

Review

Complementary and alternative therapeutic approaches in patients with early breast cancer: a systematic review

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Summary

Complementary and alternative medicine (CAM) is becoming increasingly popular, particularly among patients with breast cancer. We have done a systematic review of studies published between 1995 and February 2005, identified through a comprehensive search. CAM encompasses a wide range of treatment modalities, including dietary and vitamin supplements, mind-body approaches, acupuncture, and herbal medicines. The objectives of CAM treatments are diverse: reduction of therapy-associated toxicity, improvement of cancer-related symptoms, fostering of the immune system and even direct anticancer effects. Clinical trials have generated few or no data on the efficacy of CAM, whether regarding disease recurrence, survival, overall quality of life or safety. Some CAM methods may even have adverse effects or reduce the efficacy of conventional treatment. The primary justification for CAM is based on empirical evidence, case studies, and hypothetical physiological effects. We conclude that available data on CAM modalities in the treatment of early-stage breast cancer does not support their application.

Introduction

Every oncologist has been faced with questions from a breast cancer patient such as “*What vitamins or minerals should I be taking doctor? And how about mistletoe?*” Depending on the attitude of individual doctors, the answer will range from total rejection to complete acceptance of any kind of complementary and alternative medicine (CAM). It might be helpful for clinical oncologists to be aware of the available data regarding the efficacy and safety of the most popular CAM methods used by their patients. As shown in Figure 1 CAM does not inhibit the tumor growth.

CAM has been defined by the National Center for CAM as a group of diverse medical and health care systems, practices, and products that are not normally considered to be conventional medicine [1,2]. These treatments might be undertaken adjuvant to, or instead of, conventional treatment. Complementary medicine is extremely popular. In 1993, in a ground breaking study, Eisenberg et al. [3] showed that patients paid approximately \$13.7 billion for these treatments, mostly out of their own pocket. Recent studies have shown that 48–98% of all breast cancer patients use some form of CAM, [4,5] and that almost 50% of them never discuss their use of CAM with their oncologist [6,7].

This article will review and evaluate the relevant literature between 1995 and March 2005 on the pros and cons of CAM effectiveness for patients with early-stage breast cancer. Data for review were identified by searches of following databases:

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| PubMed | http://www.ncbi.nlm.nih.gov/entrez/query.fcgi |
| The Cochrane library | http://www.cochrane.org |
| The National Academies Press | http://www.nap.edu/ |
| National Cancer Institute/ Cancerlit | http://www.cancer.gov/ |
| National Center for Complementary and Alternative Medicine | http://nccam.nih.gov/ |
| American Society of Clinical Oncology | http://asco.org/ |
| Current Contents | http://www.isinet.com/products/cap/ccc/ |

Keywords included in the search strategy: “breast cancer survivors” or “patients with breast cancer” and

