

# Integrative approaches in breast cancer patients: A mini-review

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## Abstract

Breast cancer is the most frequent malignancy among women worldwide and represents the first cause of death for women aged 35 to 55 years. It has a tremendous impact on patients' physical and psycho-social aspects, affecting their quality of life at any ages.

Integrative oncology is a global strategy that incorporates complementary therapies to mainstream care, in order to reduce standard treatment's side effects, potentially enhance their therapeutic effectiveness and improve physical and emotional wellbeing during and after cancer treatment.

In developed countries, 40-50% of cancer patients use integrative therapies, including dietary supplements and mind-body therapy techniques.

The present paper summarizes the state of the art in clinical and scientific evidences about the main complementary treatments currently used in breast cancer management.

## Introduction

Breast cancer is the most frequent cancer in females (25% of all cancers) and represents the first cause of death among women between 35 and 55 years of age [1]. Every year in the world 1,67 million women are diagnosed with breast cancer [2]. Together with the unavoidable side effects of conventional treatments, this disease has a huge impact on the physical and psycho-social aspects, affecting quality of life at any age.

Integrative therapies (IT) in oncology can be defined as additional interventions to mainstream care, used primarily for side effects management to enhance physical and emotional health during and after standard cancer treatment.

Use of IT alongside or after conventional treatment is a widespread international phenomenon. Up to 40% cancer survivors in the USA use IT during the period following their treatment [3]. According to a research conducted in 2011 on 2,562 American breast cancer survivors, 50% of these women used IT, above all spiritual therapies and meditation [4]. In addition, the 2007 National Health Interview Survey in the USA showed that the IT use is common not only in the oncologic population but also in the general adult population with a prevalence of nearly forty percent [5]. The same trend is observed in Europe. A survey among cancer patients in 14 European countries confirmed that nearly 40% had used IT [6]. This study also assessed that recourse to complementary therapies varies from 15% to 73% among countries. Switzerland, the Czech Republic and Italy show high levels of IT use, whilst Greece low levels. Besides, it confirms that the treatments most frequently used are homeopathy, herbal medicine and spiritual therapy. In the majority of cases, the patients are young women with a high cultural level, and they used IT following the advice of friends, family, television or newspapers.

Considering the spread of the phenomenon, it is of paramount importance to develop strategies in health care systems to integrate conventional and non-conventional medicine. Family practitioners, oncologists and health care workers should be aware of this kind of treatments in order to counsel and assist their patients in therapeutic programs integrating different approaches. This complementary approach may reduce the risk of patients rejecting proven conventional cancer treatments in favor of alternative methods as only choice of cure.

Moreover, it is important to have a basic understanding of the types of IT since there are potential interactions with the traditional therapies, especially when using herbal medicine or nutrients.

Despite the common use of IT, currently no robust evidence exists from randomized controlled trials that complementary therapies favorably influence the prognosis of breast cancer. Nevertheless, a number of integrative interventions aimed at improving symptoms, adherence to mainstream cure and better results are backed up by sound scientific data.

In the following sections, we will summarize the most convincing scientific data regarding the main complementary approaches used in breast cancer management and the most validated clinical indications for each kind of procedures.

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## Nutrition

The primary role of diet during breast cancer treatments is to improve effectiveness of mainstream cares and manage the side effects [7,8]. So-called functional foods may have a potential beneficial effect to health besides the known nutritional value.

But first of all, during breast cancer treatment a specific diet aimed at weight management plays an important role in these population since, unlike other cancer patients, they often undergo weight gain due to hormonal imbalance and menopausal state induced by treatments. Obesity and/or weight gain are related with poorer breast cancer prognosis, as well as prevalent comorbid conditions, such as cardiovascular disease and diabetes, poorer surgical outcomes in terms of recovery times and infection rates. In addition, weight influences lymphedema, fatigue, bone health and overall quality of life [9].

An example of functional food is the Omega-3 polyunsaturated fatty acids abundantly found in walnuts, flax seeds and fatty fish as salmon and sardines. They are important inflammatory modulators and known to be beneficial in the prevention of many chronic diseases that involve inflammatory processes like the cardiovascular diseases. In experimental models Omega-3 fatty acids showed even a beneficial modulation of carcinogenesis that may be useful in the adjuvant setting but further data is needed to be able to confirm this hypothesis [10].

