopausal women. In contrast to the Thune study, no association was found between physical activity and breast cancer risk in premenopausal women; reduced risk was noted, but only in postmenopausal women. When comparing those women divided by the highest quartile of metabolic activity (> 161 MET-hrs/wk/yr) vs. those in the lowest quartile (< 104.8 MET-hrs/wk/yr) of lifetime total physical activity, the adjusted odds ratio (OR) was 0.70 (95% CI 0.52-0.94). When type of activity was further evaluated in postmenopausal women, household and occupational activity conferred the largest risk reductions (OR 0.57, 95% CI 0.41-0.79; and OR 0.59, 95% CI 0.44-0.81, respectively).

Although there are no consistent data on when during a woman's life physical activity might influence breast cancer risk, the data do support a consistent and dose-responsive relationship between the two. Possible physiological mechanisms may include: 1) maintenance of low body fat and moderation of extraglandular estrogen; 2) a reduction in ovarian estrogen production; 3) enhancement of immune function; and 4) an association between exercise and other healthy lifestyle habits.[4-6] Why some types of occupational activities appear more favorable than certain recreational activities remains puzzling. Certainly data support recommendations for regular, moderate exercise for at least four hours per week.

Physical Activity in the Setting of Adjuvant Therapy for Breast Cancer

After breast cancer diagnosis, advantages of physical activity include weight control, and physical and psychological benefits. Despite previous concerns that it would be unsafe or unrealistic for women to perform exercise during breast cancer treatment, seven studies support the safety and efficacy of exercise during treatment.[7-14] Six studies included a total of 271 women with early-stage breast cancer receiving adjuvant chemotherapy,[7-13] while one study evaluated 46 women receiving adjuvant radiation therapy.[14]

The length of the exercise programs ranged from six weeks to six months, using primarily a moderate intensity, aerobic-based exercise intervention (e.g., walking or a stationary cycle ergometer). Most programs were supervised; two were home-based. All studies followed traditional exercise prescription guidelines. Biosocial outcomes included functional capacity, body composition, fatigue, mood states, and symptoms. Although

Alternative Therapies in Women's Health, ISSN 1522-3396, is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/PUBLISHER: Brenda L. Mooney.
EDITORIAL GROUP HEAD: Lee Landenberger.
MANAGING EDITOR: Paula L. Cousins.

GST Registration Number: R128870672.

Periodical rate postage pending at Atlanta, GA.

POSTMASTER: Send address changes to *Alternative Therapies in Women's Health*, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $38. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Subscription Prices

United States
$279 per year (Student/Resident rate: $110).
Multiple Copies
1-9 additional copies: $206 each; 10 or more copies: $183 each
Outside the United States
$309 per year plus GST (Student/Resident rate: $125 plus GST).

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Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Education guidelines, physicians have reported the following relationships with companies related to the field of study covered by this CME program. Dr. Bratman, Dr. Cates, Dr. Fugh-Berman, Dr. Greenwood, Dr. Kronenberg, Dr. McPartland, and Dr. Massion have reported no relationships with companies related to the field of study covered by this CME program. Dr. Awang has the following relationships: consultant for Leiner Health Products, and Global Botanical/Health 4 All. Dr. Low Dog is a consultant for the Materia Medica Group. Dr. Pan is a researcher for Chitosan. Dr. Scialli has the following relationships: consultant for TAP and Merck; speaker for TAP; researcher for TAP, Wyeth-Ayerst, and Balance Pharma. Dr. Segal is a consultant and researcher for OrthoBiotech, and receives grant funding from Aventis.

there were methodological concerns, such as small sample size, relatively short exercise interventions, and limited follow-up, all studies demonstrated significant beneficial effects of exercise during adjuvant therapy, and none reported any adverse events.