- safety or side effects
- Mistletoe

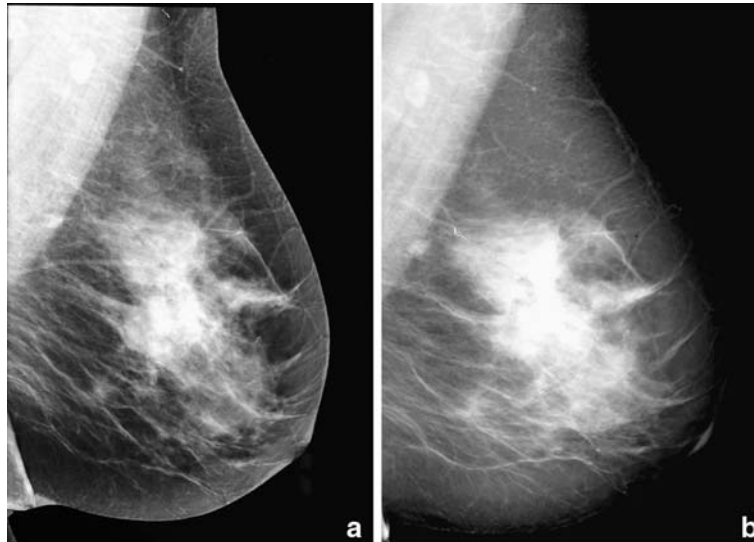


Figure 1. Mammograms of a 50 year old patient and histological proven breast cancer and tumor growth during CAM application: (a) before and (b) 6 months after own treatment with isopathic therapies and other approaches: *Mucoracemosus fresenius*, *aspergillus niger*, black cohosh, revitalization of gastroenteron by special diet and Chinese massage, electroacupunctur to splen, gaster, pancreas and pericard, alcalization of urine and twice daily pH control, complete tooth revitalization, reduction of psychologic stress, 12 h sleep per day, diet without any dairy products, pork, sweets or alcohol, megadosis of vitamin C infusions (45 g/week), Se, Zn, Mg, Mn, Cu, Coenzyme Q10, immunomodulation with utilin, latensin and recarcin.

- Phytoestrogens
- Vitamins,
- Minerals,
- Trace elements, copper, selenium, zinc
- Enzymes
- Herbal medical products
- Acupuncture
- Psychological therapies/hypnosis

Search was limited to: Clinical trials, human, animal, cell culture and English language. Case reports were excluded.

Although many useful articles on unconventional therapies appear in the lay literature, magazines and books these articles were not considered.

Is the use of CAM for breast cancer supported by evidence-based medicine?

Decision-making in conventional medicine should ideally be based on biological mechanisms, clinical experience and statistical evidence. It treats by removing a presumed cause of sickness and success is measured by determining distinct treatment endpoints [8]. CAM methods tend to stimulate innate and individual healing forces, which are known by many names and appear in different facets. Many of these methods are based on a view of life that integrates physical as well as meta-physical aspects into one non-analytical and often semi-religious picture. In many cases of CAM there are even *in vitro* and *in vivo* data from animal models to support such hypotheses. Clinical data are rare and consist mainly of empirical work or case reports. Finally, data from primary prevention studies have been applied to patients who have already had early-stage breast cancer.

The US National Cancer Institute (NCI) [9] provides a detailed report on the “Level of Evidence for Human Studies of Cancer CAM”. So far, CAM methods for breast cancer survivors do not meet evidence-based medicine criteria [8]. Most studies are epidemiological multicentre retrolective cohort study, qualifying for LOE “3a”. Therefore we could not use the comprehensive search strategies described by Robinson and Dickersin [10].

Who uses CAM?

Factors favoring the use of CAM in cancer patients are quite diverse. In general, these patients are not dissatisfied with conventional medicine, but find alternatives to be more congruent with their own beliefs and philosophical orientations towards health and life [11,12]. Patients gather information from various sources, including personal communication with friends and relatives, print media, television programs and the Internet. Archetypal patients who request and use CAM are usually well-informed, young, urban professionals with a higher income [13–16]. The heterogeneity of coverage practice for CAM is caused by different insurance policies, practitioner requirements and health plans within each carrier [17–19]. Own, unpublished data revealed that 45% of patients included in randomized studies used any kind of oral or parenteral applicable CAM (data prepared for publication).

There are marked cultural differences in the way that doctors, as well as patients, integrate CAM into treatment regimens. While only 4% of Norwegian doctors believe that CAM might have a role in the treatment of cancer patients, roughly 20% of German doctors do so [20,21]. In Europe, for example, preferred therapies

include mistletoe extracts, vitamin therapies, selenium, and phytoestrogens, while in Asia traditional Chinese or Japanese medicine, spiritualism, hypnosis and aromatherapy enjoy widespread popularity. North American cancer patients are commonly treated using acupuncture, hypnosis and spiritualism, as well as vitamin therapies and extracts from various plants [22,23]. Special diets or mixtures such as “macrobiotica”, [24] “garlic” (*Allium sativum*), [25] “ginger” (*Zingiberaceae*), [26] and mixtures of nutrients, such as “Nitter therapy”, [27] “Gerson”, [28] “di Bella Multitherapy”, [29] and “Ukrain” [30] enjoy only local popularity.

