Complementary Therapy

Survivorship
Complementary Therapy – Hormonal Treatment and Alternatives in Breast Cancer Survivors – Survivorship

- **Version 2002–2013:**
  Bauerfeind / Blohmer / Gerber / Göhring / Hanf / Janni / Kümmel / von Minckwitz / Oberhoff / Scharl / Schmidt / Schütz / Thomssen

- **Version 2014:**
  Albert / Hanf / Fersis / Friedrich
### „Alternative“ Therapies

<table>
<thead>
<tr>
<th>CAM</th>
<th>„Integrative Oncology“</th>
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<tr>
<td>Complementary + alternative medicine</td>
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<table>
<thead>
<tr>
<th>UCT</th>
<th>„Unconventional methods“</th>
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<tr>
<td>Unconventional Thx</td>
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#### Complementary vs. Alternative

- **Complementary**
  - In addition to scientifically based medicine

- **Alternative**
  - Instead of scientifically based medicine

- **Unconventional**
  - Unproven outsider methods

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**Further Information**

**References**
Complementary Therapy
Pre- and Postoperative

Preoperative:
- Hypnosis (reduces anxiety, pain, fatigue, nausea) 1b B +/-

Postoperative:
- Acupuncture (pain relief) 2b B +/-
- Acupuncture (nausea, vomiting) 2b B +
- Early postop. exercise reduces upper-limb dysfunction (beware: increased wound drainage) 1a A +
- Prophylactic lymph drainage 1b B -
Complementary Treatment Impact on Toxicity I

While on anti-cancer treatment:
beware of drug interactions

- **Mistletoe (Viscum album)** in order to reduce side effects of therapy (influence on efficacy of antitumortheraphy unknown)
  - 1a B +/-

- **Thymic peptides** (lowered the risk of severe infections)
  (influence on efficacy of antitumortheraphy unknown)
  - 2a B +/-

- **Ginseng (in order to reduce cancer rel. fatigue)**
  
  HR: 3b C +/-  
  HR+: 

- **Ginger** (consider interaction with antitumor drugs)
  - 1b C +/-
### Complementary Treatment Impact on Toxicity II

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
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<tbody>
<tr>
<td>Antioxidant supplements</td>
<td>1b B -</td>
</tr>
<tr>
<td>High dose vitamine C</td>
<td>1b C -</td>
</tr>
<tr>
<td>Vitamine E</td>
<td>2b D -</td>
</tr>
<tr>
<td>Selenium for alleviating side effects of therapy</td>
<td>1b B -</td>
</tr>
<tr>
<td>Co-Enzyme Q 10 (fatigue, QoL)</td>
<td>1b B -</td>
</tr>
<tr>
<td>Proteolytic enzymes in order to reduce chemotherapy-induced toxicity</td>
<td>3b B -</td>
</tr>
<tr>
<td>Chinese herbal medicine improves wound healing after mastectomy</td>
<td>1b B -<em>inf</em></td>
</tr>
<tr>
<td>Oxygen and ozone therapy</td>
<td>5 D - -</td>
</tr>
</tbody>
</table>

*inf: i.v.-infusion (in Germany not approved)
Additional Complementary Therapy
Side Effects Related to Cancer Treatments
e.g. Chemotherapy

<table>
<thead>
<tr>
<th>Additional Complementary Therapy</th>
<th>Oxford LoE / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese medicinal herbs to treat the side effects of chemotherapy in breast cancer patients</td>
<td>1b B -</td>
</tr>
<tr>
<td>May offer some benefit to breast cancer patients in terms of bone marrow improvement and quality of life</td>
<td></td>
</tr>
<tr>
<td>Homoeopathic medicines for adverse effects of cancer treatments</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>Topical calendula (&gt;= 20% Calendula amount) for prophylaxis of acute dermatitis during radiotherapy</td>
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<tr>
<td>Traumeel S mouthwash to treat chemotherapy-induced stomatitis</td>
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<tr>
<td>Topical Silymarin for prophylaxis of acute dermatitis during radiotherapy</td>
<td>3a B +/-</td>
</tr>
<tr>
<td>Acupuncture in order to improve on</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy-induced &gt;=nausea and vomiting</td>
<td>1a B +</td>
</tr>
<tr>
<td>Aromatase-inhibitor treatment induced arthralgia</td>
<td>2b C +</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>5 D +/-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1a B +/-</td>
</tr>
<tr>
<td>Pain</td>
<td>1a B +/-</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>2b B -</td>
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</tbody>
</table>
Complementary Treatment
Mind-Body Medicine I

MBSR (Mindfulness-Based Stress Reduction) Programme improves quality of life, coping strategies, attentiveness, lowers stress and depressive syndromes)

Physical exercise / sport
min. 150 min. moderate endurance training per week in combination with work out exercises (2x per week) improve quality of life, cardio-respirat. fitness, physical performance and fatigue
Complementary Treatment
Mind-Body Medicine II

Yoga
Improves sleep, quality of life, stress, anxiety, depression
Improves fatigue

Qi Gong
May improve quality of life, fatigue, mood

Tai Chi
Improves quality of life, physical performance

Hypnosis (in combination with cognitive training)
Improves fatigue and muscle weakness under radiation therapy

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Complementary Treatment</th>
<th>LoE</th>
<th>Grade</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Yoga</td>
<td>1b</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Qi Gong</td>
<td>2a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Tai Chi</td>
<td>2b</td>
<td>D</td>
<td>+/-</td>
</tr>
<tr>
<td>Hypnosis</td>
<td>2a</td>
<td>B</td>
<td>+/-</td>
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Modifiable Lifestyle Factors
Prevention of Recurrence I

- **Physical exercise**
  
  (Equivalents to 3–5 hrs moderate walking per week improves DFS and OS, cardio-respiratory fitness, physical functioning)

- **Smoking**

- **Alcohol consumption (>6 g/die)**
Modifiable Lifestyle Factors

Nutrition after Breast Cancer Diagnosis
Prevention of Recurrence II

- Adherence to normal BMI/weight loss if overweight
  (improves prognosis – DFS/OS)

- Low fat diet
  (improves prognosis – DFS – esp. post-menopausal, ER neg.; <20% fat calories, only with dietary counseling!)

- Flaxseed/increased fibre intake

- Adherence to general nutrition guidelines (e.g. DGE, WCRF)

- Dietary extremes
  (are associated with less favourable outcomes)

Oxford /AGO
LoE / GR

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of Evidence</th>
<th>Grade</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence to normal BMI/weight loss if overweight</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Low fat diet</td>
<td>1b(+)</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Flaxseed/increased fibre intake</td>
<td>2a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Adherence to general nutrition guidelines (e.g. DGE, WCRF)</td>
<td>2a</td>
<td>B</td>
<td>+</td>
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<tr>
<td>Dietary extremes</td>
<td>1b</td>
<td>B</td>
<td>- -</td>
</tr>
</tbody>
</table>
### Complementary Treatment

#### Prevention of Recurrence III

**Dietary Supplements – Herbal Therapies**

<table>
<thead>
<tr>
<th>Compl./alternative methods instead of systemic treatment:</th>
<th>Oxford</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>While on anti-cancer treatment: beware of drug interactions;</td>
<td></td>
<td></td>
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<tr>
<td><strong>Antioxidants</strong></td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td><strong>Orthomolecular substances</strong></td>
<td>5</td>
<td>D</td>
</tr>
<tr>
<td>(Selenium, Zinc...)</td>
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<tr>
<td><strong>Vitamines</strong> (in pts. on a balanced diet)</td>
<td>2b</td>
<td>B</td>
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<tr>
<td><strong>Proteolytic enzymes</strong></td>
<td>3b</td>
<td>B</td>
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<tr>
<td>(Papain, Trypsin, Chymotrypsin)</td>
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<tr>
<td><strong>Soy</strong> (phytoestrogens)</td>
<td>2b</td>
<td>B</td>
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<tr>
<td>In receptor-positive tumors</td>
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<tr>
<td><strong>Black Cohosh</strong> (Cimicifuga racemosa)</td>
<td>2b</td>
<td>C</td>
</tr>
<tr>
<td><strong>Mistletoe</strong> (Viscum album)</td>
<td>1b</td>
<td>C</td>
</tr>
<tr>
<td><strong>Thymic peptides</strong> (impact on OS)</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td><strong>Oxygen- and ozone therapy</strong></td>
<td>5</td>
<td>D</td>
</tr>
<tr>
<td><strong>Antioxidant supplements</strong> (after completion of radiotherapy)</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td><strong>Laetrile</strong></td>
<td>1c</td>
<td>D</td>
</tr>
<tr>
<td><strong>Cancer bush</strong> (Sutherlandia frutescens), Devil’s claw (Harpagophytum procumbens), Rooibos tea (Aspalathus linearis), Bambara groundnut (Vignea subterranean)</td>
<td>5</td>
<td>D</td>
</tr>
</tbody>
</table>

**LoE / GR**:
- 2b: B - 2b: B +/-
- 5: D - 5: D -
# Alternatives to Reduce Menopausal Symptoms after BC

## General approaches:

- **Physical exercise**
  
  Oxford / AGO LoE / GR
  
  General approaches:  

  - **Physical exercise**
    
    2b D +

  - **Mind Body-medicine (yoga, hypnosis, education, counselling)**
    
    1b B +

  - **Acupuncture**
    
    1a A +

  (take note: no acupuncture in tumor bearing region, possibility of cell seeding)
“Herbal” Approaches to Reduce Menopausal Symptoms

While anti-cancer treatment: Beware of drug interactions!

