REVIEW ARTICLE

Research on Complementary/Alternative Medicine for Patients With Breast Cancer: A Review of the Biomedical Literature

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Purpose: **This article reviews English-language articles published in the biomedical literature from 1980 to 1997 that reported results of clinical research on complementary and alternative medical treatments (CAM) of interest to patients with breast cancer.**

Methods: **We searched 12 electronic databases and the bibliographies of the retrieved papers, review articles, and books on CAM and breast cancer. The retrieved articles were grouped by end point: breast cancer (eg, tumor size, survival), disease-related symptoms, side effects of treatment, and immune function. Within each end point, we organized the articles by modality and assessed study design, findings, and qualitative aspects.**

Results: **Of the more than 1,000 citations retrieved, 51 fit our criteria for review. Of the articles reviewed, 17 were randomized clinical trials; three of these were trials of cancer-directed interventions, two of which involved the same treatment (melatonin). Seven articles described observational studies, and the remainder were reports of phase I or II trials. Relatively few CAM modalities reportedly used by many breast cancer patients were mentioned in articles retrieved by this process. Most articles had shortcomings.**

Conclusion: **Although many studies had encouraging results, none showed definitively that a CAM treatment altered disease progression in patients with breast cancer. Several modalities seemed to improve other outcomes (eg, acupuncture for nausea, pressure treatments for lymphedema). If CAM studies are well-founded, well-designed, and meticulously conducted, and their hypotheses, methods, and results are reported clearly and candidly, research in this controversial area should acquire credibility both in the scientific community and among advocates of unconventional medicine.**

J Clin Oncol 18:668-683.

PATIENTS WITH BREAST cancer increasingly explore on their own and ask their physicians about measures they can take in addition to receiving conventional treatment to enhance their prospects for survival, reduce their risk of disease recurrence, relieve disease-related symptoms, and/or minimize side effects associated with conventional treatment.[1-6] To learn what scientific information was available about the efficacy of complementary and alternative medical treatments (CAM) for women with breast cancer, we reviewed the biomedical literature published in English from 1980 through 1997.

METHODS

For the purposes of this review, we defined CAM as treatments that are available to patients outside conventional medical settings and that are not normally used in conventional settings to treat breast cancer or its associated symptoms or treatment side effects.

We searched the mainstream biomedical literature for studies of CAM used to treat patients with breast cancer. We grouped the retrieved citations by intended end point as follows: (1) to alter disease progression (eg, by prolonging survival, reducing tumor size, or preventing recurrence or metastasis); (2) to alleviate symptoms caused by breast cancer; (3) to relieve or prevent treatment side effects; and (4) to improve immune function.

Within each end-point category, we grouped studies by modality using a modified version of the classification system proposed by the National Institutes of Health Office of Alternative Medicine, now the National Center for Complementary and Alternative Medicine.[7]

We included studies that had immune parameters as end points because, although their association with cancer progression and survival is poorly understood, immune factors are used as intermediate end points in some conventional research.[8,9] Patients often encounter claims that a CAM treatment enhances immune function and is therefore beneficial, as well as criticism of conventional medicine for seeking to eliminate disease rather than to fortify the patient. Therefore, although an effect on immune function may not predict a survival benefit, we believed that it was necessary to review studies in which an effect of CAM treatment on immune function was assessed.

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Submitted June 17, 1998; accepted September 15, 1999.

Supported in part by Public Health Service grants no. 5 R21 CA66224-03 from the National Cancer Institute and U24-HD 33199 from the National Institutes of Health Office of Alternative Medicine, Bethesda, MD, and the Carol Ann Schwartz Cancer Initiative of the Rosenthal Center for Complementary and Alternative Medicine at Columbia University, New York, NY.

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0732-183X/00/1803-668

Table 1. Electronic Databases Searched

Agricola (National Agricultural Library, USA)
Biosis (biological science literature)
CATS/AMED (Current Awareness Topics/Alternative and Allied Medicine Database, United Kingdom)
CANCERLINE
CINAHL (nursing and allied health literature)
CISCOM (Centralised Information Service for Complementary Medicine, United Kingdom)
Embase (coverage of pharmacologic and biomedical research, the Netherlands)
General Science Citation Index
MEDLINE
Psych Abstracts
Psych Info
Social Science Citation Index

Table 2. Reasons for Exclusion of Articles Evaluated for Review

Reasons for Exclusion	No. of Articles
Animal study	24
Basic science	4
Case report	10
Commentary	23
Description of intervention	16
Etiology	30
Foreign language	24
In vitro study	26
Not breast cancer	92
Not CAM	20
Not treatment study	19
Prevention	20
Psychosocial intervention/psychosocial outcome	11
Review	32
Total	351

We excluded mind/body and psychosocial interventions in which the end point was psychological, such as using support groups or hypnosis to improve mood or body image or to relieve emotional distress. However, we included articles that reported the effects of support-group participation on biomarkers, such as immune cell function, or survival, and the effects of nutritional interventions on mood because these studies are based on hypotheses about mind–body relationships that are not part of conventional medicine.

Categorizing CAM treatments is difficult. For example, the Office of Alternative Medicine's category "alternative systems of medical practice" is usually understood to refer to traditional (or ethnic) health-enhancing and healing practices such as traditional Chinese medicine and Ayurveda (a traditional medical/philosophical system from India). A few treatment agents and procedures, although part of such traditional systems, also have been studied outside the context of the system in which they originated. We have classified studies of such treatments according to their specific characteristics (eg, herbal medicine, energy therapy). We have also developed another category, "alternative programs of medical practice," for multimodality treatment regimens not necessarily based on traditional medicine systems.