Why do patients turn towards CAM?

Although expectations are quite individual, cancer patients may have quite specific goals. By using CAM they hope to achieve a strengthen of the immune system (91%), a decrease in therapy-associated toxicity (61%), assistance of conventional therapies (58%), a direct anti-cancer effect (42%) and to alleviate cancer-derived symptoms (34%) [31]. A correlation between any form of CAM and disease-free or overall survival has not been demonstrated yet.

Many cancer patients try to look for some sort of reason to explain the onset of their disease, or they may feel some sort of guilt regarding their illness. They often come to the conclusion that they have led an “unhealthy life” and that now might be the time to start to care for their body in various ways. They might act to reduce stress, and add vitamins, trace elements or other substances to their diet. Most of these substances are said to “strengthen” the immune system. Another feature is a fear of the side effects of conventional therapy. Finally, some practitioners may find it easier to prescribe some CAM agent, rather than facing the up to the dismal outlook of incurable disease, and consequently CAM is prescribed mainly by General Practitioners and other non-specialized doctors, whereas oncologists tend to be quite restrictive in recommending it to their patients [21].

Complementary and alternative medicines

Mistletoe

Mistletoe preparations are particularly popular in Europe. They are usually extracts from common mistletoe plants that live in symbiosis with many European trees. These extracts contain mistletoe lectines and viscotoxines, which have been shown to modify intracellular protein synthesis, stimulate cytokine production, inhibit tumor colonization and induce cell necrosis *in vitro*. Simultaneous treatment of breast carcinoma cells (MCF-7) with mistletoe lectines rendered them more sensitive to the induction of apoptosis by TNF- α . Data from mice models suggested an anti-cancerous, anti-metastatic, pro-apoptotic and cytotoxic effect [32,33].

However, 84 non-randomized clinical trials have failed to establish whether use of mistletoe preparations lead to an increased overall survival. Many of the studies examine the issue of improving quality of life using mistletoe preparations, while undergoing conventional chemotherapy [34,35]. A randomized, placebo-controlled, double-blind, multicenter clinical trial included 272 breast cancer patients receiving adjuvant cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy. In this study, the standardized mistletoe extract lead to a significant improvement in quality of life [36]. Furthermore, standardized mistletoe extract was shown to significantly influence the immune status of tumor patients [37].

In a recent meta-analysis, Kienle et al. report that most of the 23 examined studies were based on very poor quality data [38]. There are currently no placebo-controlled double-blind randomized clinical trials that prove the efficacy of mistletoe preparations in terms of recurrence-free or overall survival after breast cancer [39,40]. It seems to be extremely difficult to complete a prospective placebo-controlled, double-blind mistletoe trial in this setting: as Gerhard et al. [41] reported recently, only 6% of suitable patients agree with randomization.

There are also safety concerns regarding the use of mistletoe preparations. *In vitro* studies have shown that they enhance DNA repair mechanisms in peripheral blood mononuclear cells. Induced cytokines may stimulate tumor cells and influence apoptotic pathways in healthy tissue [42,43]. Whether these *in vitro* data are relevant to the human *in vivo* situation, in which mistletoe preparations are usually given concomitantly with conventional chemotherapy, remains an unresolved question.

Phytoestrogens

Phytoestrogens are classified as water-soluble isoflavones and lipophilic lignanes. Isoflavones are found mainly in soya beans and lignanes in linseed wheat, fruit, flaxseed and vegetables. Depending on their metabolism and concentration, phytoestrogens execute antiestrogenic (2-hydroxyestron) or estrogenic (16- α -hydroxyestron) effects. They block estrogen receptors and lead to decreased activation of estrogen, compared to physiologic estrogen effects in premenopausal women. Furthermore, they have been shown to stimulate the synthesis of sex hormone-binding globulin, inactivate estrogen and to inhibit tyrosine kinase activity, aromatase activity and angiogenesis [1,44-47]. Phytoestrogens increased estrogen-responsive human breast cancer cell proliferation at low doses, but paradoxically caused profound inhibition of growth at higher doses (Figure 2). There are currently six published randomized controlled trials, only one of which was able to show a positive effect in cancer patients [48]. A meta-analysis of 18 epidemiological studies on the incidence of breast cancer was not able to show any