Likewise, sulforaphane, a natural compound derived from broccoli and broccoli sprouts, has been proved to inhibit breast cancer stem cell growth both in vitro and in vivo. Studies support the study of sulforaphane as chemoprevention and in the adjuvant setting [11].

Furthermore, there are increasing evidences supporting the relationship between olive oil's use and improvement of breast cancer patient's outcomes. Olive oil is the main dietary source of oleic acid (OA). In vitro findings demonstrate that OA, suppresses Her-2/neu overexpression and interacts with anti-Her-2/neu immunotherapy by enhancing the cell death of Her-2 positive breast cancer cells [12]. In addition, olive oil is rich in phenolic constituents that confer the bitter and pungent taste to the oil. In vitro, the phenolic compounds show direct antioxidant capacity and are even able to enhance the effects of aromatase inhibitors [13].

Finally, a high-fiber, low-fat diet works to reduce serum estradiol that may be involved in the progression of hormonal dependent breast cancer [14-16]. In addition, these foods appear to increase serum insulin and serum IGF-I levels which appear to stimulate cancer cell growth [17]. That is why current recommendations in cancer prevention related to nutrition suggest avoiding low-quality foods including highly processed snack foods, sugar-sweetened beverages and refined sugar [18].

## Acupuncture

Acupuncture is a modality of complementary medicine that has its origin in traditional Chinese medicine. Unlike many other traditional methods of treatment, which tend to be specific to their national or cultural context, acupuncture has been used throughout the world particularly since the 1970s. If performed properly by a trained practitioner, today it represents a well-established, safe and reliable way of treating patients.

Thanks to its 2500 years of development, acupuncture has proven to effectively treat a wide range of diseases and conditions, even addressing some of the unmet needs of cancer patients. Unlike drugs, it

is non-toxic and adverse reactions are minimal or absent.

To our knowledge, no RCT has evaluated the efficacy of acupuncture as sole treatment of cancer. Nevertheless, plenty of studies on acupuncture in the complementary setting have been carried out, in order to ascertain the statistical significance of this approach in comparison with mainstream treatments. The interpretation of the data is difficult and controversial since many studies have major methodological defects and there is the objective problem to obtain a real "placebo" acupuncture control group. This group is often given "sham" acupuncture, with needling performed at random sites. Some controlled trials demonstrate that real acupuncture is superior to sham acupuncture but other studies show considerable therapeutic effects of both the genuine and the sham acupuncture with no significant difference between them.

A systematic review published by the National Cancer Institute, revised in January 2013, analyzes the efficacy of acupuncture on chemotherapy and radiotherapy-induced symptoms [19]. The conclusion is that the greatest efficacy of acupuncture in the field of oncology is its use for treating chemotherapy-induced nausea and vomiting.

Few studies have analyzed the effect of acupuncture on anxiety or depression in the oncologic setting. However, several studies conducted on non-oncological patients, suggest that acupuncture and acupressure are effective in treating depression and anxiety, with very few side effects in comparison to conventional treatments [20].

Lu et al. reviewed some pilot not controlled clinical studies which show improvement in patients with fatigue correlated to chemotherapy [21]: in patients with persistent asthenia after cytotoxic therapy, acupuncture use resulted in an improvement of 31,3%.

According to the Guidelines of the Society for Integrative Oncology (SIO) [22], acupuncture treatment is recommended in cancer-related fatigue as support to therapy, but further studies are needed.

In the literature there is growing evidence, that acupuncture can improve menopausal state-related vasomotor symptoms in women with breast cancer with effects lasting up to 6 months.

Regarding acupuncture's effectiveness on pain, the majority of high quality studies refer to non-oncological pain. A very important study is a meta-analysis published by Vickers et al. in 2012; the authors confirmed that acupuncture is effective for the treatment of chronic pain and therefore a reasonable referral option and a promising option for the cancer population [23].

A systematic review on acute postoperative pain management concluded that postoperative pain intensity was significantly decreased with acupuncture and therefore a lower incidence of opioid-related side-effects was observed in the acupuncture treatment group [24].

The efficacy of acupuncture on cancer-related pain is less certain. Despite a methodological high-quality RCT [25] showed a clear benefit from the complementary pain treatment with auricular acupuncture in cancer patients when conventional drugs do not suffice, the data on the efficacy of acupuncture in this field is controversial. A Cochrane Review on acupuncture confirms this statement and adds that positive results in favour of acupuncture should be viewed with caution due to methodological limitations, small sample sizes, poor reporting and inadequate analysis [26].