- Soy-derived phytoestrogens – isoflavonoids (might stimulate BC especially in endocrine responsive disease)  
- Flaxseed-supplementation (40 g/d) (in HR+ ≤ 10 g/d)  
- Black Cohosh for hot flushes (effectiveness could not be clearly shown)  
- St. John’s Wort in combination-therapy (pharmacokinetic interference with endocrine therapy, cytotoxic drugs and tyrosinkinase inhibitors)  
- Kava-Kava (Piper methysticum)  
- Red Clover leaf (Trifolium pratense)  
- Dong Quai root (Angelica sinensis)  
- Ginseng root (Panax ginseng or P. quinquefolius)  
- Bromelain + Papain + Selen + Lektin (vs. AI induced joint symptoms)
Complementary Treatment
Cancer Pain Reduction

- Acupuncture for cancer pain in adults
- Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults

Cave: No delay in diagnostic process
Immunodiagnostic Tests and Immunotherapy

Immunodiagnostic tests:

- Analysis of:
  - Immunological parameters in peripheral blood

Local immunotherapy

- Imiquimod topically for skin metastases

Systemic immunotherapy - including items below – only within clinical trials:

- HER2-vaccination in high risk population
- Immunomodulation (e.g. addition of Nov-2 to AC –T)
- Dendritic cell intradermal vaccination
- Active vaccination
- Passive vaccination
- Therapy with oncolytic viruses
- Cytokines
Further information:

Screened Data Sources:
Pubmed 2003 -01/2014
ASCO 2003 – 2013
Cochrane library summary Jan. 2014:

There are 149 results out of 7646 records for: "Complementary & alternative medicine and cancer” in Record Title in Cochrane Database of Systematic Reviews"

External advice:

The commission wants to thank the following external advisors for their contribution:

2010: Advice on nutritional facts by Prof. Dr. G. Stangl, Martin-Luther-University Halle Wittenberg, Germany
2011+ 2013: Prof. Dr. G. Dobos and team,
Alfred Krupp von Bohlen und Halbach-Stiftungsprofessur für Naturheilkunde an der Universität Duisburg-Essen,
Klinik für Innere Medizin V, Naturheilkunde und Integrative Medizin

No references
"Alternative" Therapies (3/16)

Further information:

The term "alternative therapies" has to be more precisely defined. The above scheme divides the subject into two main aspects:

- UCT refers to unconventional therapies with unproven methods; they frequently include outsider methods with possible considerable inherent risks.
- CAM includes both alternative therapies, which are used instead of conventional, scientifically based medicine, and complementary methods, which are used in addition to conventional methods. While conventional clinicians tend to more readily approve of the complementary approach than one of the other options, complementary approaches, if administered simultaneously with conventional therapies, always carry the risk that the treatments unexpectedly interfere with each other to produce untoward effects, i.e., drug interactions with partially incalculable outcomes.

No references
Complementary Pre- and Postoperative Therapy (4/16)

Further information and references:

Statement on preoperative hypnosis
Briefly hypnotizing patients before they underwent breast cancer surgery reduced the amount of anesthesia administered during the operation, the level of postoperative pain, and the cost of the procedure according to an RCT with 200 patients. The patients, who were scheduled to undergo excisional breast biopsy (72%) or lumpectomy (28 %), were randomly assigned to a 15-minute presurgical hypnosis session (n = 105) conducted by a psychologist or to a nondirective empathic listener (attention control) (n = 95). Patients in the hypnosis group required less propofol (means = 64.0 versus 96.6) and lidocaine (means = 24.2 versus 31.1 mL) than patients in the control group. Patients in the hypnosis group also reported less intense postoperative pain (means = 22.4 versus 47.8 mm VAS), less unpleasantness of pain (means = 21.2 versus 39.1 mm VAS), less nausea (means = 6.6 versus 25.5 mm VAS), less fatigue (29.5 vs. 54.2 mm VAS), less discomfort (23.0 vs. 43.2 mm VAS), and less emotional upset (8.7 vs. 33.5 mm VAS). No statistically significant differences were seen in the use of fentanyl, midazolam, or recovery room analgesics.


In another RCT ninety patients who were awaiting excisional breast biopsy were randomly assigned to undergo either a 15-minute presurgical hypnosis session (n = 49) or a 15-minute presurgical attention control session (n = 41). Results of this trial indicated that hypnosis prior to surgery helps control presurgical distress in women awaiting diagnostic breast cancer surgery.

A meta-analysis across surgical settings demonstrated large effects (d=1.2) on emotional distress. Surgical patients in hypnosis groups had better outcomes than 89% of patients in control groups. Further beneficial effects were found on pain, pain medication, nausea, fatigue, and treatment time.


A recent review on hypnosis for cancer care conclude that the use of hypnosis for side effects of cancer surgery is strong and consistent. Clinical and cost-effectiveness has been demonstrated.


**Acupuncture and Postoperative Pain**


Acupuncture and Postoperative Nausea and Vomiting


Statement on postoperative exercise

A recently published Cochrane analysis of the effects of postoperative exercise included 24 studies involving 2132 participants. The methodological quality of 10 of the 24 studies was considered adequate. Ten studies examined the effect of early versus delayed implementation of post-operative exercising. Early exercising was more effective than delayed exercising in the short term recovery of shoulder flexion ROM (abbr.: „range of movement“) (Weighted Mean Difference (WMD): 10.6 degrees; 95% Confidence Interval (CI): 4.51 to 16.6); however, early exercising also resulted in a statistically significant increase in wound drainage volume (Standardized Mean Difference (SMD) 0.31; 95% CI: 0.13 to 0.49) and duration (WMD: 1.15 days; 95% CI: 0.65 to 1.65). Fourteen studies compared the effect of structured exercising with that of the usual care. Of these, six were post-operative trials, three were carried out during adjuvant treatment, and five following cancer treatment. Structured exercise programs in the post-operative period significantly improved shoulder flexion ROM in the short run (WMD: 12.92 degrees; 95% CI: 0.69 to 25.16). Physical therapy yielded additional benefit for post-intervention shoulder function (SMD: 0.77; 95% CI: 0.33 to 1.21) and at the 6-month follow-up (SMD: 0.75; 95% CI: 0.32 to 1.19).

There was no evidence of increased risk of lymphedema from exercise at any time. The authors concluded that exercise results in a significant and clinically meaningful improvement in postoperative ROM of the shoulder in women with breast cancer. In the early post-operative period, exercising may be beneficial, although it may increase the volume and duration of wound drainage. Trials that closely monitor both exercise prescription factors (e.g., intensity) and persistent upper-limb dysfunction are needed.

A literature review of 4 RCT’s indicates that weight training exercises do not appear to increase lymphedema risk under structured conditions. All four of the studies reviewed report results of either a decrease in the development of lymphedema or no increased risk of development of lymphedema when early exercise regimens are incorporated into postoperative care.


Statement on prophylactic lymph drainage
Manual lymph drainage applied after axillary lymph node dissection for breast cancer is not effective in the short-term prevention of lymphedema of the arm.

**Complementary Treatment. Treatment phase. Impact on Toxicity I-II (5-6/16)**

**Further information and references:**

**Misteltoe**

The evidence from RCTs to support the view that the application of mistletoe extracts has impact on survival or leads to an improved ability to fight cancer or to withstand anticancer treatments is weak. The 5-years-data from a randomized trial with Viscum album additional to chemotherapy with CAF did not influence frequency of relapse or metastasis.

- Tröger W, Zdrale Z, Stankovic N, Matijasevic M: Five-year follow-up of patients with early stage breast cancer after a randomized study comparing additional treatment with viscum album (L.) extract to chemotherapy alone. Breast Cancer 2012, 6:173-80

Nevertheless, there is some evidence that mistletoe extracts may offer benefits on measures of QOL during chemotherapy for breast cancer, but these results need replication. Overall, more high quality, independent clinical research is needed to truly assess the safety and effectiveness of mistletoe extracts. Patients receiving mistletoe therapy should be encouraged to take part in future trials.


Thirteen prospective and controlled studies which met the inclusion/exclusion criteria reported positive effects in favor of the Iscador application. A random-effect meta-analysis estimated the overall treatment effect at standardized mean difference = 0.56 (CI: 0.41 to 0.71, P < .0001). However, the methodological quality of the studies was poor. Conclusions. The analyzed studies give some evidence that Iscador treatment might have beneficial short-time effects on QoL-associated dimensions and psychosomatic self-regulation.

Further references:


**Thymus**

In the recent Systematic Review Thymic peptides for treatment of cancer patients in addition to chemotherapy or radiotherapy, or both purified thymus extracts (pTE) and synthetic thymic peptides (sTP) were thought to enhance the immune system of cancer patients in order to fight the growth of tumour cells and to resist infections due to immunosuppression induced by the disease and antineoplastic therapy.

The authors identified 26 trials (2736 patients). Twenty trials investigated pTE (thymostimulin or thymosin fraction 5) and six trials investigated sTP (thymopentin or thymosin α1). Twenty-one trials reported results for OS, six for DFS, 14 for TR, nine for AE and 10 for safety of pTE and sTP. Addition of pTE conferred no benefit on OS (RR 1.00, 95% CI 0.79 to 1.25); DFS (RR 0.97, 95% CI 0.82 to 1.16); or TR (RR 1.07, 95% CI 0.92 to 1.25). Heterogeneity was moderate to high for all these outcomes. For thymosin α1 the pooled RR for OS was 1.21 (95% CI 0.94 to 1.56, P = 0.14), with low heterogeneity; and 3.37 (95% CI 0.66 to 17.30, P = 0.15) for DFS, with moderate heterogeneity. The pTE reduced the risk of severe infectious complications (RR 0.54, 95% CI 0.38 to 0.78, P = 0.0008; I² = 0%). The RR for severe neutropenia in patients treated with thymostimulin was 0.55 (95% CI 0.25 to 1.23, P = 0.15). Tolerability of pTE and sTP was good.

Most of the trials had at least a moderate risk of bias. Overall, the authors found neither evidence that the addition of pTE to antineoplastic treatment reduced the risk of death or disease progression nor that it improved the rate of tumour responses to antineoplastic treatment. For thymosin α1, there was a trend for a reduced risk of dying and of improved DFS. There was preliminary evidence that pTE lowered the risk of severe infectious complications in patients undergoing chemotherapy or radiotherapy.

Ginseng

The pilot study of Barton et al. investigated whether American ginseng (Panax quinquefolius) helps alleviate cancer-related fatigue. In addition, they evaluated its toxicity. Eligible adults with cancer were randomized in a double-blind manner to receive American ginseng in doses of 750, 1,000, or 2,000 mg/day or placebo, divided into two daily doses for 8 weeks. Outcome measures included the Brief Fatigue Inventory, vitality subscale of the medical outcome scale Short Form-36 (SF-36), and the Global Impression of Benefit Scale at 4 and 8 weeks.

Two hundred ninety patients took part in this trial. Nonsignificant trends for all outcomes were seen in favor of the 1,000- and 2,000-mg/day doses of American ginseng. Area-under-the-curve analysis of activity interference from the Brief Fatigue Inventory was 460-467 in the placebo group and 750 mg/day group versus 480-551 in the 1,000- and 2,000-mg/day arms, respectively. Change from baseline in the vitality subscale of the SF-36 was 7.3-7.8 in the placebo and the 750-mg/day arm versus 10.5-14.6 in the 1,000- and 2,000-mg/day arms. Over twice as many patients on ginseng as on placebo perceived a benefit and were satisfied with treatment. There were no significant differences in any measured toxicities between any of the arms. Since American ginseng appears to be somewhat active and its toxicity is tolerable at 1,000-2,000 mg/day doses, further trials to evaluate its efficacy in alleviating cancer-related fatigue are warranted.

Since ginseng contains phytoestrogens, its use is discouraged for women with hormone-receptor-positive breast cancer. Depending on its dose, in vitro ginseng inhibits cytochrome P enzymes (e.g. CYP 3A4). Interactions are possible and need to be considered.