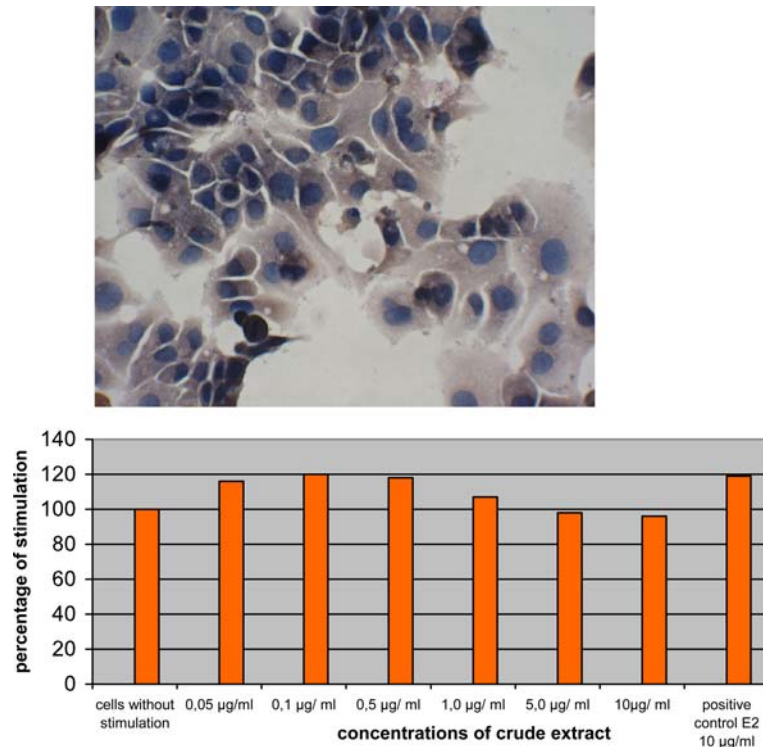


Figure 2. Influence of a flaxseed crude extract on the ER-positive breast cancer cell line MCF-7: higher concentrations of the flaxseed crude extract show an inhibitory effect, whereas lower concentrations provide stimulatory effects in comparison to 17 β -Estradiol.

preventive effect of soya beans [49]. At present, there is no evidence to support recommendations to use phytoestrogens, either to treat breast cancer nor to ease nor to prevent climacteric symptoms [50–53].

Phytoestrogens, especially soya-derived products, are extremely popular for treating postmenopausal symptoms in women with breast cancer while undergoing tamoxifen therapy. The principal constituents of soy, isoflavones genistein and daidzein, are structurally similar to 17 β -estradiol and produce weak estrogenic effects [54]. Genistein, has been shown to counteract the inhibitory effect of tamoxifen on breast cancer growth and increased expression of estrogen-responsive genes *in vitro* [55,56]. Experimental data indicate that soya can stimulate the growth of estrogen-dependent tumors in mice [57,58]. Recent findings suggest that oxidative DNA damage by isoflavone metabolites plays a role in tumor initiation. Isoflavones may increase cell proliferation by estrogen receptor binding and induce tumor promotion and/or progression, leading to cancer in estrogen-sensitive organs [59]. Moreover, some phytoestrogens, like *Trifolium pratense* (red clover), *Cimicifuga racemosa* (black cohosh), *Humulus lupulus* (hops), *Angelica sinensis* (dong quai), and *Glycyrrhiza glabra* (licorice), may exert their estrogenic influence through receptor-dependent and/or -independent mechanisms. These findings have led to speculation that phytoestrogens should not be given to patients with hormone-dependent cancers [60].

At present, it seems sensible to discourage the use of soya-derived products by patients with estrogen-dependent tumors (e.g., breast or endometrial cancer).