Overall, the benefits of acupuncture for cancer patients in the

treatment of pain, chemotherapy associated nausea and vomiting associated and hot flashes have been shown to clearly outweigh the risks. Thus, according to the 2009 SIO Guidelines acupuncture may be recommended as complementary treatment in cancer patients [22].

## Phytotherapy

Following the industrial revolution and the introduction of modern drugs, the use of medicinal plants in clinical practice fell into disuse. More recently, a growing interest in adopting natural compounds in pharmaceuticals has been registered [27,28]. Herbal compounds have received considerable attention as potential chemotherapeutic agents. At least more than one thousand plants have been found to possess significant anticancer properties [29]. In 2012 a study reported that among the 121 drugs approved for cancer treatment, 90 derived from herbal medicine [30]. Some of the best-known cancer drugs are obtained from natural products. For example, Vinca alkaloids (eg. vinorelbine) are extracted from the Madagascan periwinkle plant *Catharanthus roseus* and Taxanes from the Chinese happy tree *Camptotheca*.

Moreover, phytotherapy has been used to treat different conditions, including cancer-related symptoms and reduce drug-induced toxicity [31]. Several national surveys indicate that at least one third of American adults take some form of dietary supplement and botanicals [32].

Most clinical trials of herbal medicine have focused on either extracts of single herbs or standardised formulae. No solid evidence is available on the effectiveness of individualized herbal medicine for any indication. This tailored approach, in which patients receive prescriptions comprising a mixture of herbs is not supported by solid data [33]. Nevertheless there is evidence supporting the clinical use of phytotherapy in the complementary management of chemotherapy-induced nausea and vomiting and radiotherapy-induced dermatitis.

The antiemetic effect of ginger root (*Zingiber officinale*) on nausea and vomiting is validated in a randomized, prospective, cross-over, double-blind study [34]. In patients undergoing combination chemotherapy including cyclophosphamide ginger was compared to metoclopramide and to ondansetron in terms of nausea and vomiting control. The complete symptomatic control was achieved in 62% of patients with ginger, 58% with metoclopramide and 86% with ondansetron. The antiemetic effect of metoclopramide and ginger was similar whereas, not surprisingly, ondansetron was statistically significantly more effective.

A RCT compared the incidence of acute dermatitis in breast cancer patients undergoing adjuvant radiotherapy when applying on the skin calendula (*Calendula officinalis*) and trolamine ointments. Acute dermatitis of grade 2 or 3 was observed in 41% in the Calendula treatment arm and in 63% in the trolamine arm ( $P < .001$ ). Moreover, patients receiving calendula had less frequent interruptions of treatment and significantly reduced radiation-induced pain [35].

## Mind and body therapies

Over the last two decades, mind-body therapies (MBTs) including Qi Gong, Yoga, Thai-Chi and meditation, have received increasing attention from the scientific community in order to understand the safety and efficacy of these widely used practices [36]. MBTs seem to improve the psychological well-being reducing stress, anxiety, depression and mood disturbances [37] improving disease coping, quality of life and well-being. Growing evidence suggests that mindfulness-based stress reduction techniques (eg. meditation,

relaxation, diaphragmatic breathing) improve quality of life, sleep quality and reduce physiological stress [38-40]. Although practicing one of these techniques appears to be helpful in reducing psychological distress, a more complex mind-body intervention combining many of these techniques may be more effective [41].

One complex form of MBT frequently used by cancer patients is Qigong. The aim of this ancient Chinese practice is to manipulate the body energy (qi) to achieve a health improvement (gong). Through integration of specific movements, breathing techniques, meditation and a mindful focus on the body, qigong tries to control the flow and balance of energy.

The effect of Qigong in breast cancer patients during radiotherapy was studied in a RCT with 96 patients undergoing treatment. Women were randomised in a qigong intervention group and a control group that was not performing MBTs during treatment. For women with high baseline depressive symptoms qigong has significantly decreased depressive symptoms, fatigue and overall quality of life, whilst there were no significant differences between the patients with low baseline depressive symptoms. Interestingly, the differences only emerged starting 1 month after the completion of treatment. The authors suggest that Qigong may prevent delayed symptom burden or help the radiotherapy recovery process [42].