**Ginger**

In this double blind, multicenter trial, 744 cancer patients were randomly assigned to four arms: 1) placebo, 2) 0.5 g ginger, 3) 1.0 g ginger, or 4) 1.5 g ginger. Nausea occurrence and severity were assessed at a baseline cycle and the two following cycles during which patients were taking their assigned study medication. All patients received a 5-HT3 receptor antagonist antiemetic on Day 1 of all cycles. Patients took three capsules of ginger (250 mg) or placebo twice daily for 6 days starting 3 days before the first day of chemotherapy. A total of 576 patients were included in final analysis Mixed model analyses demonstrated that all doses of ginger significantly reduced acute nausea severity compared to placebo on Day 1 of chemotherapy (p=0.003). Ginger supplementation at a daily dose of 0.5 g–1.0 g significantly aids in reduction of the severity of acute chemotherapy-induced nausea in adult cancer patients.


Preclinical studies have shown that ginger is effective as an anti-emetic agent and that it possesses 5HT3 antagonistic activity, which is responsible for reducing chemotherapy induced nausea. The clinical data are insufficient to draw firm conclusions.


In this pilot, randomized, open-label clinical trial, 100 women (mean age = 51.83 ± 9.18 years) with advanced breast cancer who were initially assigned to standard chemotherapy protocol with docetaxel, epirubicin, and cyclophosphamide...
(the TEC regimen) were randomized to receive ginger (1.5 g/d in 3 divided doses every 8 hours) plus standard antiemetic regimen (granisetron plus dexamethasone; the ginger group) or standard antiemetic regimen alone (control group). The duration of treatment with ginger was specified to 4 days from the initiation of chemotherapy. Addition of ginger (1.5 g/d) to standard antiemetic therapy (granisetron plus dexamethasone) in patients with advanced breast cancer effectively reduces the prevalence of nausea 6 to 24 hours postchemotherapy. However, there is no other additional advantage for ginger in reducing prevalence or severity of acute or delayed CINV.


**Antioxidant supplements**

Greenlee et al. (2009) concluded that current evidence on the administration of antioxidant supplements during breast cancer treatment does not suffice to provide clinicians and patients with guidelines for their use. Because of possible interactions between chemotherapy and the antioxidants selenium, coenzyme Q10, and vitamin E, these antioxidants are rated (–).


**Vitamin C**

In their review, Ohno et al. (2009) mention case reports and clinical trials in which intravenous high-dose vitamin C prolonged survival in patients with advanced cancer. However none of the trials was randomized or placebo controlled. Two randomized clinical trials with orally administered vitamin C conducted by the Mayo Clinic did not show any benefit. Because it may interact with chemotherapy, high-dose vitamin C therapy is rated (–).


Selen
This is an updated version of the original Cochrane review published in Issue 3, 2006. Selenium supplements are frequently used by cancer patients. Selenium is an essential trace element and is involved in antioxidant protection and the redox-regulation in humans. Several adverse effects of radiotherapy and chemotherapy in cancer patients as well as cellular processes that maintain chronic lymphoedema have been linked to oxidative cell processes in the human body. Selenium has been claimed to alleviate side effects of conventional cancer therapy and recently been investigated as a remedy against chemotherapy and radiotherapy-associated side effects and secondary lymphoedema. There is insufficient evidence at present that selenium supplementation alleviates the side effects of tumour specific chemotherapy or radiotherapy treatments or that it improves the after-effects of surgery, or improves quality-of-life in cancer patients or reduces secondary lymphoedema. To date, research findings do not provide a basis for any recommendation in favour or against selenium supplementation in cancer patients. Potential hazards of supplementing a trace mineral should be kept in mind. Since the last version of this review, the one new additional study has not provided information to change the conclusions of the original review.


Further references:

Coenzym Q10
Eligible women with newly diagnosed breast cancer and planned adjuvant chemotherapy were randomized to oral supplements of 300 mg CoQ10 or placebo, each combined with 300 IU vitamin E, divided into 3 daily doses. Treatment
was continued for 24 weeks. Blood tests, QOL measures, and levels of plasma CoQ10 and vitamin E were obtained at baseline and at 8, 16, and 24 weeks. Supplementation with conventional doses of CoQ10 led to sustained increases in plasma CoQ10 levels but did not result in improved self-reported fatigue or QOL after 24 weeks of treatment.


Further references:

Proteolytic enzymes and toxicity of chemotherapy:
Wobe Mugos®, a mixture consisting of an extract of the calf thymus gland and enzymes (the proteases trypsin and papain) from plant and animal sources, is commonly used in complementary medicine. Data from non-randomized studies have indicated that it has multiple favorable effects, and in particular that it reduces the side effects of radiotherapy and chemotherapy in oncology patients. Patients with invasive breast cancer receiving adjuvant or palliative chemotherapy between 2005 and 2006 and who were scheduled for at least two further cycles of that specific chemotherapy were included in this pilot study of Petru et al. (2). During the preceding cycle these patients had experienced a specific toxicity of at least grade 2 according to the NCI common toxicity criteria, indicating that it was relevant to the patient. To determine whether Wobe Mugos® reduces the side effects in individual patients, it was coadministered during two further chemotherapy cycles, and this specific toxicity, e.g. grade 2 emesis, was again evaluated. The majority of the 57 consecutive patients received palliative chemotherapy. The enzyme therapy, orally administered as two uncracked coated tablets three times daily on all days of a chemotherapy cycle except the day of chemotherapy administration, was well
tolerated. Positive and neutral effects on toxicity parameters were observed in 11 and 42 patients, respectively, and a negative influence was observed in 4 women. Petru et al. (2) observed only a marginal influence of Wobe Mugos® in patients with breast cancer who had experienced at least a grade 2 toxicity in the preceding cycle and who received two further identical cycles of this chemotherapy in conjunction with the enzyme preparation. There are no randomized studies.


**Bromelain**

**Chinese herbal medicine and wound healing**
Skin flap ischemia and necrosis are common complications of mastectomy. Chen et al. (4) from the Sichuan University in China evaluated the influence of anisodamine and Salvia miltiorrhiza on the complications of wound healing after mastectomy for breast cancer. Ninety patients undergoing mastectomy for breast carcinoma were divided into three groups. Demographic characteristics did not differ among the groups. Group 1 received routine wound care, group 2 received intravenous Salvia miltiorrhiza after surgery for 3 days, and group 3 similarly received intravenous anisodamine. Skin flaps were observed on postoperative days 4 and 8; areas of wound ischemia and necrosis were graded and adverse events recorded. Four days after surgery the rate of ischemia and necrosis in groups 2 and 3 was significantly less than that in control group 1 (median wound score 6·80 versus 23·38, P = 0·002, and 3·76 versus 23·38, P < 0·001, respectively). This improvement in groups 2 and 3 continued to postoperative day 8 (both P < 0·001), but wound scores at this stage were better in group 3 than in group 2 (1·82 versus 6·92 respectively; P = 0·022). The volume of wound drainage was lower in group 3 than in group 1 (P = 0·004). The incidence of adverse effects was highest in group 3, and two patients in this group discontinued treatment. No significant complications were noted in group 2. Anisodamine and S. miltiorrhiza were both effective in reducing skin flap ischemia and necrosis after mastectomy, although anisodamine was associated with a higher rate of adverse effects. In Germany these drugs have not been tested and are not approved for patient administration!
Additional Complementary Therapy - Side effect Related to Cancer Treatments (7/16)

Further information and references:

Chinese medicinal herbs
Zhang et al. reviewed the effectiveness and safety of Chinese medicinal herbs in alleviating chemotherapy-induced short term side effects in breast cancer patients. The authors identified seven randomised controlled trials involving 542 breast cancer patients undergoing or having recently undergone chemotherapy. All studies were conducted and published in China. Authors did not pool the results because few studies were identified and no more than two used the same intervention. All were of low quality and used CMH plus chemotherapy compared with chemotherapy alone.

This review provides limited evidence about the effectiveness and safety of Chinese medicinal herbs in alleviating chemotherapy induced short term side effects. Chinese medicinal herbs, when used together with chemotherapy, may offer some benefit to breast cancer patients in terms of bone marrow improvement and quality of life, but the evidence is too limited to make any confident conclusions. Well designed clinical trials are required before any conclusions can be drawn about the effectiveness and safety of CHM in the management of breast cancer patients.


Homeopathic medicines for adverse effects of cancer treatments
The review evaluates the effectiveness and safety of homeopathic medicines used to prevent or treat adverse effects of cancer treatments.
This review found preliminary data in support of the efficacy of topical calendula for prophylaxis of acute dermatitis during radiotherapy and Traumeel S mouthwash in the treatment of chemotherapy-induced stomatitis. These trials need replicating. There is no convincing evidence for the efficacy of homeopathic medicines for other adverse effects of cancer treatments. Further research is required.


**Topical use of Silymarin**

A total of 101 patients were evaluated after breast-conserving surgery followed by RT with 50.4 Gy plus boost 9–16 Gy. Of these, 51 patients were treated with the silymarin-based cream. In addition, 50 patients were documented receiving a panthenol-containing cream interventionally, if local skin lesions occurred. The median time to toxicity was prolonged significantly with silymarin-based cream (45 vs. 29 days (SOC), p < 0.0001). Only 9.8% of patients using silymarin-based cream showed grade 2 toxicity in week 5 of RT in comparison to 52% with SOC. At the end of RT, 23.5% of patients in the silymarin-based study group developed no skin reactions vs. 2% with SOC, while grade 3 toxicity occurred only in 2% in the silymarin-based arm compared to 28% (SOC). Silymarin-based cream Leviaderm® may be a promising and effective treatment for the prevention of acute skin lesions caused by RT of breast cancer patients. To confirm the results of this nonrandomized, observational trial, this component should be tested in larger multicenter studies in this setting.


**Acupuncture**


Chemotherapy-induced Nausea and Vomiting

Cognitive dysfunction

Fatigue
Three hundred two outpatients with breast cancer participated. 75 patients were randomly assigned to usual care and 227 patients to acupuncture plus usual care (random assignment of 1:3 respectively) with minimization controlling for baseline general fatigue and maintenance treatment. Treatment was delivered by acupuncturists once a week for 6 weeks through needling three pairs of acupoints (Ma 36, MP 6, Di 4). The usual care group received a booklet with information about fatigue and its management. Primary outcome was general fatigue at 6 weeks, measured with the Multidimensional Fatigue Inventory (MFI). Other measurements included the Hospital Anxiety and Depression Scale, Functional Assessment of Cancer Therapy–General quality-of-life scale, and expectation of acupuncture effect. Two hundred forty-six of 302 patients randomly assigned provided complete data at 6 weeks. The difference in the mean General Fatigue score, between those who received the intervention and those who did not, was -3.11 (95% CI, -3.97 to -
The intervention also improved all other fatigue aspects measured by MFI, including Physical Fatigue and Mental Fatigue (acupuncture effect, -2.36 and -1.94, respectively; both at P < .001), anxiety and depression (acupuncture effect, -1.83 and -2.13, respectively; both at P < .001), and quality of life (Physical Well-Being effect, 3.30; Functional Well-Being effect, 3.57; both at P < .001; Emotional Well-Being effect, 1.93; P = .001; and Social Functioning Well-Being effect, 1.05; P < .05).