Vitamins

Vitamins A, B and E, as well as trace elements, like selenium, are known to capture free radicals. They have a role in preventing lipids from oxidizing, are involved in DNA-repair mechanisms and influence apoptotic pathways [61–63]. An anti-cancer effect has been shown *in vitro*. To date, no studies have established a role for vitamins and selenium in the prevention of breast cancer [64]. In a randomized controlled trial, 2972 patients with invasive or non-invasive breast carcinoma received either 200 mg of the vitamin A preparation (Fenretinide) per day or no therapy [65]. After a median follow-up of 97 months, no significant differences in distant disease-free or overall survival could be demonstrated. This trial, however, was able to show a significant reduction in local breast cancer recurrence for premenopausal women (HR: 0.65; 95% CI: 0.46–0.92). Bexarotene, a retinoid X receptor-selective retinoid with preclinical antitumor activity in breast cancer, revealed only limited efficacy in 145 patients with refractory metastatic breast cancer [66].

A cohort study, examining high doses of vitamin preparations with beta-carotene, vitamin C, niacin, vitamin B3, selenium, coenzyme Q and zinc, started 6 months after diagnosis in addition to standard therapy, showed a marginal negative effect after a median follow up of 68 months [67]. Another study established that above-normal serum concentrations of vitamin E had a negative effect on breast cancer patients [68].

In conclusion, there is no role for supplementation of vitamins or trace elements in breast cancer patients,

providing they adopt a balanced and healthy diet [69]. The only exception to this rule seems to be patients suffering from a concomitant illness leading to malabsorption or maldigestion. For example, patients, who develop mucositis with chemotherapy may be supplemented with the recommended daily allowance of vitamins, minerals and trace elements [70].

Trace elements

Selenium is known to enhance the number of natural killer cells and interferon- γ -secretion *in vitro*. Preventive effects have also been demonstrated in patients with prostate and gastric cancer, but not breast cancer [64,71,72]. Selenium is an integral part of the tertiary structure of many enzymes (e.g. superoxididismutase, catalase, glutathionperoxidase) that are known to safeguard cells against oxidation by free radicals. In our daily diet, selenium is found mostly in broccoli, leek and red meat, and a single Brazil nut per day provides enough selenium to meet the regular daily uptake. It may also provide between chemotherapeutic agents, such as doxorubicin or paclitaxel, and selenium has been shown in studies with breast cancer cell-lines [73]. Among other mutations, tumor cells are known to show exceptionally high expression of antioxidizing enzymes. As selenium is needed by many of these enzymes in order for them to function, it may well be possible that selenium reduces the susceptibility of cancer cells to chemotherapy rather than protecting healthy tissue. Alterations in serum concentrations of selenium in women with breast cancer appear to be a result, rather than a cause of cancer [72].

Copper and zinc also form part of many enzyme complexes known to protect against free radicals [74–76]. The frequency of distant metastasis was shown to be significantly higher in 182 breast cancer patients with decreased serum copper levels [77]. In another study, however, *N*-methyl-*N*-nitrosurea-induced breast carcinoma tissue of the rat was shown to accumulate zinc to a significantly higher degree than surrounding tissue. This suggests a potential role for zinc in tumor genesis [78].

Changes in serum levels of trace elements may generally be the result rather than the cause of breast cancer, while tumor cells have an increased requirement for trace elements. There are few clinical data to support the use of selenium, zinc or copper supplementation in the prevention or treatment of breast cancer and, so far, no randomized clinical trials have demonstrated improved quality of life or prolonged overall survival using trace element supplementation [15,79].

Enzymes

The popularity of enzyme preparations has decreased markedly since the advent of bovine spongiform encephalopathy (BSE) some years ago. One of the most-studied enzymes, with respect to its presumed anticancer

effect, is coenzyme Q10 (synonyms: *Q10*, *Co Q10*, *vitamin Q10*), which is synthesized by human cells as an anti-oxidizing agent. Since it was shown to have an antiproliferating effect *in vitro*, *Q10* has been studied as a cytostatic agent in the adjuvant setting [80], as well as a protective agent during chemotherapy [81]. Case reports describing instances of complete remission while using Q10 [82] have never been backed up by clinical trials and in fact Q10 has even been shown to decrease the efficacy of radiotherapy in an animal model [83]. An epidemiological retrospective cohort analysis provides evidence that oral enzymes in breast cancer patients improves the quality of life by reducing signs and symptoms of the disease and the side effects of adjuvant antineoplastic therapies [84].