We limited our review to studies published from the beginning of 1980 through 1997. We included only studies published in English, although the literature available in other languages is probably extensive and should also be reviewed.

Table 1 lists the 12 electronic databases we searched as the first step in the review. In our searches, we used as key words "breast cancer" and "breast neoplasms" in combination with "alternative medicine," "unconventional therapies," "complementary therapies," "holistic health," and a long list of specific treatment terms (available from the authors on request). This process generated more than 1,000 citations and abstracts, from which we selected articles for retrieval and consideration. In addition we hand-searched the reference listings in review articles and books.

We excluded articles that described primary preventive interventions (those used or intended to be used by individuals who have never been diagnosed with breast cancer) or experimental agents available only through participation in conventional clinical trials, did not include breast cancer patients, focused on an end point of interest but not in relation to an intervention or treatment, did not involve an end point of interest, were secondary reviews only, were preclinical, were case reports, were published before 1980, or were written in a foreign language.

For each article, we identified the following: (1) details of the intervention (dosage, schedule); (2) intended end points; (3) study design; (4) sample size, including number of patients with breast cancer; and (5) findings. In addition, we assessed the quality of each article by the following criteria: (1) study participants: information about the study population, recruitment or selection procedures, and, where appropriate, inclusion and exclusion criteria; (2) justification: basis for the study hypothesis, including, where appropriate, review of literature; (3) sample size: whether sample size was adequate given the study design; (4) informed consent: mention of consent as having been obtained from study participants where appropriate given the study design; (5) specifics of the intervention: adequacy of information about the treatment and control procedures; (6) adverse-event reporting: specific data about adverse events or at least consideration of the possibility of adverse events or toxicity; and (7) measurement of outcomes: definition of end points and criteria for success and a quantitative description of results.

We tried to hold descriptions of the intervention to normal standards of clarity and completeness in conventional research. For some modalities, such as strictly psychosocial interventions, we considered that adverse-event reporting might not have been necessary, but we noted its absence.

RESULTS

Of the more than 1,000 citations generated by our search, most fell into the aforementioned exclusion categories. We obtained and reviewed 403 articles and, of these, excluded 352 because they, too, fit into one or more exclusion categories (Table 2). The remaining 51 articles described treatments that fit our definition of unconventional therapy and were studied in at least some patients with breast cancer. However, even within modalities, the specific treatments were too diverse to permit systematic comparisons. Tables 3 through 6 list the articles grouped by end-point category. Information is included about modality, dosage, end point(s), design, sample size, findings, and shortcomings.

Table 3. Studies of Effects of Unconventional Therapies on Breast Cancer Progression

First Author, Year, Location	Modality	Dosage	End Points	Design	Sample Size		Findings	Shortcomings
					No.	% Breast Cancer		
Alternative programs of medical practice								
Bagenal,[13] 1990, United Kingdom	Bristol Cancer Help Center diet, counseling, meditation, yoga, orthomolecular medicine	Details of treatment regimen not specified	Survival	Cohort study	795	100	Center patients showed no significant survival benefits (RR = 1.26) compared with controls	Study participants, study justification, measurement of outcomes, informed consent for controls
Diet, nutrition and lifestyle change								
Brittenden,[12] 1994, United Kingdom	Oral L-arginine + chemotherapy, radiation therapy	10 g tid	Tumor size and histology	Phase II trial	24	100	22% complete response, 67% partial response, 89% experienced ≥ 50% reduction in tumor size	Study participants, study justification, informed consent
Hoffer,[17] 1993, Canada	Vitamin C B_3 Folic acid Vitamin E Other vitamins and minerals	12 g/d 1.5-3.0 g/d 5-10 mg/d 800 IU/d NS	Survival time	Retrospective cohort	170	24	23 adherent and 1 nonadherent alive at end of study (≥ 2 yr); mean survival adherent group 4× that of nonadherent group	Study participants, study justification
Lockwood,[47] 1994, Denmark	Vitamin C Beta carotene Selenium Gamma linoleic acid n-3 fatty acids Coenzyme Q10	2,850 mg/d 325 IU/d 387 μg/d 1.2 g/d 3.5 g/d 90 mg/d	Survival, further metastases, weight loss, pain, remission	Phase II trial	32	100	No patients died, none showed signs of further metastases, no weight loss, reduced use of pain killers, 6 patients showed apparent partial remission	
Recchia,[48] 1995, Italy	Retynil palmitate Interferon β Tamoxifen	50 IU bid 10 IU 3×/wk 10 mg tid	Survival, remission, disease stabilization	Phase II trial	36	100	31 mo median response duration, 64% response rate, 31% complete remission, 33% partial remission, 19% stable disease, 17% progressive disease	
Recchia,[49] 1995, Italy	Retynil palmitate Interferon β Tamoxifen	15-50 IU bid 10-30 IU 3×/wk NS	Survival, remission, disease stabilization	Phase II trial	49	100	55% clinical response, 20% stable disease, 25% disease progression, 19.2-mo median survival	
Herbal medicine								
Kovacs,[50] 1991, Switzerland	Iscador	0.33 mg/kg body weight, single IV infusion	DNA repair	Phase I trial	14	100	86% improved by day 7-8, DNA repair values 2.7 times higher	Informed consent
Mind/body control								
Gellert,[51] 1993, Santa Ana, CA	Peer support groups, family therapy, individual counseling, meditation and imagery	Weekly 90-min sessions	Survival	Retrospective cohort	136	100	Mean survival was 96 mo for intervention group and 85 mo for controls ($P = 0.1$)	