Segal et al performed the largest randomized trial to date, designed to evaluate the effects of a structured exercise program on physical functioning and other dimensions of health-related quality of life in women with early-stage breast cancer.[13] One hundred twenty-three women were randomized to usual care, a self-directed exercise group, or a supervised exercise group for 26 weeks. Quality-of-life, aerobic capacity, and body weight measures were evaluated. The results supported previous studies: Physical functioning declined in the control group by 4.1 points and increased by 5.7 points and 2.2 points in the self-directed and supervised exercise groups, respectively ($P = 0.04$). Post-hoc analysis showed a moderately large and clinically important difference between the self-directed and the usual care group ($P = 0.01$); there was no significant difference between the supervised and control groups. In a secondary analysis of participants stratified by type of adjuvant therapy, only participants not receiving chemotherapy in the supervised exercise group demonstrated improved aerobic capacity by maximal oxygen uptake (+3.5 mL/kg/min; $P = 0.01$) and reduced body weight (-4.8 kg; $P < 0.05$) compared with participants in the usual care group.

Rehabilitation for Breast Cancer Patients

There is an increasing body of literature that has examined exercise after breast cancer treatment,[15-22] including both correlational and experimental designs. Six correlational studies in which patients were surveyed for several months to many years after completing one or more adjuvant therapies focused on psychosocial outcomes including self-esteem, body image, anxiety, and depression.[15-20] Sample sizes ranged from 54 to 500 patients. Four of the six studies found benefits of exercise on the psychosocial outcomes listed above.[15,18-20]

Six prospective trials were quite small; sample sizes ranged from 12 to 28 patients.[21-26] All studies incorporated aerobic exercise into their programs; two studies combined aerobics with weight training.[21,23] All studies followed the traditional exercise prescription guidelines in terms of frequency, intensity, and duration of exercise. Outcomes included immune functioning,[22-24] lymphedema,[21] and other psychosocial outcomes.[25,26] Generally speaking, these studies were less methodologically sound.

Three studies that evaluated immune function were conflicting. Peters found an increase in natural killer cell activity while Nieman[23] found no change. In a subsequent study, exercise increased the number of granulocytes with a corresponding decrease in the number of lymphocytes and monocytes.[24] Importantly, all patients had completed therapy at least six months previously. Two further studies found increased physical fitness[25] and decreased anxiety and depression[25,26] in patients who exercised after completing adjuvant therapy.

Exercise and Lymphedema

It has been suggested that exercise—or even lifting heavy objects—increases the risk of lymphedema, but this appears to be a myth. A case series by Harris et al assigned 20 breast cancer survivors, who had undergone surgery with axillary dissection 1-17 years earlier, to a program of upper extremity exercises, including both aerobic and resistance maneuvers. The program was performed three times weekly, for 20-30 minutes at a moderate intensity, for eight months. The primary outcome, change in arm circumference at four locations over time, was unaffected, and there were no differences between arms ipsilateral or contralateral to the side on which surgery was performed.

Conclusion

There is mounting evidence that exercise positively influences several aspects of breast cancer, including prevention, biopsychosocial aspects, and rehabilitation. Promoting exercise is scientifically justified and safe. ❖

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Hair Analysis

By Steven Bratman, MD

FOR MANY YEARS, CERTAIN BRANCHES OF ALTERNATIVE medicine have utilized hair analysis to diagnose nutritional status and to identify the presence of toxins. According to a recent report, approximately 225,000 hair mineral tests are performed each year, costing between $30 and $69 per sample, for an annual total of $9.6 million.[1]

In 1985, hair samples from two healthy teenagers were sent to 13 commercial labs; results were very inconsistent. Sixteen years later, the situation has not improved. In a recent study, nine laboratories conducting hair analysis in the United States were identified, and hair samples from one volunteer were sent to the six largest labs. All laboratories claimed to be certified under the Clinical Laboratory Improvement Act (CLIA). However, one laboratory turned out not to be CLIA-certified, and the remaining laboratories were CLIA-certified in chemistry, toxicology, or another specialty area (certification is done by specialty, not specific tests, so certification specifically for hair analysis does not exist).