Herbal medical products

Numerous herbal medical products are promoted as CAM. *In vitro* studies of individual components or mixtures have shown some biological activity, comprising antioxidant, endocrine, immunostimulant and antitumor properties. Preparations of plants, based on ancient recipes from Chinese or Japanese medical tradition, are mainly popular in Asia and North America [85]. Many mixtures are known to have an anticancerous effect *in vitro* [86–88], yet, no clinical trials have been performed to study efficacy and safety in breast cancer patients.

Although at first sight, herbal remedies appear safer and “more natural” than conventional drugs, significant adverse effects and drug interactions may still need to be considered. Many herbs exert an anticoagulatory effect via induction of cytochrome P450 pathways [89], Kava and Comfrey are known to be hepatotoxic. Saffrol, one of the ingredients of “Dong Quai” has been shown to be tumorigenic, while many herbs, including *Aristolochia fangchi*, are potentially nephrotoxic and have been shown to cause acute interstitial nephritis and carcinoma of the transitory epithelium [1,70]. A complete review of herbal remedies and their potential adverse effects has recently been published by Sparreboom et al. [23].

Green tea is said to prevent cancer because of its antioxidating ingredients as well as its cytotoxic polyphenols. However, in a current meta-analysis of studies comparing the daily intake of 1 versus 5 cups of green tea with respect to the risk of developing breast cancer, no correlation (relative risk: 0.84, 95% CI: 0.57, 1.24, $p=0.69$) could be established [90]. Breast cancer patients consuming more than 5 cups per day were seen to have a prolonged recurrence-free and overall survival [91]. Other data, involving patients with prostate cancer, revealed a significant increase in the frequency of diarrhea and vomiting while showing no benefit with regard to the malignant disease [92]. It should also be noted that various additives are used to alter the taste or tolerability of tea are sometimes seen to have other side effects [26].

Isopathic therapies is a system of healing using isopathic/homeopathic medicines that assist in restoring balance and harmony to an organism. The main objective is to stabilize the pHs and slowly bring the fungus/mold back to a normal symbiotic state by using the isopathic remedies.

Acupuncture

Very few asymptomatic breast cancer survivors use acupuncture [4]. Acupuncture has been studied in breast cancer patients primarily with the intention of reducing chemotherapy-induced nausea and vomiting, menopausal symptoms and pain perception [4,93,94]. An increasing body of data supports the efficacy of acupuncture for cancer-related pain [95] and reducing the frequency of vomiting [96]. This effects, however, were of limited duration.

Psychological therapies/hypnosis

Many patients with cancer turn to psychological therapies like praying, spirit medicine, hypnosis, meditation, affirmation, imagery or rituals. Many studies have demonstrated interactions between the central nervous and the immune systems. While a negative effect of stress on immune responses has been demonstrated, there have also been published reports that psychological treatments can positively alter the immune system [97–99].

Is CAM safe?

While many forms of CAM are associated with minimal or no risk, this is not true for all such therapies. On the contrary, the combined use of CAM with certain anticancer drugs may increase or reduce the effects of either component [23,100]. Obviously, synergistic therapeutic effects may complicate the dosing regimen of long-term medications or lead to undesired toxicities. Herbal preparations may interact with enzymes and transport proteins in charge of drug metabolism. Although interactions are most likely to arise secondary to altered pharmacokinetics of the involved drugs [101], pharmacodynamic interactions [102] and the intrinsic toxicity of several herbs have also been documented. Aristolochic acids, for example, which are present in the Chinese herb *Aristolochia fangchi* may undergo a chemical reduction by hepatic cytochrome P450 (CYP1A1/2) or peroxidases in extrahepatic tissues to form reactive cyclic nitrenium ions. The latter has been found to be capable of reacting with DNA and proteins, potentially resulting in activation of H-ras oncogene, gene mutations and finally carcinogenesis [103]. When herbal preparations are taken by patients currently on chemotherapy, uncontrolled induction of various enzymes and transporters may also take place in tumor cells, subsequently resulting in resistance to