Table 3. *Continued*

First Author, Year, Location	Modality	Dosage	End Points	Design	Sample Size		Findings	Shortcomings
					No.	% Breast Cancer		
Morgenstern,[52] 1984, New Haven, CT	Support groups	90 min weekly	Survival	Retrospective cohort	136	100	Support groups and controls did not differ in survival (RR = 1.1; CI = 0.5-2.2)	
Newton,[26] 1983, Los Angeles, CA	Hypnosis and psychotherapy	1-10+ 1-hour sessions	Mortality, remission, disease stabilization, quality of life	Retrospective cohort	283	NS	Improved survival when compared with national and other center's data, mortality lower with more treatment, of the 24 patients with more hypnosis and psychotherapy treatment, 9 were in full remission	Study participants, measurement of outcomes
Simonton,[53] 1980, Ft. Worth, TX	Psychotherapy involving groups, individual counseling, relaxation, imagery	3-7 days of 6 to 9-h group sessions, then 5-day sessions every 3 mo	Survival	Retrospective cohort	225	33	Survival times of study patients were greater than those reported in the literature and national statistics	Study participants, measurement of outcomes
Spiegel,[11] 1989, Stanford, CA	Self-hypnosis and support therapy	Weekly 90-min sessions	Survival	Randomized clinical trial	86	100	Median survival of both groups was 20 mo, mean survival in treatment group was 18 mo longer ($P < .001$)	
Pharmacologic and biologic treatments								
Burzynski,[54] 1987, Stafford, TX	Antineoplaston A5	25 mg to 2.5 g/d	Efficacy in tumor regression, side effects	Phase I trial	15	20	9 of 15 patients had tumor regression and/or reduced symptoms; 6 had mild adverse effects: fever, arthralgia, arrhythmias	Informed consent, study participants, study justification, measurement of outcomes
Lissoni,[55] 1991, Italy	Melatonin	10 and 20 mg/d	Survival, disease progression	Phase II trial	54	6	21 of 54 had < 25% lesion increase, median survival 4 mo for the 3 breast cancer patients	Informed consent
Lissoni,[10] 1994, Italy	MLT + IL-2 IL-2 alone	40 mg/d 3 million IU/d, 6 d/w	Complete response: complete resolution clinically assessable disease at least 1 mo; partial response: some tumor regression; stable disease: no or minimal tumor growth; progressive disease: > 24% increase in lesions or new lesions; survival	Randomized clinical trial	80	9	Complete response in 3 of 41 IL-2+MLT patients and no IL-2-alone patients; partial response 8 of 41 IL-2+MLT group and 1 of 39 with IL-2 alone; stable disease in 12 of 41 with Il-2+MLT and 11 of 39 in IL-2-alone group; progressive disease in 18 of 41 with IL-2+MLT and 27 of 39 with IL-2-alone; 1-yr survival	Informed consent

Table 3. *Continued*

First Author, Year, Location	Modality	Dosage	End Points	Design	Sample Size		Findings	Shortcomings
					No.	% Breast Cancer		
							significantly higher in MLT+IL-2 group (19 of 41 *v* 6 of 39)	
Lissoni,[28] 1994, Italy	Melatonin Supportive care (corticosteroids and anticonvulsants)	20 mg/d NS	Survival and metabolic and infective complications	Randomized clinical trial	50 with brain metastases	20	Survival at 1 yr, free-from-brain-progression period and mean survival time were significantly higher in patients treated with melatonin (9 of 24 overall, 1 of 4 breast cancer) than in controls (3 of 26 overall, 1 of 6 breast cancer); steroid-induced metabolic and infective complications were significantly more frequent in those with supportive care only	Specifics of intervention
Lissoni,[29] 1995, Italy	Melatonin Tamoxifen	20 mg/d 20 mg/d	Disease progression, tamoxifen toxicity, serum IGF-1 and prolactin levels	Phase II trial	14 with metastases and history of failure to respond to tamoxifen alone	100	Partial response achieved in 4 of 14, 8 had stable disease and 2 progression; 10 patients survived > 1 yr from treatment onset; no melatonin-induced enhancement of tamoxifen toxicity; mean IGF-1 levels decreased ($P < .01$) and significantly more in responders ($P < .05$)	
Moertel,[56] 1981, Rochester, MN	Laetrile IV Oral	 4.5-7 g/m^2 0.5 g tid	Plasma and urine cyanide levels, metastases, progression	Phase I trial	6	NS	Few clinical side effects	
Moertel,[57] 1982, Rochester, MN	Laetrile IV Oral	 4.5 g/m^2 0.5 g tid-qid	Tumor regression, survival, disease progression	Phase II trial	178	12	1 patient showed signs of partial response, 54% got worse, there were signs of toxicity	Informed consent

Abbreviations: bid, two times per day; tid, three times per day; NS, not specified; IV, intravenous; RR, relative risk; CI, confidence interval; MLT, melatonin; IL, interleukin; IGF, insulin-like growth factor; qid, four times per day.

Table 4. Studies of the Effects of Unconventional Therapies on Symptoms Caused by Breast Cancer