A review of clinical trials has examined the effects of Qigong in cancer patients receiving chemotherapy and revealed inconclusive finding regarding quality of life parameters mostly due to the methodological weaknesses of the studies, but the results were nevertheless encouraging regarding psychological and health-restorative effects and especially in relation to reducing inflammation [43]. In fact, Qigong may play a promising role in regulating the immune system. A meta-analysis including thirty-four published studies reveals that after 7 to 16 weeks of mind-body intervention, there was a moderate but not statistically significant effect on reduction of C-reactive protein and a similar effect on reduction of interleukin-6. The clinical implications of these immunomodulatory effects induced by Qigong have yet to be studied [44].

## Homeopathy

Homeopathy is one of the most commonly used complementary therapy among patients with cancer in Europe<sup>6</sup>. It uses minute doses of a drug (called 'remedy') that produces symptoms in healthy persons similar to those of the disease. 'Classical' homeopathy employs highly diluted remedies, whereas 'complex' homeopathy uses combinations of dilute agents for specific clinical conditions. Usually, the patients use it for symptomatic relief and general supportive care, as well to reduce side effects of treatments [45,46].

Homeopathy is very controversial since the currently existing evidence is insufficient to support the clinical efficacy of these remedies in cancer care. Nevertheless, according to a systematic review of existing RCTs, the results are encouraging and homeopathy appears to be effective in the treatment of chemotherapy-induced stomatitis and radiodermatitis [47]. Furthermore, a Cochrane review of 8 controlled trials (664 patients) analysed the safety of this type of IT during cancer treatments and found no serious side effects or interactions during radiotherapy and chemotherapy [48].

A popular homeopathic medication is Traumeel S. It is a homeopathic combination of remedies and contains various medicinal plants and minerals in very low concentrations. Traditionally, it is used to reduce inflammation. In cancer care the effect of this compound is

controversial. One small single-center trial reported a beneficial effect of Traumeel S on chemotherapy-induced mucositis compared with placebo [49] whereas a multi-center, double-blind, placebo-controlled randomized trial did not confirm these positive results [50]. However, a trend towards less narcotic usage in the Traumeel-arm group was still observed.

Another common IT medication is Arnica. It can be extracted from several plant species belonging to the Aesteraceae family and it is sold as tincture, ointment, cream and tablet. Arnica can be used as a homeopathic remedy or as phytotherapeutic extract. Arnica has been used as homeopathic remedy for the treatment of inflammation and pain management to support wound healing. A recent review on the effectiveness and safety of Arnica in the postoperative setting is very promising, suggesting even that, in selected cases, this remedy may be used instead of conventional anti-inflammatory drugs [51].

Finally, data from a high-quality RCT [52] on the homeopathic treatment of hot flushes in menopausal women with the complex remedy BRN-01 is encouraging. According to the results of this clinical trial, BRN-01 may be even considered as new therapeutic non-hormonal option for the treatment of hot flashes.

## Reflexology

Reflexology is the ancient practice of applying pressure to specific parts of the feet, hands, and ears to harmonize bodily functions and thus obtain a healing and relaxing effect [53]. This popular IT technique is based on the premise that "there are reflex areas in the feet and hands that correspond to all of the glands, organs, and parts of the body" [54]. Reflexology has been used since ancient times to promote relaxation [55,56].

As for the other above-mentioned IT options, the literature offers inconsistent data on reflexology efficacy in management of cancer patients [57]. Still, studies show that the administration of foot reflexology in addition to the usual postoperative pain management may be an effective symptom management with patients receiving significantly less opioid analgesics compared to the control group [58]. Other studies, like an English RCT involving 385 women with breast cancer undergoing active systemic adjuvant treatment [59], interestingly revealed no improvement in the emotional status but a significant reduction of dyspnea with the use of reflexology.

## Conclusion

In today's concept of Medicine, the patient-centered approach addresses also unmet concerns and needs thorough discussion of complementary resources of cure as additional therapeutic tools.

Integrative oncology combines complementary therapies with mainstream care, trying to optimize physical, psychological and spiritual well-being of the patient. This approach has a high regard of each patient individual's values and priorities and it may improve the comprehension of therapeutic choices, enhancing patient's involvement and increasing compliance and adherence to the protocols.

Even if the existing data on IT are mostly inconsistent mainly due to methodological flaws of the studies, the amount of promising literature is growing. Therefore, complementary therapies should be integrated into regular cancer care to improve patient quality of life and outcomes, in the attempt to achieve the goal of taking care of every patient with cancer, rather than only curing the disease.

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