The mineral content reported by various labs differed by as much as a factor of 10. There were significant differences among laboratories in reference ranges, hair test values, and interpretations of the hair element

concentrations and ratios. Laboratories did not agree on the characterization of toxic concentrations of metals.

All of the laboratories identified at least six element concentrations associated with health risks, and results from various laboratories indicated that the healthy 40-year-old donor was at increased risk of adrenal insufficiency, anemia, cardiovascular disease, dysinsulinism, and passive-aggressive behavior. One laboratory identified the patient as a "fast metabolizer" and another classified him as a "slow metabolizer." Four laboratories recommended vitamin/mineral supplementation, and three recommended proprietary products that cost up to $100/month.

Although laboratories claimed that element ratios could provide information on health effects (including energy levels and carbohydrate sensitivity), no evidence linking element ratios and health effects was provided or identified through a MEDLINE search.

Hair analysis is considered reliable to confirm mercury or arsenic poisoning, and can be useful to survey population exposures to heavy metals.[2] However, suspicion of heavy metal poisoning surely does not account for most submissions for hair analysis.

Although a painless test that identifies a tailored supplementation regimen clearly is attractive to consumers, little is known about the relationship between mineral content in hair and blood or other tissues. Additionally, hair treatments, different rates of hair growth, external environmental factors, and variations associated with hair color, location, and diameter all affect results.[3] (In rabbits, manganese concentrations are twice as high in black hair than white hair, even if taken from the same rabbit.) Internet sites promote hair analysis, and some provide consumers direct access to testing.[1] Recommendations of supplements based on such analyses are unethical. Physicians should not use hair analysis for assessing nutritional state or environmental exposures, and should warn patients about the unreliability of these tests. ❖

Dr. Bratman is the former medical director of TNP.com.

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Label Review

With Comments by Adriane Fugh-Berman, MD

METAB-O-LITE®

Package Information

"Thermogenic dietary supplement for METABOLISM and ENERGY with ephedra"

Suggested Usage

Only for use by, and sale to, adults 18 years of age and older: 1 bottle per serving. Do not exceed two (2) bottles in a four (4) hour period and eight (8) bottles per day. This product contains 12 mg concentrated ephedrine group alkaloids per serving in the form of herbal extracts. DO NOT EXCEED 100 mg ephedrine alkaloids from the combination of all sources per day—it will not improve results.

Supplement Facts

Serving size: 1 bottle (10.5 fl oz, 310 mL)

Amount per serving	% Daily Value
Calories 220	
Calories from fat 25	
Total fat 3 g	5%
Saturated fat 2 g	10%
Cholesterol 10 mg	4%
Total carbohydrate 40 g	13%
Dietary fiber 5 g	20%
Sugars 35 g	*
Protein 10 g	
Vitamin A 2,000 IU	40%
Vitamin C 60 mg	100%
Vitamin D 160 IU	40%
Vitamin E 30 IU	100%
Vitamin K 20 mcg	25%
Thiamin (vitamin B_1) 0.53 mg	35%
Riboflavin (vitamin B_2) 0.6 mg	35%
Niacin 7 mg	35%
Vitamin B_6 0.7 mg	35%
Folic acid 120 mg	30%
Vitamin B_{12} 2.1 mcg	35%
Biotin 105 mcg	35%
Pantothenic acid 3.5 mg	35%
Calcium 400 mg	40%
Iron 7.2 mg	40%
Phosphorus 600 mg	60%
Iodine 52.5 mcg	35%
Magnesium 140 mg	35%
Zinc 2.25 mg	15%
Selenium 17.5 mcg	25%
Manganese 0.7 mg	35%
Chromium 42 mcg	35%
Molybdenum 26 mcg	35%
Sodium 360 mg	15%
Potassium 525 mg	15%
Ephedrine alkaloids 12 mg from Ephedra (Ma-Huang) extract (aeriel parts)	

Percent Daily Values are based on a 2,000-calorie diet.