First Author, Year, Location	Modality	Dosage	End Points	Design	Sample Size		Findings	Shortcomings
					No.	% Breast Cancer		
Alternative programs of medical practice								
Clover,[27] 1995, United Kingdom	Homeopathy, acupuncture, autogenic training, diet, Iscador	Treatments varied, dosages not specified	Health-related quality of life measured by Rotterdam Symptoms Checklist and Hospital Anxiety and Depression Scale	Prospective cohort	50	36	Significant improvements in psychological distress and anxiety, stable physical symptoms; the proportion of patients found to have normal anxiety levels increased from 48% to 75%	Informed consent, specifics of intervention, adverse-event reporting
Energy therapies								
Filshie,[19] 1985, United Kingdom	Acupuncture	Points not specified	Pain relief	Phase II trial	183	20	52% of patients significantly helped, 47% had reduced pain; 47% of postsurgery, chemotherapy, radiation therapy breast cancer patients reported improved power and pain relief from first to fourth visit	Informed consent, study participants, specifics of intervention, adverse-event reporting, measurement of outcomes
Herbal medicine								
Kuttan,[58] 1987, India	Topical turmeric and curcumin	0.5% ointment	Smell, itching, exudate, pain, lesion size	Phase II trial	62	11	90% reduction in smell, 70% in exudate, 10% in lesion size, and elimination of almost all itching	Informed consent
Manual healing								
Sims,[59] 1986, United Kingdom	Slow stroke back massage	3 10-min massages	Symptom distress (nausea, pain, appetite, etc), mood	Randomized crossover	6	100	Statistically nonsignificant reduction in symptom distress	Study participants, informed consent, sample size
Mind/body control								
Arathuzik,[60] 1994, Boston, MA	Relaxation, visualization and cognitive coping skills training	75- to 120-min sessions	Perceptions of pain intensity, pain distress, pain control, anxiety, depression, hostility, fatigue, confusion, and vigor	Randomized clinical trial	24	100	No significant differences in pain intensity and distress or mood, significant differences in ability to decrease pain ($P = .05$)	
Beck,[61] 1991, Salt Lake City, UT	Music therapy	2 45-min sessions with music for 3 days	Pain, anxiety, depression	Randomized crossover	15	47	75% had at least some response to music, statistically significant decrease in pain ($P < .05$), no effect on mood, no significant difference between sound and music	
Davis,[62] 1986, Canada	Biofeedback and cognitive therapy	4 biweekly 45-min session and 3 once-weekly sessions	Urinary cortisol and state anxiety	Randomized clinical trial	25	100	Greater improvement in treatment groups *v* controls, cognitive group better on cortisol, biofeedback better on anxiety	Informed consent

Table 4. *Continued*

First Author, Year, Location	Modality	Dosage	End Points	Design	Sample Size		Findings	Shortcomings
					No.	% Breast Cancer		
Spiegel,[63] 1983, Stanford, CA	Hypnosis and support groups	Weekly 90-min sessions over 1 yr	Self-rated pain	Randomized clinical trial	58 followed to end point, 86 recruited	100	Controls reported most pain, hypnosis group least, support group members median amount ($P < .05$)	
Pharmacologic and biologic treatments								
Chlebowski,[64] 1987, Los Angeles, CA	Hydrazine sulfate	60 mg tid	Weight gain, appetite, caloric intake, toxicity	Phase II-III trial	101	7	Treatment group had better weight control, appetite, and caloric intake ($P < .05$) and more toxic effects, although these effects were generally mild	Informed consent, adverse-event reporting
Lissoni,[65] 1995, Italy	Melatonin IL-2	40 mg/d 3 million IU/d	Platelet counts	Phase II trial	20	30	70% achieved normalization of platelet counts	
Lissoni,[66] 1996, Italy	Melatonin and/or supportive care (NSAIDS, opioid drugs, and corticosteroids)	20 mg/d	Weight loss, toxicity, disease progress, TNF-α	Randomized clinical trial	100*	19	Weight loss > 10% in 4% treatment group (melatonin plus supportive care) and 32% controls (supportive care alone) ($P < .01$); no melatonin toxicity observed; percent progressive disease was significantly less in treatment group (53% *v* 90%; $P < .05$); mean serum TNF increased in comparison group (ns) and significantly decreased in melatonin group ($P < .05$)	

Abbreviations: NSAIDS, nonsteroidal antiinflammatory drugs; TNF, tumor necrosis factor; ns, not significant.

*All patients had untreatable metastatic solid tumors.

Table 5. Studies of the Effects of Unconventional Therapies on Immune Function in Breast Cancer Patients

First Author, Year, Location	Modality	Dosage	End Points	Design	Sample Size		Findings	Shortcomings
					No.	% Breast Cancer		
Diet, nutrition, and lifestyle change								
Black,[67] 1984, Valhalla, NY	High-dose vitamins:							
	A E	100,000-300,000 IU/d 400-1,200 IU/d	Skin window reactivity to gp55 (a marker of cell-mediated immune function)	Phase I trial	30	100	Reaction to gp55 among > 60% only at high doses of vitamin A or vitamin E for > 18 days	Specifics of intervention, measurement of outcomes
Brittenden,[12] 1994, United Kingdom	L-Arganine supplementation	30 g/d	Peripheral-blood lymphocyte mitogen transformation assays, NK cell cytotoxicity, cytokines	Phase II trial	24	100	L-Arganine significantly increased lymphocyte mitogenic reactivity and enhanced NK cell and lymphokine-activated killer cell cytotoxicity ($P < .001$)	Informed consent
Garritson,[68] 1995, Denton, TX	Low-fat diet and fish high in omega-3 fatty acids	American Cancer Society dietary guidelines	T-cell function, urinary prostaglandins, NK cells, B cells	Phase II trial	9	100	Increased CD4 percentages and proliferation, decreased cytotoxic/suppressor T-cell (CD8) percentages and increased CD4/CD8 ratios ($P < .05$); did not change cytolytic activity of T cells, NK cells, total T and B cells, or urinary prostaglandins significantly	Sample size, adverse-event reporting (NA)
Energy therapies								
Chengjiang,[20] 1987, China	Microwave acupuncture Other therapy group All patients: vitamin B_4, leucogen + butyl alcohol; some patients: Chinese herbs, interferon, transfer factor + anion inhalation	25-30 *v* 20 min/d No dosages specified	WBC counts	Controlled trial, *v* leukopoietic drugs	49	30	90% treatment group, 80% control responded; $P < .001$ for response in treatment group, ns in controls	Study justification, study participants, informed consent, adverse-event reporting
Herbal medicine								
Beuth,[69] 1992, Germany	Galactoside-specific lectin from mistletoe	1 ng/kg body weight twice/wk	Pan T cells, helper T cells, NK cells, IL-2 and HLA-DQ receptors	Phase II trial	10	100	Increased levels of all immune function parameters with treatment	Sample size
Hajto,[70] 1986, Switzerland	Iscador	Mean dose, 36 mg/kg, single IV infusion	LGL NK cell activity	Phase II trial	20	100	LGL and NK cell activity increased 24 h after IV Iscador infusion	Informed consent
Hajto,[71] 1986, Switzerland	Iscador	Mean dose, 21-38 mg/kg, single IV infusion	Changes in immunomodulatory parameters	Phase II trial	22	100	Significant enhancement of immunomodulatory parameters	