Further references:

Pain

Leucopenia
Acupuncture therapy has not been shown to prevent leucopenia. Since leucopenia may increase the risk of infection through acupuncture, patients with leucopenia should not be encouraged to undergo acupuncture treatment.

**ALC to prevent chemotherapy induced peripheral neuropathy**

Chemotherapy-induced peripheral neuropathy (CIPN) is common and leads to suboptimal treatment. Acetyl-L-carnitine (ALC) is a natural compound involved in neuronal protection. A total of 409 patients were evaluable (208 received ALC; 201, placebo). In a multivariate linear regression, week-12 scores were 0.9 points lower (more CIPN) with ALC than placebo (95% CI, -2.2 to 0.4; P = .17), whereas week-24 scores were 1.8 points lower with ALC (95% CI, -3.2 to -0.4; P = .01). Patients receiving ALC were more likely to have a > 5-point decrease in FACT-NTX scores (38% v 28%; P = .05), and FACT-TOI scores were 3.5 points lower with ALC (P = .03). Grade 3 to 4 neurotoxicity was more frequent in the ALC arm (eight v one). No differences between arms were observed for FACIT-Fatigue or other toxicities. Serum carnitine level increased with ALC but remained stable with placebo.

Conclusion: There was no evidence that ALC affected CIPN at 12 weeks; however, ALC significantly increased CIPN by 24 weeks. This is the first study to our knowledge showing that a nutritional supplement increased CIPN. Patients should be discouraged from using supplements without proven efficacy.

**Complementary Therapies - Mind-Body-Medicine I-II (8/16 and 9/16)**

**Further information and references:**

*Mind-Body Medicine (MBM)*
In the absence of an adequate equivalent that does not have other connotations, the term mind/body medicine (MBM), denoting a concept of methods and therapeutic programs developed and scientifically evaluated in the United States and integrated into European medicine, has been entered everyday Speech ist Rede, language ist Sprache - NB: hat der Term das geschafft???) in the German language. The National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes for Health (NIH) defines MBM as “Practices that focus on the interactions among the brain, mind, body and behavior with the intent to use the mind to affect physical functioning and promote health.”
http://nccam.nih.gov/health/whatiscam/ 20.10.10

Its main goal is the activation and promotion of the patient’s ability for self-regulation and thereby his or her power of self-healing in the sense of salutogenesis.

A general overview of mind/body therapies in cancer survivorship


*MBSR*
Mindfulness based stress-reduction (MBSR) is an 8-week program, covering 24 contact-hours and 45 minutes daily home practice. The program aims at developing participants’ coping resources and developing participants’ mindful awareness. Thus the program consists of guided meditations, guided body scan (a specific awareness exercise)and through meditation, yoga and psychoeducation concerning stress and stress-reactions, while meditation and bodyscan is practiced at home by the use of specific audio-CDs guiding the patient.
In 2011 three systematic reviews on MBSR have been published. All of them found evidence of improved psycho-social factors which are often associated with cancer diagnosis and treatment e.g. stress, depression, reduced mood and quality of life. The review of Matchim et al. (2011) which included only women with breast cancer alone and some in heterogeneous cancer populations where breast cancer was the most common diagnosis found a large effect of MBSR on psychological symptoms, mainly stress and anxiety, but a meta-analysis was not performed.


In 2012 two systematic reviews and meta-analyses in patients with breast cancer showed positive effects on the mental health of breast cancer patients. The metanalysis of Cramer et al. (2012), that included only RCT’s, reported small effects on depression and moderate effects on anxiety. Zainal et al. (2012) included both RCT’S and uncontrolled trials and reported moderate to large effects on stress, depression and anxiety.


A recent rct of 336 women who had been operated on for breast cancer (stage I-III) found clinically meaningful, statistically significant effects of an 6 week MBSR Program in comparison to usual care on depression and anxiety after 12 months’ follow-up and medium-to-large effect sizes. Another publication of the same RCT reported that MBSR had a statistically significant effect on sleep quality just after the intervention but no long-term effect.


A randomized controlled trial of 82 breast cancer patients found that MBSR promotes a more rapid recovery of functional T cells capable of being activated by a mitogen with the Th1 phenotype, whereas substantial recovery of B and NK cells after completion of cancer treatment appears to occur independent of stress-reducing interventions


Another RCT of MBSR (n= 68) reported improved the symptoms and quality of life of breast cancer patients across a variety of cancer symptoms and quality-of-life measures


A recent RCT of good methodological quality carried out in 229 women after surgery, chemotherapy, and radiotherapy for breast cancer, found significant improvements in mood, breast- and endocrine-related quality of life, and well-being in the MBSR group compared with standard care. These results persisted at three months.


Physical exercise

Physical training has been shown to be an efficacious adjuvant to breast cancer therapy. Physical exercise appears to be safe during and after cancer treatments and results in improvements in physical functioning, quality of life, and cancer-related fatigue.

Breast cancer patients can generally be advised to avoid physical inactivity and to return to normal physical activities as soon as possible after surgery. Patients should be physically active and should exercise throughout the whole period of medical treatment. The intensity of exercise depends on the phase of medical treatment, the individual’s general condition, and the patient’s possibilities. Generally patients should begin exercising slowly to avoid excessive strain.

The American College of Sports Medicine (ACSM) published a comprehensive review of exercise intervention studies in breast cancer populations as part of a recent roundtable discussion of exercise in cancer survivors. The review included data from 54 rct’s of exercise in breast cancer patients: 22 in the adjuvant setting and 32 in the posttreatment setting. The authors found consistent evidence that exercise could be performed safely in both the adjuvant and post-treatment settings. Exercise led to significant improvements in aerobic fitness and strength in both settings and led to increased flexibility and physical functioning in the posttreatment setting. A moderate level of evidence also suggested that exercise led to improvements in quality of life, anxiety, depression, fatigue, body image, body size, and body composition in breast cancer survivors, although findings were not always consistent. Furthermore, the ACSM guidelines cite that exercise may be associated with a reduced risk of developing a recurrence or secondary cancer.


This narrative literature review indicates that regular participation in physical activity after breast cancer diagnosis may mitigate common side effects of breast cancer adjuvant therapy, including fatigue, depression, impaired quality of life, decreased muscular strength, decreased aerobic capacity, and weight gain.

A randomized trial of exercise showed that starting a supervised exercise regimen that is tailored to an individual's strength following breast cancer surgery appears safe and may lead to improvements in physical functioning.


A systematic review identified 7 studies addressing resistance exercise (6 rct’s), seven studies on aerobic and resistance exercise (3 rct’s), and five studies on other exercise modalities (4 rct’s). Studies concluded that slowly progressive exercise of varying modalities is not associated with the development or exacerbation of breast cancer-related lymphedema and can be safely pursued with proper supervision. Combined aerobic and resistance exercise appear safe, but confirmation requires larger and more rigorous studies. It was concluded that it is safe for breast cancer survivors to exercise throughout the trajectory of their cancer experience, including during treatment.


A small study examining the effect of a home-based exercise program on lymphedema and QOL in postmastectomy patients showed that an individualized home-based exercise program led to improvement in affected upper-limb volume and circumference and QOL of postmastectomy lymphedema patients.

A recent trial randomizing sedentary breast cancer survivors between telephone-based exercise intervention or usual care as control group reported that patients randomized to a telephone-based physical activity intervention had increased physical activity and experienced significant improvements in fitness and physical functioning.


According to the guidelines of the American Cancer Society and the American College of Sports Medicine (Schmitz, 2010, see above) adults aged 18 to 64 years should engage in at least 150 minutes per week of moderate intensity or 75 minutes per week of vigorous intensity aerobic physical activity, or an equivalent combination of moderate and vigorous intensity aerobic physical activity. Some activity is better than none and exceeding the guidelines is likely to provide additional health benefits. Activity should be done in episodes of at least 10 minutes per session and preferably spread throughout the week. Furthermore, adults should do muscle-strengthening activities involving all major muscle groups at least 2 days per week. Adults aged older than 65 years should also follow these recommendations if possible, but if chronic conditions limit activity, older adults should be as physically active as their abilities allow and avoid long periods of physical inactivity.


Exercising is contraindicated with fever or body temperature > 38°C, diarrhea, vomiting, pain, acute infection (during antibiotic treatment), non-medicated hypertension, acute bleeding, bone or bone marrow metastases with a high likelihood of fracture, severe thrombocytopenia (under 20/ nl), circulatory problems, confusion, hemoglobin < 8 g/dl, reduced consciousness, cardio- or nephrotoxicity, chemotherapy (earliest physical activities after 1 day), or chemotherapy + Herceptin (earliest physical activities after 1 day).
Further References:


Statement on quality of life:
This systematic review of 9 randomized controlled trials with an average quality only presents components of exercise programmes that are effective for QoL. From this review, it is evident that aerobic exercise has a favourable effect on the QoL for patients with, and survivors of, breast cancer. Clinicians Results are optimal when performed thrice a week, at a moderate intensity (50–70% of HRmax) for greater than 30 minutes for at least 8 weeks, under supervision. This result would be regardless of the stage of breast cancer and the medical management the participants may be undergoing.


A meta-analysis on 56 RCT’s provides a comprehensive summary of studies exploring the effectiveness of a range of behavioral techniques and physical exercise interventions, during and after treatment, on long-term sequelae such as fatigue, depression, anxiety, body-image, stress and HRQoL in breast cancer patients and survivors. Statistically significant, but modest, results were found for the effect of behavioral techniques on fatigue and stress, with stronger
effects found on depression and anxiety. No significant effects were observed for body-image or HRQoL. For physical exercise interventions (17 studies), statistically significant and moderate effects were observed for fatigue, depression, body-image and HRQoL. The effect on anxiety was in the expected direction, but was not statistically significant. Only one study assessed the effect of physical exercise on stress, and thus a summary effect size could not be calculated. The results indicate that behavioral techniques and physical exercise improve psychosocial functioning and HRQoL in breast cancer patients and survivors.


A Cochrane review of 40 (RCTs) and controlled clinical trials (CCTs) with 3694 participants indicates that exercise may have beneficial effects on HRQoL and certain HRQoL domains including cancer-specific concerns (e.g. breast cancer), body image/self-esteem, emotional well-being, sexuality, sleep disturbance, social functioning, anxiety, fatigue, and pain at varying follow-up periods. Cancer diagnoses in study participants included breast, colorectal, head and neck, lymphoma, and other. Thirty trials were conducted among participants who had completed active treatment for their primary or recurrent cancer and 10 trials included participants both during and post cancer treatment. Mode of the exercise intervention included strength training, resistance training, walking, cycling, yoga, Qigong, or Tai Chi. The positive results must be interpreted cautiously due to the heterogeneity of exercise programs tested and measures used to assess HRQoL and HRQoL domains, and the risk of bias in many trials.