anthracyclines, epipodophyllotoxins, cisplatin, taxanes, and vinca alkaloids [104,105]. Likewise, catalytic inhibition of topoisomerase II α in tumor cells by some herbs [106] might diminish the therapeutic response to anthracyclines, dactinomycin, and etoposide [107]. Phytoestrogens may also counteract the inhibitory effect of tamoxifen on breast cancer growth [55,59]. Otherwise black cohosh extracts increased the cytotoxicity of doxorubicin and docetaxel in cell culture [104]. Finally, there are also serious safety concerns about mistletoe applications [42,43].

A Norwegian longitudinal study, following 515 patients with different cancer types for a median of 8 years, suggests that use of several types of specific alternative medicine may be associated with shorter survival (79% versus 65%). In a Cox regression model adjusted for demographic, disease and treatment factors, the hazard ratio of death for any use of CAM compared with no use was 1.30, (95% CI: 0.99–1.70; $p=0.056$), suggesting that CAM use may predict a shorter survival [27,108].

Conclusion: so, what should oncologists advise?

Oncologists should be aware of CAM approaches prevalent in their patient population, should inquire about their use and should be able to counsel for or against them. There is no compelling evidence that any of the numerous complementary treatments available is sufficiently effective in breast cancer patients to justify its use (Table 1). It should be the responsibility of those who claim efficacy for CAM to support these claims with acceptable evidence, rather than the responsibility of those who criticize CAM to prove its non-efficacy. On the one hand, if more convincing data existed, there might be far less room for disagreement. On the other hand, if the medical profession rejects CAM because it is not evidence based this could be counter productive, as medical therapy is not merely concerned with evidence. The patient–doctor relationship and an individual's beliefs concerning health and life are equally important. Empathic and supportive communication with the patient about complementary forms of treatment may well strengthen the patient–doctor relationship. Doctors should ask patients about their use of CAM and should talk openly and objectively about the evidence, or lack of it, for alternative or complementary cancer therapies. Discussions might include the fact that some forms of CAM are potentially linked with considerable risks, and that some are associated with neither prolongation of life nor improved quality of life. A particularly poorly documented aspect of CAM is its potential interaction with other medical agents or cancer treatments.

The concept of *evidence*, however, is a mainstay of conventional medicine to which these therapeutic approaches are proud to be an alternative to. Nevertheless, in the U.S. the National Institutes of Health (NIH) Center for CAM [1] and the NCI are supporting