Table 5. *Continued*

First Author, Year, Location	Modality	Dosage	End Points	Design	Sample Size		Findings	Shortcomings
					No.	% Breast Cancer		
Heiny,[72] 1994, Germany	Iscador	1 ng/kg body weight twice/wk	Lymphocyte counts, cytokine release, β endorphin levels	Phase II trial	36	100	Stabilization of lymphocyte counts, increased cytokine release, increased β-endorphin levels	Informed consent, adverse-event reporting
Hou,[73] 1991, China	Simple and compound gymnostemma pentaphyllum makino and radix astragali seu hedysari	30 g/d both compounds	Lymphocyte transformation test, immunoglobulin levels	Randomized clinical trial	40	20	Lymphocyte transformation test enhanced in both gymnostemma groups ($P < .05$)	Study justification, informed consent, adverse-event reporting
Li,[74] 1993, China	Yi Qi Sheng Xue decoction	1 dose/d	WBC counts	Randomized clinical trial	62	53	13% leukopenia morning treatment, 48% evening ($P < .01$)	Study justification, informed consent, adverse-event reporting
Mind/body control								
Gruber,[75] 1993, Chevy Chase, MD	Relaxation, guided imagery, biofeedback	Practice twice daily	Immune response assays, electromyographic activity, temperature, psychological status	Crossover, nonrandom	13	100	Intervention produced significant effects on immune measures, no psychological changes	
Richardson,[76] 1997, Aliso Viejo, CA	Support groups or imagery sessions	Weekly	NK cell cytotoxicity, cytokine levels, β endorphins, quality of life	Randomized clinical trial	47	100	No significant differences among those receiving support groups or imagery sessions and standard care for any measure of immune function. Improved coping strategies for support group participants ($P < .01$) and imagery sessions (ns). All women, regardless of treatment group, reported improved quality of life	Informed consent, adverse-event reporting (NA)

Abbreviations: NK, natural killer; LGL, large granular lymphocyte.

Table 6. Studies of the Effect of Unconventional Therapies on Side Effects of Conventional Treatment

First Author, Year, Location	Modality	Dosage	End Points	Design	Sample Size		Findings	Shortcomings
					No.	% Breast Cancer		
Diet, nutrition, and lifestyle change								
Loprinzi,[77] 1996, Rochester, MN	Dietician counseling	6 monthly sessions	Weight gain during chemotherapy	Randomized controlled trial	107	100	Median weight gain 2.0 kg in treatment group and 3.5 kg in control group (ns), more calorie reduction in treatment group, significantly more on weekends ($P < .05$)	
Myers,[78] 1983, Bethesda, MD	*N*-acytylcysteine	5.5 g/m^2	Ejection fractions, congestive heart failure, tumor response	Treatment group matched to untreated controls	54	24	Ejection fractions and heart failure rates similar in both groups, 33% controls, 50% treatment group, partial remission or stable disease (not an a priori end point)	Informed consent, measurement of outcomes
Energy therapies								
Dundee,[79] 1990, Ireland	Sea band after P6 acupuncture	Patients pressed P6 point with band 5 min every 2 h	Nausea and vomiting	Phase II trial	40	38	Antiemetic action of P6 acupuncture was maintained for 24 h in 95% of patients	Study participants, informed consent, adverse-event reporting, measurement of outcomes
Dundee,[80] 1989, Ireland	Electroacupuncture	15 min at P6 point	Vomiting and nausea	Crossover with placebo control, nonrandom	130	49	61 of 64 breast cancer patients reported a benefit from electroacupuncture for an 8-h period	
Lundeberg,[81] 1988, Sweden	Electrical nerve stimulation	2 h twice/d	Skin flap survival and blood flow	Randomized clinical trial	24	100	Treatment restored capillary filling in 78% with stasis	
Herbal medicine								
Maiche,[82] 1991, Sweden	Chamomile cream *v* almond ointment	Applied to skin bid, 30 min before irradiation and before bed	Skin radiation reaction	Simultaneous treatments, patient as own control	50	100	No significant difference in skin reactions, both had < 10% severe reactions	Informed consent, measurement of outcomes
Manual healing								
Hornsby,[83] 1995, United Kingdom	Graduated compression sleeve	28 days	Arm circumference, degree lymphoedema	Randomized clinical trial	25	100	Reduction in 86% treatment group and 36% controls	Study participants, adverse-event reporting
Zanolla,[84] 1984, Italy	Uniform manual massage Differential pneumatic manual massage	1 wk 6 h/d 1 mo, 1 h, 3 times/wk	Arm circumference	3-arm trial	60	100	Significant reduction in arm circumference for uniform pressure, pneumatic and manual massage, but not for differential pressure; mood improved most in uniform pressure group (ns)	Study justification, informed consent, adverse-event reporting
Pharmacologic and biologic treatments								
Lissoni,[85] 1997, Italy	Melatonin	20 mg/d	Chemotherapy toxicity	Randomized controlled trial	80	39	Thrombocytopenia, malaise and asthenia less frequent in melatonin group ($P < .05$); stomatitis and neuropathy less frequent in melatonin group (ns); alopecia and vomiting not different in the two groups	