* Daily Value not established.

Ingredients: Skim milk, sugar, chicory fiber (inulin), sweet cream, cocoa, dimagnesium phosphate, natural and artificial flavors, sodium ascorbate, mono- and diglycerides, sodium phosphate, ephedra (ma-huang) extract (aeriel parts), calcium carbonate, sodium citrate, sodium hexametaphosphate, carrageenan, di-alpha-tocopheryl acetate, ferric orthophosphate, zinc gluconate, niacinaminde, salt, calcium d-pantothenate, manganese, sulfate, pyridoxine hydrochloride, retinyl palmitate, thiamin mononitrate, riboflavin, folic acid, biotin, chromium chloride, sodium selenite, sodium molybdate, phytonadione, potassium iodide, cyanocobalamin, and cholecalciferol.

Warning: Do not use if pregnant or nursing. If you have, or have a family history of, heart disease, thyroid disease, diabetes, high blood pressure, recurrent headaches, depression or other psychiatric condition, glaucoma, difficulty in urinating, prostate enlargement, or seizure disorder, consult a health care provider before using this product. Do not use if you are using monoamine oxidase inhibitors (MAOI) or for two weeks after stopping an MAOI drug; certain drugs for depression, psychiatric or emotional conditions; drugs for Parkinson's disease, methyldopa, or any product containing ephedrine, pseudoephedrine, or phenylpropanolamine (ingredients found in allergy, asthma, cough/cold, and weight control products). Stop use and call a health care professional immediately if dizziness, severe headache, rapid nausea, noticeable changes in behavior, or loss of consciousness occur. Discontinue use at least two weeks prior to surgery. Exceeding recommended dosage or consuming products with caffeine may cause serious adverse health effects, including heart attack and stroke. The maximum recommended dosage of ephedrine for a healthy adult human is no more than 100 mg in a 24-hour period for not more than 12 weeks.

Keep out of reach of children.

This supplement has not been evaluated by the Food & Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

Distributed by Richardson Labs, Inc., Boca Raton, FL 33487 USA. Telephone: (888) 776-5383.

Price: $2.49/bottle

Comments

Now here's a weight loss product for people who can't add. At 220 calories a drink, drinking eight bottles would add 1,760 calories to daily intake, a hefty caloric load for someone trying to lose weight. Of even more concern is the amount of ephedrine in this product: 12 mg ephedrine/bottle (or 96 mg/8 bottles).

Health care practitioners should discourage the use of any ephedrine-containing products for weight loss, bodybuilding, or energy. An orally active sympathomimetic amine, ephedrine is an α-1 agonist and a nonselective β-agonist. One hundred forty adverse events associated with ephedra-containing products were reported to the Food and Drug Administration between June 1997 and March 1999; among cases considered definitely, probably, or possibly related (62%), 10 deaths and 13 cases of permanent disability resulted.[1] Most adverse events involved cardiovascular symptoms (most commonly hypertension, followed by palpitations or tachycardia) and central nervous system effects (stroke and seizures).

Although this product contains appropriate warnings, there is no evidence that the upper limit of intake recommended (100 mg) is safe. In fact, it is not clear that any dose of ephedra is safe; many adverse effects have occurred with doses of ephedra alkaloids of less than 60 mg/d, and one death from cardiac arrest occurred in a 38-year-old male with no known concurrent risks who was consuming about 20 mg ephedrine daily.[1]

There also is no good evidence that ephedra is effective for weight loss. Ephedra increases thermogenesis, as do many sympathomimetic agents, but results from trials of ephedra or ephedra/caffeine combination products have been mixed and have shown significant adverse effects *(see Table and* Alternative Therapies in Women's Health *November 2000 for more information on ephedra and weight loss)*.