Table 1. Proven effects of different CAM approaches in breast cancer

| Approach | Effects | <i>In vitro</i> data | Animal model | Randomized trial available | Recent references |
|----------------------------------|--|----------------------|--------------|----------------------------|-------------------|
| Mistletoe | Preventive effect on breast cancer incidence | | | - | No data |
| | Anti-cancerous/-metastatic, pro-apoptotic, cytotoxic | + | + | | [32,33] |
| | Immunomodulation | | + | | [37] |
| | Improved quality of life during systemic treatment | | | + | [35,36] |
| | Improved disease free survival | | | | No data |
| Phytoestrogens | Preventive effect on breast cancer incidence | - | - | - | [48,49,59] |
| | Block estrogen activity in premenopause | +/- | - | - | [57,109-111] |
| | Abrogates tamoxifen effects | | + | | [56] |
| | Improved quality of life during systemic treatment/treatment of climacteric symptoms | | | - | [52,53,112] |
| Vitamins | Improved disease free survival | | | | No data |
| | Preventive effect on breast cancer incidence | | | - | [64] |
| | Anti-cancer/-metastatic, pro-apoptotic | + | + | | [61-63,113] |
| Antioxidants/trace elements | Improved quality of life during systemic treatment | | | | No data |
| | Improved disease free survival | | | - | [65] |
| | Preventive effect on breast cancer incidence | | | - | [64,71,72] |
| | Anti-cancer/-metastatic, pro-apoptotic, antiangiogenic | + | + | | [74-76,114] |
| | Improved quality of life during systemic treatment | | | | No data |
| Proteolytic enzymes | Improved disease free survival | | | | No data |
| | Preventive effect on breast cancer incidence | | | | No data |
| | Anti-cancer/-metastatic, pro-apoptotic, antiangiogenic | | + | | No data |
| | Improved quality of life during systemic treatment | | | | [114] |
| Herbal medical products | Preventive effect on breast cancer incidence | | | | No data |
| | Anti-cancer/-metastatic, pro-apoptotic, antiangiogenic | + | + | | No data |
| | Improved quality of life during systemic treatment | | | | No data |
| | Improved disease free survival | | | | [86-88] |
| | Alter the response to agents commonly used to treat breast cancer | + | | | No data |
| Acupuncture | Improved disease free survival | | | | [104-107] |
| | Preventive effect on breast cancer incidence | | | | No data |
| | Anti-cancer/-metastatic, pro-apoptotic, antiangiogenic | | | | No data |
| | Improved quality of life during systemic treatment | | | | No data |
| Psychological therapies/hypnosis | Preventive effect on breast cancer incidence | | | | No data |
| | Anti-cancer/-metastatic, pro-apoptotic, antiangiogenic | | | | No data |
| | Improved quality of life during systemic treatment | | | + | [96] |
| | Improved disease free survival | | | | No data |
| | Preventive effect on breast cancer incidence immunomodulation | | | + | No data |
| | Improved quality of life during systemic treatment | | | + | [99] |
| | Improved disease free survival | | | + | [98] |
| | Improved disease free survival | | | - | [115] |

+ : Beneficial effect, - : Negative effect.

Table 2. Complementary treatment (tertiary prophylaxis) after breast cancer treatment with respect to improvement of disease free or overall survival. Level of evidence (LOE) and grade of recommendation (GR) according to the Oxford criteria [8] and the German Associations of Gynecologic Oncologist (AGO) "breast cancer" [116]

| | Oxford level of evidence | | Grade of recommendation | |
|---|--|-----------------|-------------------------|------|
| | Disease free survival/ Overall survival | Quality of Life | Oxford | AGO* |
| Mistletoe | 5 | 4 | D | - |
| Soy/phytoestrogens | 5 | 4 | D | - |
| Vitamins | 5 | 4 | D | - |
| Trace elements (selen, zinc...) | 5 | 4 | D | - |
| Proteolytic enzymes (coenzyme Q10, papain, trypsin, chymotrypsin) | 5 | 4 | D | - |
| Herbal medical products | 5 | 5 | D | - |
| Acupuncture | 5 | 3b | C | +/- |
| Psychological therapies/hypnosis | 5 | 2c/b | B | +/- |

*AGO: grade of recommendation

++: This investigation or therapeutic intervention is highly beneficial for patients, can be recommended without restriction, and should be performed.

+: This investigation or therapeutic intervention is of limited benefit for patients and can be performed.

+/-: This investigation or therapeutic intervention has not shown benefit for patients and may be performed only in individual cases. According to current knowledge a general recommendation cannot be given.

-: This investigation or therapeutic intervention can be of disadvantage for patients and might not be performed.

--: This investigation or therapeutic intervention is of clear disadvantage for patients and should be avoided or omitted in any case.

well-designed studies of alternative medicine. Information on CAM is available through the NCI website and a field group within the Cochrane Collaborative. Complementary and alternative approaches may supplement conventional medicine in a helpful and meaningful way in future, and may increase patients' approval of conventional treatment. However, the level of evidence for the benefits of CAM remains to be improved (Table 2). The authors cannot give any recommendations for breast cancer patients, because there are no data comparing regular adjuvant treatment with any CAM treatment.

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