Table 7. Distribution of Articles by Study Design and End Point Category

Study Design	End Point Categories: Breast Cancer Progression (Table 3, n = 19)	Disease Symptoms (Table 4, n = 11)	Immune Function (Table 5, n = 12)	Treatment Side Effects (Table 6, n = 9)	Total (N = 51)
Cohort study	1	1	0	0	2
Retrospective cohort	5	0	0	0	5
Phase I	3	0	1	0	4
Phase II	7	3	8	5	23
Phase III	3	7	3	4	17

Randomized clinical trials were the second largest group of articles, but only three of them had cancer-directed end points. All three had positive results. However, two of the three were trials of melatonin in study participants with a mix of several types of cancer, primarily with advanced disease[10]; these studies included too few breast cancer patients to yield definitive results with regard to breast cancer. The third was a trial of self-hypnosis and support-group therapy in 86 patients with advanced breast cancer.[11] Most of the other randomized trials had immune function end points that were difficult to interpret.

Nearly half of the articles were phase II studies. The rest were phase I trials or observational studies. Table 7 lists the distribution of the articles by study design and end-point category.

Table 8 summarizes the shortcomings of the articles. For the most part, the articles had few or minor shortcomings, although only 19 of 51 met every criterion. The most frequent shortcoming was failure to report whether informed consent was obtained. In one article, approval of the study by an institutional ethics committee was mentioned, but not informed consent.[12] The second most frequent shortcoming was lack of adverse-event reporting. Nine articles provided inadequate information about study participants, and nine failed to report outcomes intelligibly. Eight failed to supply an adequate rationale for the research described, and four failed to describe the intervention clearly. Only three articles had inadequate sample size for the study design. We found sample size inadequate when multiple end points were assessed or when a clinically significant effect on a single end point could not reasonably have been expected to be detected in the number of patients studied. We did not attempt to come up with a summary score for each article. Here we describe four articles in detail to highlight some of the problems of research in this area.

The first article listed in Table 3 was a cohort study of patients treated at the Bristol Cancer Help Centre in England.[13] This facility offers patients a multimodality, individualized treatment program that emphasizes diet but includes other forms of complementary medicine such as counseling, meditation, yoga, and orthomolecular medicine. In the 1980s, the Centre obtained funding from two leading cancer charities to have a study of its treatment outcomes conducted by investigators at the Institute of Cancer Research. The resulting study, published in *The Lancet*,[13] compared the survival of breast cancer patients who received complementary treatment (in addition to or after conventional treatment) at the Bristol Centre with survival among patients who received standard care in two hospitals. The members in the comparison group were identified through the cancer registries of the two hospitals and were frequency-matched to the Bristol patients on age and time since diagnosis. The article reported that the Bristol patients had poorer survival rates, on average, than the comparison

Table 8. Number of Articles Falling Short of Specified Criteria in Each End Point Category

Criteria	End Point Categories: Breast Cancer Progression (Table 3, n = 19)	Disease Symptoms (Table 4, n = 11)	Immune Function (Table 5, n = 12)	Treatment Side Effects (Table 6, n = 9)	Total (N = 51)
Study participants	6	1	0	2	9
Justification	4	0	3	1	8
Sample size	0	1	2	0	3
Informed consent	4	5	7	4	20
Specifics of intervention	1	2	1	0	4
Adverse-event reporting	0	3	6	3	12
Measurement of outcomes	4	1	1	3	9

group. The abstract stated that the same data had been obtained on both the Bristol patients and the "control" group. However, in the methods section, informed consent was mentioned only with regard to the Bristol patients, not the comparison group. The article noted that the Bristol patients had also supplied data about the unconventional modalities they used, their quality of life, and other issues, but did not present analyses of these data. The number of deaths among Bristol patients was reported, along with mortality rate ratios and confidence intervals, but the number of deaths in the comparison group was not reported.

This article has been widely criticized.[14-16] In our rating system, the article failed to meet the criteria of adequacy of information about study participants, justification, measurement of outcomes, and informed consent for controls. The article provided vague and misleading information about study participants and did not present a clear a priori hypothesis or reasons why the Bristol treatment might be expected to affect survival. The presentation of outcome data differed for the Bristol and comparison groups. The explicit mention of informed consent only for the Bristol group indicated that the design was prospective with respect to Bristol but retrospective with respect to the comparison group.

The third paper listed in Table 3 was a study of megavitamin therapy.[17] The survival of patients who adhered to the treatment was longer than that of patients who failed to adhere to it. However, the article did not mention that adherence itself may be a predictor of survival.[18] One author of the article was a psychiatrist; the study participants were patients whom he had treated with the megavitamin therapy. The article provided little in the way of a rationale for using the megavitamin regimen described to improve survival. The article also did not mention informed consent, but the study design was retrospective. The article provided tables of individual data for the 170 patients instead of statistical analysis.

The second article listed in Table 4 was a report on the use of acupuncture for pain relief among 183 cancer patients, including 36 who had just had surgery for breast cancer.[19] The article did not mention informed consent, lacked detail about the intervention, and made no mention of adverse events. The article reported that 47% of patients with breast cancer had less pain and more power in the ipsilateral arm after the fourth treatment than after the first but did not indicate how data on these changes were collected.

The fourth article listed in Table 5 described a Chinese trial of microwave acupuncture versus leukopoietic drugs to reverse neutropenia in 49 patients, including 15 with breast cancer.[20] The article failed to explain why microwave acupuncture might be expected to affect WBC counts and provided little information about study participants, none about informed consent, none about adverse events or toxicities, and none about effects among patients with breast cancer.