The goal of this systematic review was to examine the effect of exercise on the quality of life (QOL) of women with breast cancer. Nine relevant randomized controlled trials were found, four of moderate methodological quality and five of high methodological quality. Evidence was strong that exercise positively influences QOL in women with breast cancer. Thus, exercise may be an effective means of improving QOL in women with this disease. Further research is needed to determine optimal types and parameters of appropriate exercises.

A review of 14 RCTs (n=717) indicated that exercise is an effective intervention to improve quality of life, cardiorespiratory fitness, and physical functioning and to decrease fatigue in breast cancer patients and survivors.


This meta-analysis of 10 studies (N = 588) indicates that aerobic exercise significantly improved cardiopulmonary function as assessed by absolute VO2 peak (standardized mean difference [SMD] 0.916, p < 0.001), relative VO2 peak (SMD 0.424, p < 0.05), and 12-minute walk test (SMD 0.502, p < 0.001). Similarly, aerobic exercise significantly improved body composition as assessed by percentage body fat (SMD -0.890, p < 0.001), but body weight and lean body mass did not change significantly. Aerobic exercise during or after cancer adjuvant therapy seems to be an effective means of improving cardiopulmonary function and decreasing the percentage of body fat in women with breast cancer.


**Statement on fatigue**

This meta-analysis with twenty-eight studies (n = 2083 participants, n = 1172 with breast cancer) showed that exercise benefited individuals with cancer-related fatigue during and after cancer therapy. Further research is required to determine the optimal type, intensity, and timing of an exercise intervention.

This meta-analysis evaluated the effects of various exercise parameters on cancer-related fatigue (CRF) during cancer treatment. Eighteen RCTs (12 in breast cancer, 4 in prostate cancer, and 2 in other cancer patients) met all the inclusion criteria. During breast cancer treatment, home-based exercise led to a small, non-significant reduction in fatigue (standardized mean difference 0.10, 95% confidence interval -0.25 to 0.45), whereas supervised aerobic exercise showed a medium, significant reduction in CRF (standardized mean difference 0.30, 95% confidence interval 0.09 to 0.51) as compared with no exercise.


**Yoga**

Mind-body interventions like yoga receive increasing attention for breast cancer survivors.

A systematic review that included 13 RCTs with a total of 760 patients found strong evidence for anxiety, stress, depression, and health-related quality of life. Effects on fatigue were inconclusive.


A meta-analysis on 6 RCTs with a total of 382 patients that compared yoga to no interventions reported small effects on health-related quality of life (Hedge’s g=0.27) but no effects on anxiety, depression, distress, sleep, and fatigue.

A more comprehensive meta-analysis on 12 RCTs and 742 patients found small to moderate effects of yoga on global health-related quality of life, functional, social, and spiritual well-being. These effects were, however, not clearly distinguishable from bias. Large effects that were present in studies with low risk of bias were found for anxiety (g=1.51), depression (g=1.59), perceived stress (g=1.14), and psychological distress (g=0.86). Subgroup analyses revealed evidence of efficacy only for yoga during active cancer treatment (chemotherapy or radiotherapy) but not in cancer survivors after completion of active treatment.


Finally, a meta-analysis that included 6 RCTs (including 1 RCT that was not included in the above meta-analysis of Zhang et al., 2012) with a total of 362 patients found small effects on fatigue (g=0.33).


Bhargav et al. review some mechanisms by which Yoga can positively influence cancer stem cells susceptibility to conventional cancer treatment.

Qigong

The first systematic review on qigong in cancer treatment found no large RCTs. Four RCTs and 5 non-randomized trials were included. No large CRTs were found. The review found inconclusive results with some RCTs suggesting effects on overall health, and white blood cell counts. Effects on tumour progression, survival rates, and health-related quality of life were inconclusive.


A more recent systematic review on qigong in supportive cancer care included 8 RCTs and 15 non-randomized trials mainly on samples with mixed types of cancer. Five of the included RCTs suggested favorable effects of qigong exercise on symptoms, inflammation, quality of life, and mood disturbance. The other 3 RCTs showed no effect. All but 1 non-randomized trials found favorable effects of qigong.


An RCT (n=162) found improvements in QOL, fatigue, mood, and inflammation markers after qigong. The intervention was compared with TAU (treatment as usual).


A small study in 9 patients with histologically confirmed breast cancer awaiting surgery failed to confirm any effect on clinical changes in tumor measurements from pre- to post- qigong treatment. There was also no suggestion of change in QOL. However, this study was on external qigong, i.e. on a therapist-provided form of mental healing that is not comparable to internal qigong, i.e. patient-practiced aerobic exercise.

**Tai Chi**
A 2010 systematic review on Tai Chi for breast cancer patients included 3 RCTs and 4 non-randomized controlled trials. RCTs showed no effects on quality of life, psychological, and physical outcomes. The review included a meta-analysis of 2 RCTs that failed to show effects on quality of life (Hedge’s $g=0.45$; 95% Confidence Interval -0.25; 1.14). Three of the non-randomized trials found effects on quality of life, mood, self-efficacy, shoulder and upper limb function.


A more recent systematic review included 4 RCTs and found limited evidence for improved physical functioning, mental health, muscle strength, quality of life, and self-esteem.


**Hypnosis**
In a RCT, 42 women undergoing breast cancer radiotherapy, a combination of hypnosis and cognitive therapy was compared to standard medical care. In the control group, fatigue increased linearly over the course of the radiotherapy while there was no increase in the hypnosis group. Effect size was large on the FACIT-F ($d=0.82$).


A second RCT investigated the effects of this intervention on affect and lower rates of negative affect and higher rates of positive affect in the hypnosis group than in the control group. At week 5, patients in the hypnosis group had 66% lower negative affect scores and 43% greater positive affect scores than the control group.

A recent review concluded that the results of hypnosis for cancer patients undergoing are heterogeneous. The authors suggested that suggestions in the hypnosis should focus specifically on breast cancer radiotherapy and that hypnosis should be combined with cognitive therapy. (sorry das verstehe ich nicht)

Further information and references:

Data on the impact of nutrition on the risk of recurrence (secondary prevention) are rare. Therefore clinical advice during remission is often based on the extrapolation of primary prevention data. In 2007, the World Cancer Research Fund/American Institute of Cancer Research published its second expert-report. A recent prospective investigation of pre-diagnosis body mass index (BMI) and mortality among 14,948 breast cancer patients in the After Breast Cancer Pooling Project. Showed that women who were underweight and morbidly obese before breast cancer diagnosis were at the greatest risk of all-cause mortality. Morbidly obese women were also at increased risk of death from breast cancer (Kwan et al, 2011). Interestingly, a recent retrospective evaluation of treatment adherence according to body weight demonstrated that patients with increasing BMI had a higher motivation and perseverance to the recommended treatment (Schmidt et al, 2011).

However, published data of the prospective Women’s Healthy Eating and Living (WHEL) study demonstrated that diet had a beneficial effect only when combined with physical activity (Pierce et al. 2007). Nutritional advice as an adjuvant treatment can be based on recently published data from a prospective trial: the women’s intervention nutrition study (WINS). In this trial Chlebowsky et al. (2006) found significantly improved disease-free survival (DFS) for patients with ER-neg. tumors if less than 21% of the daily calorie intake was derived from fat. This dietary modification can only be achieved with the help of continual professional dietary counselling. The WHEL data did not confirm the beneficial effect of a low-fat diet in general.

Goodwin presented data indicating that adherence to a normal BMI improves disease outcome (SABCS 2009). However, being underweight seems to increase the risk of recurrence, and since up to 30% of breast cancer patients are in danger becoming cachectic, malnutrition screening seems necessary. ESPEN (The European Society for Clinical Nutrition and Metabolism) recommends the “Malnutrition Universal Screening Tool” (MUST) for adults according to Kondrup J. et al. (Clinical Nutrition 2003;22: 415-421 ww.bapen.org.uk/must_tool.html).

Dietary extremes, especially fasting excesses, are dangerous and are associated with poor survival when BMI drops pathologically low.—
Concerning cardiovascular risk factors, a recent non-randomized controlled study in breast cancer survivors comparing high fat, low carbohydrate versus low fat, high carbohydrate found a lack of evidence of a negative effect of dietary pattern on biomarkers associated with cardiovascular risk (Thompson et al, 2012)


Recently, more and more attention is being paid to diet quality, inflammation, and biomarkers of inflammation in breast cancer survivors (lower levels of chronic inflammation like low C-reactive protein at baseline have been associated with improved survival after breast cancer (Pierce et al, 2009)). Studies evaluating the effect of a low fat versus a low carbohydrate weight loss dietary intervention on biomarkers of long term survival in breast cancer patients like the 'CHOICE' protocol are underway, measuring inflammatory biomarkers like C-reactive protein among others (Sedlacek et al, 2011). Ongoing research.


There is growing evidence that the impact of dietary factors on risk of BC differs according to the particular molecular subtypes of cancer. E.g. overweight had no prognostic impact among women with early stage triple receptor-negative BC. Supervising are the findings in the research area of nutrigenomics.
Body mass Index is an established risk factor for developing breast cancer, for its recurrence, and for early death. Obese patients have a 50 to 75% higher probability of recurrence and a 36 to 50% higher risk of dying from breast cancer. A recent observational study, however, showed that obesity plays an important role in mortality among white but not black patients with breast cancer (Lu et al, 2011). A recent prospective investigation of pre-diagnosis body mass index (BMI) and mortality among 14,948 breast cancer patients in the After Breast Cancer Pooling Project showed that women who were underweight and morbidly obese before breast cancer diagnosis were at the greatest risk of all-cause mortality. Morbidly obese women were also at increased risk of death from breast cancer (Kwan et al, 2011). Interestingly, a recent retrospective evaluation of treatment adherence according to body weight demonstrated that patients with increasing BMI had a higher motivation and perseverance to the recommended treatment (Schmidt et al, 2011). Cave: Female patients often connote weight loss positively. Note the difference between intentional vs. unexplained (maybe as consequence of disease).


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becoming cachectic, malnutrition screening seems necessary. ESPEN (The European Society for Clinical Nutrition and Metabolism) recommends the “Malnutrition Universal Screening Tool” (MUST) for adults according to Kondrup J. et al. (2003)


**Further references:**


Chlebowski RT, Aiello E, McTiernan A et al. (2002): Weight loss in breast cancer patient management. J Clin Oncol 20:1128–1143. – suggest beneficial effects on overall survival extrapolated from prognostic impact of weight and by beneficial effects to other conditions


Statement on low fat diet
Besides the amount of fat, fat quality (type of fat intake) seems to count, but few in vivo data so far. Lower intake of saturated fat und trans fat (in post-diagnoses diet) could be associated with improved survival after BC diagnosis.