Ephedra is used in small doses in traditional Chinese medicine as well as in Western herbal medicine, primarily for respiratory problems; this use does not appear to be dangerous. Virtually all adverse effects reported with ephedra alkaloids have been associated with products for weight loss, exercise enhancement, energy enhancement, or recreational use. ❖

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Table

Randomized controlled trials of ephedra for weight loss*

Study	Design	Duration	Treatment	Result
Boozer et al[2] (2001)	RDBPCT 67 randomized/ 48 completed	8 weeks	Metabolife-356® (E 72 mg/d + C 240 mg/d) vs. placebo Dietary advice: 30% dietary fat Exercise advice: 3x/wk	Significantly greater weight loss in treated group (-4 kg ± 3.4 kg vs. -0.8 kg; P < 0.006); 23% treated vs. 0% placebo group withdrew because of adverse effects (including hypertension, palpitations, chest pain, and extreme irritability).
Molnar et al[3] (2000)	RDBPCT 32 obese adolescents randomized/ 29 completed	20 weeks	If < 80 kg, E 10 mg/d + C 100 mg/d If > 80 kg, E 20 mg/d + C 200 mg/d Diet: calculated energy requirement minus 500 kcal	Significantly greater relative weight loss in treated group (14.4% ± 10.5% vs. 2.2% ± 5.8%; P < 0.05).
Buemann et al[4] (1994)	RDBPCT 41 overweight women randomized/ 32 completed	8 weeks vs. placebo	E 20 mg + C 200 mg/d tid	No significant difference between groups in weight loss or loss of fat mass. Diet: 4.2 MJ/d
Breum et al[5] (1994)	RDBTCT 103 overweight subjects randomized/81 completed	15 weeks	E 20 mg/d + C 200 mg/d tid vs. dexfenfluramine (DF) 15 mg bid	No significant difference between groups (both groups lost weight: DF 6.9 kg; E + C 8.3 kg); in those with BMI > 30, weight weight loss significantly different (7 vs. 9 kg); 43% of DF group and 54% of E + C group had side effects (withdrawals: 2 DF, 6 E + C).
Astrup et al[6] (1992)	RDBPCT 180 obese subjects randomized/ 141 completed	24 weeks	E 20 mg vs. C 200 mg vs. E 20 mg + C 200 mg Diet: 4.2 MJ (low-fat, high-carbohydrate)	E + C (but not E or C alone) significantly better than placebo (P = 0.0015); weight loss: E + C = 16.6 kg; E = 14.3 kg; C = 11.5 kg; placebo = 13.2 kg. More adverse effects in E groups (including dizziness, headache, tremor, psychiatric, insomnia, dry mouth, tachycardia). Withdrawals due to adverse effects: 1 E; 2 C, 3 E + C.
Astrup et al[7] (1992)	DBPCT 14 obese women/ 12 completed	8 weeks	E 20 mg, C 200 mg tid vs. placebo Diet: 4.2 MJ/d	No significant difference in weight loss between groups
Daly et al[8] (1993)	RDBPCT 29 obese subjects randomized/ 24 completed	8 weeks	E 75 mg/d + C 150 mg/d + ASA 330 mg/d vs. placebo for four weeks, then E 105 mg/d + C 150 mg/d + ASA 330 mg/d for four weeks	Significant difference between groups at 8 weeks; weight loss: E + C + ASA = 2.2 ± 0.7 kg, placebo = 0.7 ± 0.6 kg (compared to baseline, P < 0.001).
Mancini et al[9] abstract only (1990)	RDBPCT 42 overweight women randomized/32 completed	8 weeks	Low-calorie diet and E 22 mg + C 20 mg + aminophylline 50 mg tid	Weight loss: E + C + aminophylline = 4.5 ± 3.7 kg, placebo = 2.2 ± 2.8 kg (P < 0.05, apparently between groups; unclear).
Pasquali, Casimirri[10] (1993)	PCT 22 obese women/ 20 completed	4 months	E 50 mg tid vs. E 50 mg + C 100 mg tid vs. placebo Diet: 4,180-5,016 KJ/d	No significant difference among groups.
Cesari[11] abstract only (1989)	RDBPCT 20 obese women randomized/ ? completed	4 months	E 50 mg tid (n = 6) vs. E 50 mg + C 100 mg tid (n = 7) vs. placebo (n=7)	No significant difference in weight loss or BMI.

* Four Danish studies (with no English abstracts) were omitted for lack of translation resources.

Key: E = ephedrine, C = caffeine, ASA = aspirin, RDB = randomized, double-blind, PCT = placebo-controlled, TCT = treatment-controlled, BMI = body mass index.

and placebo in obese subjects on an energy-restricted diet. A double blind trial. *Int J Obes Relat Metab Disord* 199216:269-277.

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CME Questions

18. Exercise has been associated with decreased risk of breast cancer in:
a. epidemiological studies.
b. randomized controlled trials.

19. Hair analysis is clinically useful for diagnosing:
a. nutritional state.
b. environmental exposures.
c. mercury or arsenic poisoning.
d. All of the above

20. Ephedrine is:
a. an α-1 agonist.
b. a β-agonist.
c. Both an α-1 agonist and a β-agonist.
c. None of the above

21. Adverse effects associated with ephedra appear to be dose-related.
a. True
b. False

Clinical Abstracts

With Comments by Adriane Fugh-Berman, MD

Microcalcifications from Herbal Medicine

Source: Moon WK, et al. Metallic punctate densities in the breast after Chinese herbal treatment: Mammographic findings. *Radiology* 2000;214:890-894.

PRIOR TO THE 1970S, A TOPICAL, LEAD-containing Chinese medicine, go-yak, was used to treat breast inflammation and abscess in Korea and other parts of Asia. This medication is referred to as go-yak in the article, but go-yak actually is a non-specific term for an herbal salve, so different preparations may have been used. These topical preparations often were placed in open wounds, causing metallic punctate densities that can mimic microcalcifications on mammograms.

This article analyzed mammographic findings in 34 Korean women (ages 37-73 years) with mammograms that showed metallic punctate densities resembling microcalcifications. All subjects had undergone breast abscess drainage 6-42 years prior to mammography, and had received go-yak, applied into the open wound, for 3-13 weeks afterwards.

In 71% of patients, metallic densities were in the subareolar or central breast; lesions extended into the subcutaneous fat in 85% of subjects. Most lesions were round or punctate, but rod-shaped or linear lesions were seen in seven patients. The number of lesions ranged from five to more than 50. The average size of lesions was smaller than 0.5 mm in 30 patients and between 0.5 and 1 mm in four patients. Skin thickening or nipple retraction was seen in 62% of patients. Thirty of 34 subjects were followed for 3-47 months (mean 12 months); no evidence of malignancy was seen.

In most cases the location, shape, distribution, and density of metallic punctate densities were easy to distinguish from malignant microcalcifications by experienced radiologists. This was tested by combining mammograms of subjects who had received topical Chinese medicine and 34 mammograms with microcalcifications that later proved to be malignant; these were evaluated by two radiologists, with disagreements resolved by consensus. Punctate densities were identified as metallic in 25 of 34 patients; none of the malignant calcifications were regarded as metallic. In six cases, densities were deep-seated, linear, or segmental, with densities similar to that of true calcifications; these required surgical biopsy. Biopsies in the six patients with indeterminate calcifications revealed clustered particles surrounded by a few giant cells. True microcalcifications or atypical cells were not found.

A high concentration of lead was found in tissue samples. Lead concentrations in histopathological specimens were 2,800 and 4,700 mcg/mg in two patients. Analysis of an herb sample showed that lead comprised 20.1% of sample mass.

Comments: Use of a traditional herbal product decades ago can affect diagnostic tests today. This article points out the importance of including herbal medicine use in history-taking, and the importance of knowing about traditional remedies that can have an impact on diagnosis and treatment. ❖