DISCUSSION

The literature we reviewed offers little guidance to patients with breast cancer seeking either documentation of the efficacy of popular unconventional therapies or ideas about other ways to improve their prospects for survival or disease-free survival. No data were available about the efficacy of such popular treatments as Essiac (Essiac Products, Inc, Campbellton, New Brunswick, Canada), 714-X (Cerbe West, Quebec, Canada), shark cartilage, or macrobiotic diets for breast cancer.[21]

As Tables 3 to 6 indicate, most of the studies we found reported favorable results but involved small numbers of patients with breast cancer or were intended to collect preliminary data for larger studies. Such studies should not be criticized for not being definitive. However, positive results of any sort pose serious temptations and problems of interpretation to patients yearning for a glimmer of hope. The increasing access of patients to preliminary data places a responsibility on investigators to highlight the limitations of their findings. The history of clinical cancer research is replete with examples of treatments that seemed promising in the laboratory or in a small number of patients who were monitored for a short time, but were ineffective or had intolerable side effects in larger or longer clinical trials.

It is not surprising that our search turned up few phase III studies of unconventional treatments with cancer-directed end points. Treatments that show a benefit when studied in this way are by definition no longer "unproven." Historically, bias against unconventional approaches, or a more general bias against research endeavors that run contrary to the conventional wisdom,[22,23] may have limited the funding or "publishability" of the results of studies of unconventional treatments for breast cancer. In addition, although input from practitioners may be critically important to the design and conduct of research on unconventional therapies, many practitioners of unconventional modalities lack formal research training. However, even established investigators tell anecdotes about having explored unconventional approaches in a spirit of genuine scientific curiosity and finding the results of these efforts difficult to publish and their willingness to look into the unconventional dangerous to their reputations and careers.[24] On the other hand, when conventionally credentialed investigators have published CAM studies with unfavorable results, a public outcry has ensued.[25]

Of course, no study is perfect, and practitioners of unconventional therapies often differ among themselves as to the "correct" administration of their treatment. However,

it is clearly important to try to achieve consensus among highly regarded practitioners of an unconventional therapy before undertaking a study. It may also be desirable to include such practitioners on a data and safety monitoring committee both to assure that the treatment is administered in a generally accepted way and to reduce the risk of repudiation of unfavorable results.

Several of the articles we reviewed were written by practitioners of the therapies described who seemed unfamiliar with research methods and scientific reporting but seemed to have made a serious effort to inform the medical community about treatments they believed to be effective.[17,19,26,27] A focused and constructively critical peer-review process might have made these articles more useful.

None of the shortcomings assessed in this review is unique to CAM studies. Obviously, not all studies of conventional therapies have sample sizes appropriate to their design and expected effect size. Likewise, not all reports of conventional clinical studies are based on explicit hypotheses supported by literature and/or a clear chain of reasoning; provide enough information about study participants, interventions, and outcomes to enable a reader to replicate the study; either confirm that informed consent was obtained or explain why it was not; and report the numbers and types of adverse events that occurred during the intervention and follow-up period in the intervention and comparison group. In some studies, no adverse events occur, but no treatment can be assumed to be completely harmless.

However, it is appropriate to hold studies of unconventional therapies to a higher standard for three reasons:

1. Regular readers of the biomedical literature on a particular topic tend to share a common understanding of the issues believed to be relevant to it. Such readers need relatively few cues to find their way through articles based on these common assumptions. Reports about unconventional treatments must provide the context, make their assumptions explicit, and justify their hypotheses solidly to be taken seriously by readers unfamiliar with these modalities.
2. When advocates or practitioners of unconventional therapies fail to disclose the details of an intervention, they weaken the scientific credibility of their results.
3. When conventionally credentialed investigators make vague or misleading statements about research on unconventional therapies, particularly when this research has negative results that are widely publicized, they undermine the credibility of science among both advocates of these therapies and the general public.

Of course, the criteria used in this review are useless against outright falsification or concealment of findings. A degree of trust is essential to peer review as well as other human endeavors. However, asking that investigators report clearly and completely can make dishonesty more difficult.

In our review, only one cancer-directed treatment showed positive results in a sufficient number of controlled trials to seem worthy of specific mention. In two randomized clinical trials[10,28] and a phase II trial,[29] melatonin had beneficial effects among patients with metastatic cancer, including breast cancer. Another study found that melatonin potentiates tamoxifen.[30] Additional studies have addressed the mechanisms of the effect of melatonin on estrogen receptors in breast cancer cells and the role of the pineal gland, which produces melatonin.[31] It can be argued that at this point, melatonin is not CAM. However, it is not in widespread use in conventional settings. We included it in our review because it is available over the counter; any patient with breast cancer who hears that it is beneficial can buy a bottle.

Whether melatonin at any dose, or any of the other treatments described in the studies we reviewed, can benefit patients originally treated for localized or regional breast cancer and currently free of clinically evident disease is unknown. In the United States currently, a majority of patients with breast cancer are diagnosed with early-stage disease. The studies we reviewed were conducted by a single team of investigators based in Italy and mainly included patients with advanced disease who had experienced failure with other treatment. A study of phytomelatonin for cancer prevention is now in progress in the United States, with results due in 2000.[32] That study may be more relevant to patients with no evident disease after conventional treatment.