**Statement on lignans/flaxseed**

Dietary lignans make up one class of phytoestrogens and have been identified as potentially protective against breast cancer via estrogen-dependent and independent anticarcinogenic activity. Flaxseed is a major source of lignans. Lignans are metabolized by the gut microflora into enterolignans, enterolactone is the main metabolite. A recent observational study (Buck et al, 2011) found in 1,140 postmenopausal breast cancer patients that high serum enterolactone levels were associated with an improved survival. These findings were supported by a recent meta-analysis indicating a significant inverse association between serum enterolactone and postmenopausal breast cancer risk, which was stronger for ER-PR- than for ER+PR+ tumors but not differential by further expression of HER2 (Zaineddin et al, 2011). Furthermore, a recent epidemiologic study showed that higher prediagnostic plasma levels of enterolactone were related to lower mortality among breast cancer patients (Olsen et al, 2011). Accordingly, a meta-analysis showed an overall reduction of postmenopausal breast cancer risk in women with the highest vs. lowest plant lignan consumption (Buck et al 2010). However, two epidemiologic studies concerning the association of the reported dietary intake of lignans and breast cancer prognosis gave inconsistent results (McCann et al, 2009; Fink et al, 2007). These differences might be explained by the fact that a serum biomarker, which provides an index of intake, metabolism, and absorption of phytoestrogens and is not prone to recall bias and misclassification, might be a more appropriate measure. Concerning the occurrence of hot flushes, a recent randomized phase III trial failed to demonstrate a significant reduction of hot flushes for postmenopausal patients taking additional 410 g of lignans as compared to placebo (Pruthi et al, 2012). Besides, seeds in general are a source of dietary fiber, which itself may play a protective role as a recent meta-analysis suggests. More specifically relevant for the prevention of recurrences are data from the HEAL-study: Dietary fiber was associated with a nonsignificant inverse association with breast cancer events and total mortality.


The American Journal of Clinical Nutrition published „an in-depth analysis of combined evidence from cohort studies of US and Chinese women“. Overall 9514 breast cancer patients were randomized between 1991 and 2006. A significant relative risk reduction was shown: (HR: 0.75; 95% CI: 0,61, 0,92). („Slightly stronger among women with ER-negative breast cancers…“). Similar results were demonstrated by the German study (Zaineddin et al. s.o.) a significantly decreased risk for breast cancer coinciding with increased intake of soy beans, sun flower seeds and cabage seeds independent of the patients estrogen receptor status (but statistically not significant for Lignane).
A general recommendation regarding physto-estrogen rich or enriched food cannot be made at this time while in some studies indicate, that oral intake of soy beans decreases the effectiveness of Tamoxifen on decreasing the risk for breast cancer and while the possibility is being discussed that Daidzein (the other physto-estrogen in soy beans next to Genistein) might enhance cell proliferation.
Moreover Nechuta et al. point out, that: „Limitation of this study should be considered. First, ..., a higher intake of isoflavones was associated with lifestyle-related factors, including regular exercise and higher consumption of cruciferous vegetables (...) and lower BMI and nonsmoking status (...). ... Further studies ... are needed.”

In conclusion: continued observation is advised. There are increasing evidence that oral intake of soy beans may translate into a health benefit for survivors’. In this context other mechanisms of action of Phyto-estrogens are being discussed such as enhancing apoptosis and supressing angiogenesis.


Statement on adherence to general nutrition guidelines

Because of rare data about the risk of recurrence (secondary prevention), clinical advice during remission is often based on the extrapolation of primary prevention data. In 2007 the World Cancer Research Fund published its second report. In summer 2012 for the first time ever the American Cancer Society published ‘Nutrition and Physical Activity Guidelines for Cancer Survivors’. Nutritional advice as an adjuvant treatment can be based on data from a prospective trial: the women’s intervention nutrition study (WINS). In this trial Chlebowsky et al. (2006) found significantly improved disease-free survival (DFS) for patients with ER-neg. tumors if less than 21% of the daily calorie intake was derived from fat. This dietary modification can only be achieved with the help of continual professional dietary counselling. The WHEL data did not confirm the beneficial effect of a low-fat diet in general. Published data of the prospective Women’s Healthy Eating and Living (WHEL) study demonstrated that diet had a (big) beneficial effect only when combined with physical activity (Pierce et al. 2007).

The primary prevention EPIC study did not show that dietary fruits and vegetables protected against breast cancer, and no data are available regarding the prevention of recurrence of BC. Nevertheless, EPIC shows an inverse association between the risk of BC overall and in postmenopausal women and adherence to Mediterranean diet, more pronounced in receptor-negative tumors (Buckland et al 2012, Masala et al 2012). And some studies suggest a lower risk of ER-tumors, which are harder to treat (e.g. Fung et al).
Finally, a recent study by Beasley et al (2011) suggests that lower intake of saturated and trans fat in the post-diagnosis diet is associated with improved survival after breast cancer diagnosis.

- Sofi et al. (2008): Adherence to Mediterranean diet and health status: meta-analysis. BMJ Sep 11; 337:a1344. (12 studies with a total of 1.574,299 subjects)


Statement on dietary extremes (are associated with less favorable outcomes)
Dietary extremes, especially fasting excesses, are dangerous and are associated with poor survival when BMI drops pathologically low.


Physical exercise
Physical training has been shown to be an efficacious adjuvant to breast cancer therapy. Physical exercise appears to be safe during and after cancer treatments and results in improvements in DFS and OS, physical functioning, quality of life, and cancer-related fatigue.

Breast cancer patients can generally be advised to avoid physical inactivity and to return to normal physical activities as soon as possible after surgery. Patients should be physically active and should exercise throughout the whole period of medical treatment. The intensity of exercise depends on the phase of medical treatment, the individual’s general condition, and the patient’s possibilities. Generally patients should begin exercising slowly to avoid excessive strain.

The American College of Sports Medicine (ACSM) published a comprehensive review of exercise intervention studies in breast cancer populations as part of a recent roundtable discussion of exercise in cancer survivors. The review included data from 54 RCT’s of exercise in breast cancer patients: 22 in the adjuvant setting and 32 in the posttreatment setting. The authors found consistent evidence that exercise could be performed safely in both the adjuvant and posttreatment settings. Exercise led to significant improvements in aerobic fitness and strength in both settings and led to increased flexibility and physical functioning in the posttreatment setting. A moderate level of evidence also suggested that exercise led to improvements in quality of life, anxiety, depression, fatigue, body image, body size, and body com-position in breast cancer survivors, although findings were not always consistent. Furthermore, the ACSM guidelines cite that exercise may be associated with a reduced risk of developing a recurrence or secondary cancer.


Additionally, there is increasing evidence of an inverse relationship between exercise and markers of systemic inflammation like C-reactive protein.

Another potential link between exercise and survival of breast cancer patients was described in a study suggesting that increasing physical activity after a breast cancer diagnosis may affect epigenetic regulation of tumor suppressor genes like L3MBTL1, which have favorable impact on survival outcomes of breast cancer patients.


According the guidelines of the American Cancer Society and the American College of Sports Medicine (Schmitz, 2010, see above) adults aged 18 to 64 years should engage in at least 150 minutes per week of moderate intensity or 75 minutes per week of vigorous intensity aerobic physical activity, or an equivalent combination of moderate and vigorous intensity aerobic physical activity. Some activity is better than none and exceeding the guidelines is likely to provide additional health benefits. Activity should be done in episodes of at least 10 minutes per session and preferably spread throughout the week. Furthermore, adults should do muscle-strengthening activities involving all major muscle groups at least 2 days per week. Adults aged older than 65 years should also follow these recommendations if possible, but if chronic conditions limit activity, older adults should be as physically active as their abilities allow and avoid long periods of physical inactivity.


Exercising is contraindicated with fever or body temperature > 38°C, diarrhea, vomiting, pain, acute infection (during antibiotic treatment), non-medicated hypertension, acute bleeding, bone or bone marrow metastases with a high likelihood
of fracture, severe thrombocytopenia (under 20/ nl), circulatory problems, confusion, hemoglobin < 8 g/dl, reduced consciousness, cardio- or nephrotoxicity. chemotherapy (earliest physical activities after 1 day), or chemotherapy + Herceptin (earliest physical activities after 1 day).

References:


Statement on improvements in DFS and OS
Published data have shown that physical activity (PA) reduces the risk of breast cancer. However, data on the role of PA in breast cancer outcome have been inconsistent. The lack of a meta-analysis concerning this issue prompted the current report. A comprehensive search of the literature identified eight studies, two of which could be excluded. The remaining six studies (12,108 patients with breast cancer) were included in this meta-analysis. Pre-diagnosis PA reduced all causes of mortality by 18% but had no effect on breast cancer deaths. Post-diagnosis PA reduced breast cancer deaths by 34% (HR = 0.66, 95% CI, 0.57-0.77, P < 0.00001), all causes of mortality by 41% (HR = 0.59, 95% CI, 0.53-0.65, P < 0.00001), and
disease recurrence by 24% (HR = 0.76, 95% CI, 0.66-0.87, P = 0.00001). Breast cancer mortality was reduced by pre-diagnosis PA in women with body mass index (BMI) < 25 kg/m², while post-diagnosis PA reduced that risk among those with BMI >/= 25 kg/m². On the other hand, post-diagnosis PA reduced all causes of mortality regardless of the BMI. The analysis showed that post-diagnosis PA reduced breast cancer deaths (HR = 0.50, 95% CI, 0.34-0.74, P = 0.0005) and all causes of mortality (HR = 0.36, 95% CI, 0.12-1.03, P = 0.06) among patients with estrogen-receptor (ER)-positive tumors, but not in women with ER-negative disease. The current meta-analysis provides evidence for an inverse relationship between PA and mortality in patients with breast cancer and supports the notion that breast cancer survivors should engage in appropriate PA (Ibrahim et al, 2010).

In addition, the After Breast Cancer Pooling Project (n = 13,302) reported that at least 10 MET-hours/week of PA was associated a 25% reduction in breast cancer mortality (n = 971 events, HR = 0.75, 95% CI 0.65-0.85) compared with women who did not meet the PA Guidelines (<10 MET-hours/week) (Beasley et al, 2012).


Statement on smoking
The association of smoking with outcomes following breast cancer prognosis is not well understood.

In the LACE cohort study, 2265 women diagnosed with breast cancer were followed for a median of twelve years. Compared with never smokers, women who were current smokers had a two-fold higher rate of dying from breast cancer (HR=2.01, 95% CI 1.27–3.18] and an approximately four-fold higher rate of dying from competing (non-breast cancer) causes (HR=3.84, 95% CI 2.50–5.89).

Among seven studies that met the inclusion criteria in the systematic review, four studies reported significantly increased risk of breast cancer death with current smoking. Little evidence was found of an association between former smoking and breast cancer mortality (HR=1.24, 95% CI 0.94–1.64).