A variety of CAM treatments seem to have short-term immunostimulatory effects. The relevance of these effects to breast cancer survival is unclear. Although immunocompromised individuals have a higher risk than others of developing some cancers, such as skin cancers and lymphomas, they are not at higher risk for breast cancer.[33] However, cancer and conventional therapy are known to have adverse effects on immune function, and low cell counts affect treatment schedules. Immunostimulatory agents may therefore be useful adjuncts to conventional treatment if they do not interfere with the ability of the conventional treatment to kill tumor cells. Indeed, a critically important question about all agents used to relieve the side effects of chemotherapy and radiation therapy, including effects on immune function, is whether and, if so, how they alter the effect of the treatment on cancer cells.

Little is known about the implications of immune parameters for breast cancer outcomes.[34-36] In general, more immune cells and greater immune system activity would seem to be beneficial to patients with breast cancer. How-

ever, that may not always be true; immunosuppressed kidney transplant patients have lower risk of breast cancer than the general population.[37]

Many studies with immune parameter end points assess many aspects of immune function simultaneously. If several studies of treatment X find significant associations with the same immune parameter, then it may be reasonable to conclude that treatment X has caused that effect. However, that finding does not mean that patients who receive treatment X will survive longer than other patients. Some aspects of immune function, such as natural-killer cell activity, do seem to be related to cancer survival.[35,38] But immune function can involve inflammation, pain, allergic reactions, and other effects that are not necessarily related to survival and do not enhance the quality of life of the patient. Moreover, some agents that seem to stimulate immune cell proliferation also may stimulate cancer cell proliferation.[39]

In recent years, cancer immunology has become one of the most rapidly growing fields in basic cancer research. A number of scientists are now seeking ways to promote host antitumor immune cell activity and to overcome the ability of the cancer cell to evade immune surveillance.[40] These approaches are intended, like chemotherapy and radiation therapy, to cause the destruction of tumor cells but to be much more cancer-specific than existing treatments and therefore less harmful to normal cells. These approaches are based on evidence for the phenomenon of immune surveillance against cancer, which is also the focus of CAM approaches with immune function end points.

Many patients turn to CAM when experiencing the side effects of conventional breast cancer treatment. Acupuncture seems to relieve nausea and vomiting associated with chemotherapy. Massage and pressure after mastectomy seem to reduce lymphedema. Mind/body methods of treatment also show some potential to reduce the pain and stress experienced by women undergoing treatment for breast cancer.

However, in general, the studies we reviewed are either too preliminary or too heterogeneous to provide clear direction for patients with breast cancer. What is lacking in the literature is more notable than what is present. This situation is now changing. Leading biomedical journals have publicized their interest in studies of CAM treatments.[41] In addition, several new journals have been established to publish articles about them. These new journals and some older ones are now covered by Medline and other widely used scientific bibliographic databases.

An increasing number of studies of CAM for cancer are in progress at reputable institutions. In addition, hospitals are opening facilities to provide some unconventional treatments.[42] Investigators in these settings may have unprecedented opportunities to study the treatments being provided.

Although some holistic approaches, such as traditional Chinese medicine, do not lend themselves easily to the standard clinical trial design, investigators have successfully studied such approaches in a randomized trial.[43] Other designs, such as observational studies, could also be used to assess them. Analytic techniques such as propensity scoring[44] and sensitivity analysis[45] may be useful in settings where recruitment or compliance with random assignment may be difficult to achieve or result in an excessively selected group of study participants.[46]

Common single-agent treatments, such as Essiac tea, lend themselves more readily to standard clinical trial design. Given that patients are using these agents without any valid data about their effects on breast cancer or their interactions with other treatments, such trials should be conducted promptly. The expansion of the National Center for Complementary and Alternative Medicine and of funding from private sources for CAM research, the advent of specialized CAM journals, and the increasing interest of leading biomedical journals in CAM research support the expectation that within the next few years, evidence regarding the safety and efficacy of some forms of CAM will become available.

ACKNOWLEDGMENT

We acknowledge the contributions of Daniel Eskinazi, Alison Estabrook, Pam Factor-Litvak, Adriane Fugh-Berman, Victor R. Grann, Eric Grund, Deborah D. Kennedy, Michael Lerner, Ralph Moss, Alfred I. Neugut, Gwen Nichols, Ruby Senie, Linda Vahdat, and Christine Wade, who read and commented on earlier drafts of the manuscript.

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Complementary and alternative medicine (CAM) use is common among cancer patients. This paper reviews the use of CAM in a series of patients with locally advanced breast cancer (LABC). Methods. Women with LABC attending a specialist clinic at a single Canadian cancer centre were identified and approached.Â Sixteen of the most common reasons for using CAM and patient perceptions of CAM therapy were derived from the current literature and listed as choices [2]. Patient's beliefs and perceptions of their disease were assed using a Likert scale with larger scores representing higher perceptions of risk [14]. What cancer patients, their families, and caregivers need to know about the coronavirus. Skip to Content. Cancer Helpline.Â Our team of expert journalists brings you all angles of the cancer story â€“ from breaking news and survivor stories to in-depth insights into cutting-edge research. Explore News. Latest News.Â You'll also find a wealth of information on specific complementary and alternative treatments, grouped into the five categories below. Complementary and Alternative Methods and Cancer. You may hear about alternative or complementary methods to prevent, diagnose, or treat cancer or its symptoms. Learn about what these terms mean and find information to help you think through the issues to make the most informed and safest decision possible. complementary /alternative medicine for patients with. breast cancer: a review of the biomedical literature. J Clin. Oncol 2000;18:668-83.Â Background. Today, complementary and alternative medicine (CAM) use is being routinely practiced by cancer patients worldwide. This study aimed at examining the prevalence of CAM use in patients with cancer and comparing the quality of life (QoL) in CAM users and nonusers. Methods. A cross-sectional study was employed on 195 cancer patients receiving chemotherapy at Gondar University Referral Hospital (GURH) chemotherapy center.