Further references:


Statement on alcohol
The association between alcohol intake and recurrence may depend on menopausal status at breast cancer diagnosis. In the international “After Breast Cancer Pooling Project” an investigation was conducted of postdiagnosis alcohol consumption among 9,329 women with a mean follow-up of 10.3 years. 58% of the women were considered drinkers (≥0.36g/d, median 5.3g/d). Overall, compared with nondrinking, regular alcohol intake (≥6.0g/d) was not associated with risk of recurrence. However, risk varied significantly by menopausal status. Postmenopausal women who regularly consumed alcohol (≥6.0g/d) had increased risk of recurrence (HR, 1.19; 95% CI, 1.01-1.40). Alcohol was not associated with mortality.

Accordingly, alcohol intake was not associated with survival among 3146 women diagnosed with invasive breast cancer in the Swedish Mammography Cohort. Women who consumed 10 g per day (corresponding to approximately 0.75 to 1 drink) or more of alcohol had an adjusted HR (95% CI) of breast cancer-specific death of 1.36 (0.82-2.26; p(trend)=0.47) compared with non-drinkers. Thus indicating that alcohol intake up to approximately one small drink per day does not negatively impact breast cancer-specific survival (Harris et al, 2012). This contrasts earlier findings from the LACE study showing that drinking ≥ 6 g/d of alcohol compared with no drinking was associated with an increased risk of breast cancer recurrence (HR, 1.35; 95% CI, 1.00 to 1.83) and death due to breast cancer (HR, 1.51; 95% CI, 1.00 to 2.29) (Kwan et al, 2010). Interestingly, both of these studies found an inverse relationship between alcohol intake and non-breast cancer death suggesting cardioprotective effects of alcohol on non-breast cancer death.


In addition to being a risk factor for breast cancer, a high pre-diagnostic alcohol intake also seems to have an effect on the course of the disease. Holm et al. (2013) found a modest but significant association between pre-diagnostic alcohol consumption and breast cancer recurrence with a median follow-up of six years after date of diagnosis in a prospective cohort of 29,875 women. Results for breast cancer specific mortality were also suggestive of a higher risk but were not statistically significant.


Further references:

- Reding et al.: Effect of Prediagnostic Alcohol Consumption on Survival after Breast Cancer in Young women. Cancer Epidemiol Biomarkers Prev. 2008; 17: 1988-1996. These results suggest that women who consume alcohol before a diagnosis of breast cancer have improved survival, which does not appear to be attributable to differences in stage, screening, or treatment.
Further information and references:

To make it quite clear: the biggest threat from unconventional therapies including CAM is from the danger of omitting evidence based therapy, in specific systemic therapy. This could be clearly demonstrated by Saquib et al (2012). The purpose of their study was to assess whether CAM use affected breast cancer prognosis in those who did not receive systemic therapy. They used a secondary data analysis of baseline/survey data from the Women’s Healthy Eating and Living (WHEL) study including 2562 breast cancer survivors. Mean follow-up approached 7.3 years. Those women who did not receive any systemic treatment had a higher risk for time to additional breast cancer events (HR=1.9, 95% CI: 1.32, 2.73) and for all-cause mortality (HR=1.7, 95% CI: 1.06, 2.73) compared to those who had received systemic treatment. Among 177 women who did not receive systemic treatment, CAM use was not significantly related to additional breast cancer events. The use of dietary supplements or CAM therapies did not change this risk. This indicates that complementary and alternative therapies did not alter the outcome of breast cancer and should not be used in place of standard treatment.


CAM (long-term breast cancer survivors who use CAM may have poorer emotional functioning and more medical problems than non-users)

In contrast to popular belief there’s virtually no usable data on the safety and efficacy of most CAM-modalities, let alone unconventional therapies. Fortunately some CAM approaches are now being reviewed using evidence-based rationales. However, most studies are still in the protocol stage. Lin T, Ding Z, Li N, et al: Seleno-cyclodextrin sensitises human breast cancer cells to TRAIL-induced apoptosis through DR5 induction and NF-κB suppression. Eur J Cancer. 2011 Aug;47(12):1890-907.
Many other modalities listed on this slide belong to the group of unproven methods with the potential of causing side effects and drug interaction and are therefore rejected by the guideline panel (AGO -). Mistletoe and black cohosh extracts have been “uprated“ from AGO – to AGO +/- because safety data suggest that adverse outcomes are not necessarily to be feared. Soy-derived isoflavonoids are potent phytoestrogens with complete estrogenic interaction with estrogen receptors and complicated dose-response relationships in vitro. Since they could potentially stimulate ER-responsive tumor cells under unpredictable circumstances, there is a long lasting discussion whether they can be safely consumed as medical adjuvants. Guha et al showed in a cohort of 1954 breast cancer patients with diagnoses from 1997 through 2000 an inverse association between postdiagnosis soy isoflavone intake and breast cancer recurrence. However, the inverse association was not observed among women not taking tamoxifen. Contrasting these findings, a large, population-based cohort study of 5042 female breast cancer survivors in China demonstrated that soy food consumption was significantly associated with decreased risk of death and recurrence. This association was evident among women with either estrogen receptor-positive or -negative breast cancer and was present in both users and nonusers of tamoxifen (Shu et al, 2009). Occasional consumption of soy - derived foodstuff, e.g., tofu or soy milk, as part of a vegetable-based diet is probably harmless.


**Vitamins / Antioxidants**

A population-based prospective cohort study of 4,877 women in Shanghai aged 20 to 75 years diagnosed with invasive breast cancer demonstrated that vitamin use shortly after breast cancer diagnosis was associated with reduced mortality and recurrence risk, adjusted for multiple lifestyle factors, sociodemographics, and known clinical prognostic factors. Women who used antioxidants (vitamin E, vitamin C, multivitamins) had 18% reduced mortality risk (HR = 0.82, 95% CI: 0.65-1.02) and 22% reduced recurrence risk (HR = 0.78, 95% CI: 0.63-0.95). The inverse association was found regardless of whether vitamin use was concurrent or nonconcurrent with chemotherapy, but was present only among patients who did
not receive radiotherapy. This does not support the current recommendation that breast cancer patients should avoid use of vitamin supplements (Nechuta et al, 2010). Greenlee and co-workers reported that frequent use of vitamin C and vitamin E in the period after breast cancer diagnosis was associated with a decreased likelihood of recurrence, whereas frequent use of combination carotenoids was associated with increased mortality. The effects of antioxidant supplement use after diagnosis likely differ by type of antioxidant.


Laetrile treatment for cancer

Milazzo S, Ernst E, Lejeune S, Boehm K, Horneber M. : Laetrile is the name for a semi-synthetic compound which is chemically related to amygdalin, a cyanogenic glycoside from the kernels of apricots and various other species of the genus Prunus. Laetrile and amygdalin are promoted under various names for the treatment of cancer although there is no evidence for its efficacy. Due to possible cyanide poisoning, laetrile can be dangerous.

The claims that laetrile or amygdalin have beneficial effects for cancer patients are not currently supported by sound clinical data. There is a considerable risk of serious adverse effects from cyanide poisoning after laetrile or amygdalin, especially after oral ingestion. The risk–benefit balance of laetrile or amygdalin as a treatment for cancer is therefore unambiguously negative.

Alternatives to reduce Menopausal Symptoms after BC I (13/16)

Further information and references:

Menopausal symptoms are bothersome for breast cancer survivors and affect quality of life. Since hormonal replacement therapy should be avoided in ER positive breast cancer patients alternatives are important. Antidepressants may help with hot flashes. Acupuncture and hypnosis can also be used but the evidence is conflicting. For urogenital problems vaginal moisturizers or topical estrogens can be used (Loibl et al, 2011).

General approaches

This A wait-list controlled RCT (n=422) evaluates the effect of cognitive behavioral therapy (CBT), physical exercise (PE), and of these two interventions combined (CBT/PE) on menopausal symptoms (primary outcome), body image, sexual functioning, psychological well-being, and health-related quality of life (secondary outcomes) in patients with breast cancer experiencing treatment induced menopause. Compared with the control group, the intervention groups had a significant decrease in levels of endocrine symptoms (P =.001; effect size, 0.31-0.52) and urinary symptoms (P =.002; effect size, 0.29-0.33), and they showed an improvement in physical functioning (P =.002; effect size, 0.37-0.46). The groups that included CBT also showed a significant decrease in the perceived burden of hot flashes and night sweats (P =.001; effect size, 0.39-0.56) and an increase in sexual activity (P=.027; effect size, 0.65). Most of these effects were observed at both the 12-week and 6-month follow-ups.

Conclusion: CBT and PE can have salutary effects on endocrine symptoms and, to a lesser degree, on sexuality and physical functioning of patients with breast cancer experiencing treatment-induced menopause. PE seems to affect primarily the frequency with which endocrine symptoms are experienced, as assessed by the FACT-ES, but not the frequency of hot flashes and night sweats specifically. CBT, in contrast, seems to not only affect symptom frequency, but also the perceived burden of hot flashes and night sweats. These results tend to support the hypothesis that cognitive and emotional factors can modify the experience of menopausal symptoms, whereas stress reduction techniques and physical exercise may have a more direct effect on menopausal symptoms via the thermoregulatory system and an improvement in overall physical condition.

**Physical Training**

**Mind-Body-Medicine (Relaxation training, Yoga, Hypnosis)**

A unique relaxation training consisting of deep breathing, imagination, and PME and subsequent independent practicing at home with an audiotape for 20 minutes daily one month long significantly decreased the frequency and intensity of hot flashes in n=76 women compared with n=74 women with no intervention.
Yoga (n=17), 8 monthly 120-minute units, compared with waitinglist (n=20). Result: Significant improvement in hot flashes score, joint pain, fatigue, sleep, mood, and relaxation. These results remain significant after 3 months follow-up.


RCT (n=51): 5 weekly hypnosis sessions (ca. 50 min.) and instructions on self-hypnosis compared with waiting list. Results: hot flash scores (frequency x average severity) decreased 68% compared with control group. In addition significant improvement in anxiety, depression, and sleep.


**Vaginal Lubricants**


**Acupuncture**

In their review Lee et al. assessed the effectiveness of acupuncture as a treatment option for hot flashes in patients with breast cancer. They searched the literature using 14 databases from their inceptions to August 2008, without language restrictions. They included randomized clinical trials (RCTs) comparing real with sham acupuncture or another active treatment or no treatment. Methodological quality of the trials was assessed using the modified Jadad score. Three RCTs compared the effects of manual acupuncture with sham acupuncture. One RCT showed that acupuncture reduced hot flash frequency, while the other two RCTs did not. The meta-analysis showed significant effects of acupuncture compared with sham acupuncture (n = 189, weight mean difference, 3.09, 95% confidence intervals -0.04 to 6.23, P = 0.05) but marked heterogeneity was observed in this model (chi (2) = 8.32, P = 0.02, I (2) = 76%). One RCT compared the effects of
electroacupuncture (EA) with hormone replacement therapy. Hormone therapy was more effective than EA. Another RCT compared acupuncture with venlafaxine and reported no significant intergroup difference. A further RCT compared acupuncture with applied relaxation and failed to show a significant intergroup difference. Lee et al. concluded that acupuncture is not an effective treatment for hot flashes in patients with breast cancer. Further research is required to determine whether acupuncture is suitable for treating hot flashes in patients with breast cancer.


In contrast to this, in a recent trial 94 women were randomized into three study arms: 31 had acupuncture, 29 had sham acupuncture and 34 had no treatment. In the acupuncture group, 16 patients (52%) experienced a significant effect on hot flashes compared with seven patients (24%) in the sham group (p < 0.05). The effect came after the second acupuncture session and lasted for at least 12 weeks after last treatment. A statistically significant positive effect was seen on sleep in the acupuncture group compared with the sham-acupuncture and no-treatment groups. The effect was not correlated with increased levels of plasma estradiol. No side effects of acupuncture were registered.

In this study acupuncture significantly relieves hot flashes and sleep disturbances and is a good and safe treatment in women treated for breast cancer. The project is registered at Clinical Trials.gov (no: NCT00425776).


In another trial with breast cancer survivors, acupuncture was compared with venlafaxine. It was demonstrated that acupuncture appears to be equivalent to drug therapy in these patients. It is a safe, effective and durable treatment for vasomotor symptoms secondary to long-term antiestrogen hormone use in patients with breast cancer (Walker et al, 2010).


However, in the trial of Deng et al. acupuncture and sham-acupuncture both reduced hot flash symptoms. After the cross-over, the initial sham-acupuncture group further improved after receiving true acupuncture treatment.

In the trial of Nedstrand et al. acupuncture and relaxation therapy were equally successful in reducing hot flashes. Acupuncture was also as effective as venlafaxin in reducing the symptoms.


Finally, a word of caution: acupuncture should be used by knowledgeable practitioners applying general medically sensed caution. A case report by Tseng et al (2011) sheds light of the potential risks: acupuncture in TCM with needles placed into a cutaneous tumor manifestation resulted in disseminated skin metastases. Notwithstanding the beneficial effects referenced above, even measures like acupuncture have their specific risks and should not be applied uncritically.


Further references:


Herbal Approaches to Reduce Menopausal Symptoms - (14/16)

Further information and references:

Roberts reviewed and summarised current evidence on the efficacy and safety of herbal medicinal products for the relief of hot flushes in women with previous breast cancer. The majority of studies, regarding the efficacy of herbal treatments for hot flushes, have not been conducted in women with breast cancer and many are of short duration. Increased pharmacovigilance practices for herbal medicines are required with initiatives to stimulate reporting of suspected adverse reactions.


More recently, Ma et al (2011) review a diverse array of estrogenic botanical supplement (EBS) to find out whether the use influences breast cancer survivors' health-related outcomes. The findings were also very divers and indicated that several specific types of EBS might have important influences on a woman's various aspects of quality of life, but further verification is necessary. Red clover users were less likely to report weight gain, night sweats, and difficulty concentrating (all OR approximately 0.4 and all 95% CIs exclude 1). This is the reason, why we change the AGO recommendation from -- to --.


Phytoestrogens
Soy-derived isoflavonoids are potent phytoestrogens, which can interact with estrogen receptors, and their dose-response relationships with estrogen receptors in vitro are complicated. Since they have the potential to stimulate ER-responsive tumor cells under unpredictable circumstances, they should not be consumed as medical adjuvants. For the same reason the use of red clover, ginseng and dong quai as medical adjuvants should be discouraged. However, the occasional consumption of soy - derived foodstuffs, e.g., tofu or soy milk, as part of a vegetable-based diet is probably harmless.


**Flaxseed**

Concerning the occurrence of hot flushes, a recent randomized phase III trial failed to demonstrate a significant reduction of hot flushes for postmenopausal patients taking additional 410 g of lignans as compared to placebo (Pruthi et al, 2012). Flower et al very recently performed a systematic review of the current literature and concluded that current evidence suggests that flax may be associated with decreased risk of breast cancer. Flax demonstrates antiproliferative effects in breast tissue of women at risk of breast cancer and may protect against primary breast cancer. Mortality risk may also be reduced among those living with breast cancer.


**Black cohosh (Cimicifuga racemosa)**

*(Phyto-SERM = selective estrogen receptor modulator)*


**St John’s Wort**


Red clover


Dong Quai


**Ginseng root**

In a case-control study conducted in Korea, ginseng intakers had a decreased risk [odds ratio = 0.50, 95% confidence interval (CI) = 0.44-0.58] for cancer compared with nonintakers. However, breast cancer, there was no association with ginseng intake.


**Bromelain+Papain+Selen+Lektin bei AI-induzierten Gelenkbeschwerden**


A clinical investigation (representing evidence-based medicine level III) of Uhlenbruck et al. (3) was performed to evaluate the benefit of complementary medicine in breast cancer patients undergoing adjuvant hormone therapy (HT). The patients (n=129) were treated according to international guidelines. All patients suffered from arthralgia and mucosal dryness induced by the adjuvant HT. To reduce these side effects, the patients were administered a combination of sodium selenite, proteolytic plant enzymes (bromelaine and papain), and Lens culinaris lectin as a complementary treatment. On the basis of case report formulas (CRFs), the patients’ self assessments of defined side-effects of HT (arthralgia and mucosal dryness) were documented before as well as 4 and 8 weeks after complementary treatment. Results were validated by scoring from 1 (no side-effects/optimal tolerability) to 6 (extreme side-effects/extremely bad tolerability). The severity of side effects of HT was reduced by the complementary treatment with sodium selenite, plant enzymes (bromelaine and papain) and Lens culinaris lectin. The mean score of symptoms declined from 4.2 (before treatment) to 3.2 (after 4 weeks of treatment) to 2.7 (after 8 weeks of treatment) for arthralgia and from 3.2 (before treatment) to 2.9 (after 4 weeks of treatment) to 2.6 (after 8 weeks of treatment) for mucosal dryness, the primary aims of this investigation. The reduction of
side effects of HT was statistically significant (p<0.001 after 4 weeks and p<0.0001 after 8 weeks). This investigation demonstrated the benefits of indication-based complementary treatment in breast cancer patients, e.g., reduction of the side effects of adjuvant HT. A randomized controlled trial is planned to integrate the complementary treatment of sodium selenite combined with proteolytic enzymes.
Further information and references:

A total of 15 RCTs met the inclusion criteria of this systematic review. All of the included RCTs were associated with a high risk of bias. The majority of acupuncture treatments or combination therapies with analgesics exhibited favourable effects compared with conventional treatments in individual studies. However, a meta-analysis suggested that acupuncture did not generate a better effect than drug therapy (n0886; risk ratio (RR), 1.12; 95% CI 0.98 to 1.28; P00.09). The comparison between acupuncture plus drug therapy and drug therapy alone demonstrated a significant difference in favour of the combination therapy (n0437; RR, 1.36; 95% CI 1.13 to 1.64; P00.003). The results of this systematic review provide no strong evidence for the effectiveness of acupuncture in the management of cancer pain.


Forty percent of individuals with early or intermediate stage cancer and 90% with advanced cancer have moderate to severe pain and up to 70% of patients with cancer pain do not receive adequate pain relief. It has been claimed that acupuncture has a role in management of cancer pain and guidelines exist for treatment of cancer pain with acupuncture. Three RCTs (204 participants) were included in this review.

There is insufficient evidence to judge whether acupuncture is effective in treating cancer pain in adults.


More recently a similar result was extracted from a systematic literature review by Garcia et al (2013). The authors concluded that acupuncture is an appropriate adjunctive treatment for chemotherapy-induced nausea/vomiting. For other symptoms (including pain), efficacy remains undetermined.

Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults

Cancer-related pain is complex and multi-dimensional but the mainstay of cancer pain management has predominately used a biomedical approach. There is a need for non-pharmacological and innovative approaches. Transcutaneous Electric Nerve Stimulation (TENS) may have a role for a significant number of patients but the effectiveness of TENS is currently unknown.

The aim of this systematic review was to determine the effectiveness of TENS for cancer-related pain in adults. Only two RCTs met the eligibility criteria (64 participants). These studies were heterogeneous with respect to study population, sample size, study design, methodological quality, mode of TENS, treatment duration, method of administration and outcome measures used. In one RCT, there were no significant differences between TENS and placebo in women with chronic pain secondary to breast cancer treatment. In the other RCT, there were no significant differences between acupuncture-type TENS and sham in palliative care patients; this study was underpowered.

The results of this systematic review are inconclusive due to a lack of suitable RCTs. Large multi-centre RCTs are required to assess the value of TENS in the management of cancer-related pain in adults.


Further references:

Immunodiagnostic Tests and Immunotherapy (16/16)

Further information:

Recently, the recognition that chronic inflammation in the tumor microenvironment promotes tumor growth and survival during different stages of breast cancer development has led to the development of novel immunotherapies. Several immunotherapeutic strategies have been studied both preclinically and clinically and already have been shown to enhance the efficacy of conventional treatment modalities. Therefore, therapies targeting the immune system may represent a promising next-generation approach for the treatment of breast cancers.

A prospective case series was published by Adams et al (2012) to evaluate the local tumor response rate of breast cancer skin metastases treated with topical imiquimod, applied 5 d/wk for 8 weeks. Ten patients were enrolled. Two patients achieved a partial response. Responders showed histologic tumor regression with evidence of an immune-mediated response, showed by changes in the tumor lymphocytic infiltrate and locally produced cytokines.

Dendritic cell intradermal vaccination

In a recent paper from China (Qi et al, 2012) Dendritic cell (DC) vaccines were generated from CD14+ precursors pulsed with autologous tumor lysates. DCs were matured with defined factors that induced surface marker and cytokine production. Individuals were immunized intradermally four times. Overall survival and disease progression rates were compared with those of contemporaneous patients who were not administered DC vaccines. There was no difference in overall survival between the patients with and without DC vaccine. The 3-year progression-free survival was significantly prolonged: 76.9% versus 31.0% (with vs. without DC vaccine, p < 0.05). The authors concluded that their findings strongly suggest that tumor lysate-pulsed DCs provide a standardized and widely applicable source of breast cancer antigens that are very effective in evoking anti-breast cancer immune responses.
Recently, quite a number of preliminary clinical trials have been evaluated and published reporting on immunotherapeutic interventions yielding promising early results. In this context, Montero et al (2012) reported on the addition of NOV-002 (a formulation of disodium glutathione disulfide) to chemotherapy, which has been shown to increase anti-tumor efficacy in animal models and some early phase oncology trials. Concurrent NOV-002 resulted in 38% pCR rate for AC → T chemotherapy higher than previously reported e.g. in the B27 or the Geparduo trials.

This and other early indications of efficacy do not at all allow general recommendation, however they show, that further evaluation in the context of randomised trials should be actively supported.

References: