# Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

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Guidelines Breast
Version 2019.1D

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## Gynäkologische Probleme bei Mammakarzinompatientinnen

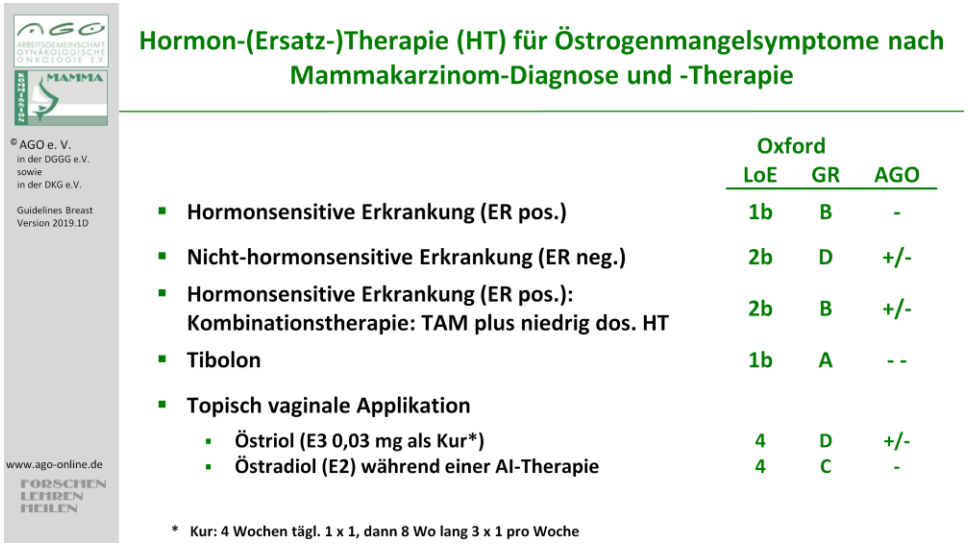

# Gynäkologische Probleme bei Mammakarzinompatientinnen

- **Version 2015–2018:**
  **Albert / Bauerfeind / Fersis / Gerber / Hanf / Loibl / Maas / Scharl / Thill / Witzel**
- **Version 2019:**
  **Blohmer / Huober**

Screened data bases:

| | |
|---|---|
| Pubmed | 2009 –2018 |
| ASCO | 2009 - 2018 |
| Cochrane | 2009 - 2018 |
| Medline | 2009 - 2018 |

Screened: Metaanalyses/ Systematic reviews / RCT / Cohort studies





Endocrine responsive disease

1. Wang Y, Lewin N, Qaoud Y et al. The oncologic impact of hormone replacement therapy in premenopausal breast cancer survivors: A systematic review. Breast. 2018 Aug;40:123-130. doi: 10.1016/j.breast.2018.05.002. Epub 2018 May 12.

Endocrine non-responsive disease

1. Wang Y, Lewin N, Qaoud Y et al. The oncologic impact of hormone replacement therapy in premenopausal breast cancer survivors: A systematic review. Breast. 2018 Aug;40:123-130. doi: 10.1016/j.breast.2018.05.002. Epub 2018 May 12.

Endocrine responsive disease: combined treatment TAM plus low-dose-HT

1. Holmberg L: Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. J Natl Cancer Inst 100:475-82, 2008.
2. Fahlén M: Hormone replacement therapy after breast cancer: 10 year follow up of the Stockholm

randomised trial. Eur J Cancer. 2013 Jan;49(1):52-9.

3. Lupo M, Dains JE, Madsen LT. Hormone Replacement Therapy: An Increased Risk of Recurrence and Mortality for Breast Cancer Patients? J Adv Pract Oncol. 2015 Jul-Aug;6(4):322-30. Epub 2015 Jul
4. Kuhle CL, Kapoor E, Sood R et al.: Menopausal hormone therapy in cancer survivors: A narrative review of the literature. Maturitas. 2016 Oct;92:86-96.

Tibolone

1. Sismondi P., Kimmig R., Kubista E. et al.: Effects of Tibolone on climacteric symptoms and quality of life in breast cancer patients—Data from LIBERATE trial. Maturitas. 2011;70:365–372.
2. Bundred NJ: Tibolone increases bone mineral density but also relapse in breast cancer survivors: LIBERATE trial bone substudy. Breast Cancer Res. 2012 Jan 17;14(1):R13.


## Weitere Methoden zur Erleichterung post-menopausaler Symptome nach Mamma-Ca

| Medikamentöse Ansätze: | Oxford LoE | GR | AGO |
|---|---|---|---|
| ▪ Selektive Serotonin-Reuptake-Inhibitoren und Serotonin-(Noradrenalin) Reuptake-Inhibitoren (SSRI-SNRI): zur Reduktion von Hitzewallungen | | | |
| ▪ Venlafaxin | 1a | A | + |
| ▪ Desvenlafaxin | 1b | A | +/- |
| ▪ Sertralin, Escitalopram | 1b | A | +/- |
| ▪ Gabapentin (MaCa-Pat. unter Tamoxifen-Therapie) | 1a | A | + |
| ▪ Pregabalin | 1b | A | +/- |
| ▪ Clonidin (MaCa-Pat. unter Tamoxifen-Therapie) | 1a | A | + |
| ▪ Oxybutynin (2,5mg/5 mg) | 1b[a] | A | +/- |
| ▪ MPA (i.m. 500 mg single shot) | 1b | A | +/- |
| ▪ Vitamin E | 1b | A | - |
| ▪ Omega 3-Fettsäuren | 1b | A | +/- |
| ▪ Melatonin (verbesserte Schlafqualität) | 2b | C | + |
| ▪ Duloxetin (zur Therapie von Arthralgien nur unter AI-Therapie) | 1b | B | + |


1. Chubak J, Bowles EJ,Yu O, Buist DS et al.: Breast cancer recurrence in relation to antidepressant use. Cancer Causes Control. 2016 Jan;27(1):125-36.
2. Haque R, Shi J, Schottinger JE et al.:Tamoxifen and Antidepressant Drug Interaction in a Cohort of 16 887 Breast Cancer Survivors.J Natl Cancer Inst. 2015 Dec 1;108(3).
3. L'Espérance S: Pharmacological and non-hormonal treatment of hot flashes in breast cancer survivors: CEPO review and recommendations. Support Care Cancer. 2013 May;21(5):1461-74
4. Kelly CM, Juurlink DN, Gomes T et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. *BMJ*. 2010;340:c693.
5. Bordeleau L: Multicenter, randomized, cross-over clinical trial of venlafaxine versus gabapentin for the management of hot flashes in breast cancer survivors. J Clin Oncol. 2010 Dec 10;28(35):5147-52.
6. Wiśniewska I, Jochymek B, Lenart-Lipińska M et al.: The pharmacological and hormonal therapy of hot flushes in breast cancer survivors. Breast Cancer. 2016 Mar;23(2):178-82.
7. Antoine C, Ameye L, Paesmans M et al.: Treatment of climacteric symptoms in breast cancer patients: a retrospective study from a medication databank. Maturitas. 2014 Jul;78(3):228-32.

8. Drewe J, Bucher KA, Zahner C. A systematic review of non-hormonal treatments of vasomotor symptoms in climacteric and cancer patients. Springerplus. 2015:10;4:65.
9. Leon-Ferre RA, Majithia N, Loprinzi CL. Management of hot flashes in women with breast cancer receiving ovarian function suppression. Cancer Treat Rev. 2017 Jan;52:82-90.

SSRI

1. Shams T1, Firwana B, Habib F et al.: SSRIs for hot flashes: a systematic review and meta-analysis of randomized trials. J Gen Intern Med. 2014 Jan;29(1):204-13.

Duloxetin

1. Henry NL, Unger JM, Schott AF et al. Randomized, Multicenter, Placebo-Controlled Clinical Trial of Duloxetine Versus Placebo for Aromatase Inhibitor-Associated Arthralgias in Early-Stage Breast Cancer: SWOG S1202. J Clin Oncol. 2018 Feb 1;36(4):326-332. doi: 10.1200/JCO.2017.74.6651. Epub 2017 Nov 14.

Venlafaxine

1. Ramaswami R, Villarreal MD, Pitta DM et al.: Venlafaxine in management of hot flashes in women with breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat. 2015 Jul;152(2):231-7.
2. Boekhout AH, Vincent AD, Dalesio OB et al: Management of hot flashes in patients who have breast cancer with venlafaxine and clonidine: a randomized, double-blind, placebo-controlled trial. J Clin Oncol. 2011 Oct 10;29(29):3862-8.
3. Bordeleau L, Pritchard KI, Loprinzi CL et al: Multicenter, randomized, cross-over clinical trial of venlafaxine versus gabapentin for the management of hot flashes in breast cancer survivors. J Clin Oncol. 2010 Dec 10;28(35):5147-52.

Desvenlafaxine

1. Archer DF, Dupont CM, Constantine GD et al.: Desvenlafaxine for the treatment of vasomotor symptoms associated

with menopause: a double-blind, randomized, placebo-controlled trial of efficacy and safety. Am J Obstet Gynecol. 2009;200(3):238 e231–238 e210.

2. Speroff L, Gass M, Constantine G et al.: Efficacy and tolerability of desvenlafaxine succinate treatment for menopausal vasomotor symptoms: a randomized controlled trial. Obstet Gynecol. 2008;111(1):77–87.
3. Deecher DC, Alf inito PD, Leventhal L et al.: Alleviation of thermoregulatory dysfunction with the new serotonin and norepinephrine reuptake inhibitor desvenlafaxine succinate in ovariectomized rodent models. Endocrinology. 2007;148(3):1376–1383.

Paroxetine

1. Simon JA, Portman DJ, Kaunitz AM et al.: Low-dose paroxetine 7.5 mg for menopausal vasomotor symptoms: two randomized controlled trials. Menopause. 2013 Oct;20(10):1027-35. doi: 10.1097/GME.0b013e3182a66aa7.

Fluoxetine

1. Loprinzi CL, Sloan J, Stearns V et al.: Newer antidepressants and gabapentin for hot flashes: an individual patient pooled analysis. J Clin Oncol. 2009;27(17):2831–2837.

Citalopram

1. Barton DL, LaVasseur B, Sloan JA et al.: A phase III trial evaluating three doses of citalopram for hot flashes: NCCTG trial N05C9. J Clin Oncol. 2008;26(20):9538.
2. Kalay AE, Demir B, Haberal A et al.: Efficacy of citalopram on climacteric symptoms. Menopause. 2007;14(2):223–229.

Gabapentin

1. Bordeleau L, Pritchard KI, Loprinzi CL et al: Multicenter, randomized, cross-over clinical trial of venlafaxine versus gabapentin for the management of hot flashes in breast cancer survivors. J Clin Oncol. 2010 Dec 10;28(35):5147-52

Pregabalin

1. Loprinzi CL, Qin R, Baclueva EP et al.: Phase III, randomized, double-blind, placebo-controlled evaluation of pregabalin for alleviating hot flashes, N07C1. J Clin Oncol. 2010;28(4):641–647.

Clonidin

1. Drewe J, Bucher KA, Zahner CA.: systematic review of non-hormonal treatments of vasomotor symptoms in climacteric and cancer patients. Springerplus. 2015 Feb 10;4:65. doi: 10.1186/s40064-015-0808-y. eCollection 2015.
2. Boekhout AH, Vincent AD, Dalesio OB et al: Management of hot flashes in patients who have breast cancer with venlafaxine and clonidine: a randomized, double-blind, placebo-controlled trial. J Clin Oncol. 2011 Oct 10;29(29):3862-8
3. Friedman GD, Udaltsova N, Habel LA: Norepinephrine antagonists and cancer risk. Int J Cancer 2011. 128(3):737–738, doi:10.1002/ijc.25351 (Clonidin)

Oxybutynin

1. Roberto A. Leon-Ferre, Paul J. Novotny, Stephanie S. Faubion et al. A randomized, double-blind, placebo-controlled trial of oxybutynin for hot flashes : ACCRU study SC-1603. SABCS 2018, abstract GS6_2

(D) MPA (depo-) (Medroxyprogesterone acetate)

1. Prior JC, Nielsen JD, Hitchcock CL et al.: Medroxyprogesterone and conjugated oestrogen are equivalent for hot flushes: a 1-year randomized double-blind trial following premenopausal ovariectomy. Clin Sci (Lond). 2007;112(10):517–525.
2. Loprinzi CL, Levitt R, Barton D et al.: Phase III comparison of depomedroxyprogesterone acetate to venlafaxine for managing hot flashes: North Central Cancer Treatment Group Trial N99C7. J Clin Oncol. 2006 Mar 20;24(9):1409-14. Epub 2006 Feb 27.

Vitamine E

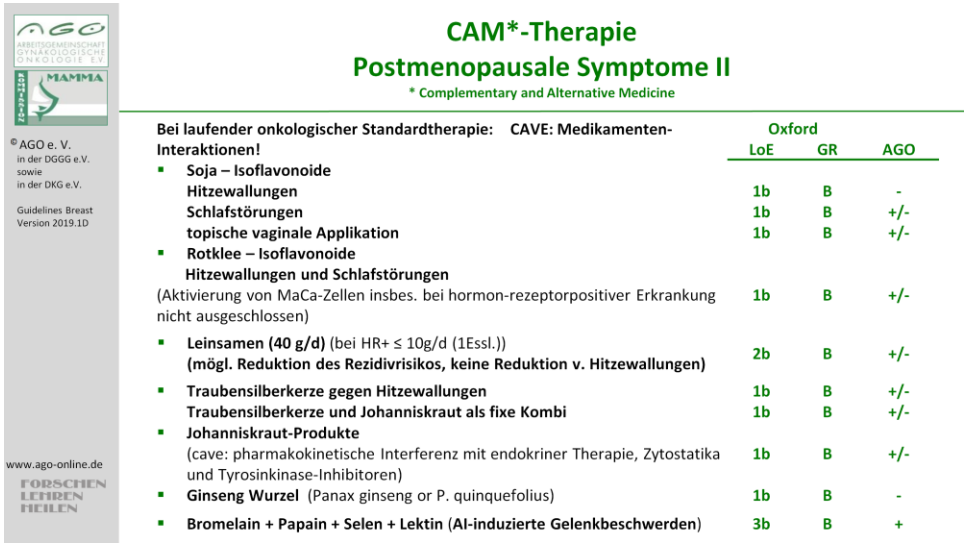

1. Rada G: Non-hormonal interventions for hot flushes in women with a history of breast cancer (Review). The Cochrane Library 2010, Issue 9.
2. Greenlee H, Hershman DL, Jacobson JS: Use of antioxidant supplements during breast cancer treatment: a comprehensive review. Breast Cancer Res Treat. 2009 Jun;115(3):437-52.
3. Biglia N, Sgandurra P, Peano E et al.: Non-hormonal treatment of hot flushes in breast cancer survivors: gabapentin vs. vitamin E. Climacteric. 2009 Aug;12(4):310-8.


Omega 3-Fettsäuren


1. Lustberg M´B, Orchard TS, Reinbolt R et al. Randomized placebo-controlled pilot trial of omega 3 fatty acids for prevention of aromatase inhibitor-induced musculoskeletal pain. Breast Cancer Res Treat. 2018 Feb;167(3) 709-718. doi: 10.1007/s10549-017-4559-z. Epub 2017 Nov 3.


Melatonin


1. Chen WY, Giobbie-Hurder A, Gantman K et al.: A randomized, placebo-controlled trial of melatonin on breast cancer survivors: impact on sleep, mood, and hot flashes. Breast Cancer Res Treat 2014. 145(2):381–388, doi:10.1007/s10549-014-2944-4



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## CAM*-Therapie
## Postmenopausale Symptome II

* Complementary and Alternative Medicine

| Bei laufender onkologischer Standardtherapie: CAVE: Medikamenten-Interaktionen! | Oxford LoE | GR | AGO |
|---|---|---|---|
| ▪ **Soja – Isoflavonoide** | | | |
| **Hitzewallungen** | 1b | B | - |
| **Schlafstörungen** | 1b | B | +/- |
| **topische vaginale Applikation** | 1b | B | +/- |
| ▪ **Rotklee – Isoflavonoide** | | | |
| **Hitzewallungen und Schlafstörungen** (Aktivierung von MaCa-Zellen insbes. bei hormon-rezeptorpositiver Erkrankung nicht ausgeschlossen) | 1b | B | +/- |
| ▪ **Leinsamen (40 g/d)** (bei HR+ ≤ 10g/d (1Essl.)) **(mögl. Reduktion des Rezidivrisikos, keine Reduktion v. Hitzewallungen)** | 2b | B | +/- |
| ▪ **Traubensilberkerze gegen Hitzewallungen** | 1b | B | +/- |
| **Traubensilberkerze und Johanniskraut als fixe Kombi** | 1b | B | +/- |
| ▪ **Johanniskraut-Produkte** (cave: pharmakokinetische Interferenz mit endokriner Therapie, Zytostatika und Tyrosinkinase-Inhibitoren) | 1b | B | +/- |
| ▪ **Ginseng Wurzel** (Panax ginseng or P. quinquefolius) | 1b | B | - |
| ▪ **Bromelain + Papain + Selen + Lektin (AI-induzierte Gelenkbeschwerden)** | 3b | B | + |


1. Roberts H. Safety of herbal medicinal products in women with breast cancer. Maturitas. 2010;66(4):363-9.
2. Ma H: Estrogenic botanical supplements, health-related quality of life, fatigue, and hormone-related symptoms in breast cancer survivors: a HEAL study report. BMC Complement Altern Med. 2011;11:109.
3. Kim W, Lee WB, Lee JW et al.: Traditional herbal medicine as adjunctive therapy for breast cancer: A systematic review. Complement Ther Med. 2015 Aug;23(4):626-32. doi: 10.1016/j.ctim.2015.03.011.
4. Lethaby A, Marjoribanks J, Kronenberg F et al.: Phytoestrogens for menopausal vasomotor symptoms. Cochrane Database Syst Rev. 2013 Dec 10;(12):CD001395. doi: 10.1002/14651858.CD001395.pub4.


Soy- derieved isoflavonoids

Red clover-derived isoflavonoids


1. Chen MN: Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic

review. Climacteric. 2015 Apr;18(2):260-9.

2. Lethaby A: Phytoestrogens for menopausal vasomotor symptoms. Cochrane Database Syst Rev. 2013 Dec 10;12:CD001395.
3. Fritz H, Seely D, Flower G et al.: red clover, and isoflavones and breast cancer: a systematic review. PLoS One. 2013 Nov 28;8(11):e81968.
4. Ghazanfarpour M, Sadeghi R, Latifnejad Roudsari R et al.: Effects of red clover on hot flash and circulating hormone concentrations in menopausal women: a systematic review and meta-analysis. Avicenna J Phytomed. 2015 Nov-Dec;5(6):498-511.
5. Shakeri F: Effectiveness of red clover in alleviating of menopausal symptoms: A 12-week randomized, controlled trial. Climacteric. 2015;18(4):568-73.
6. Ghazanfarpour M, Latifnejad Roudsari R, Treglia G et al.: Topical administration of isoflavones for treatment of vaginal symptoms in postmenopausal women: A systematic review of randomised controlled trials. J Obstet Gynaecol. 2015 Nov;35(8):783-7.
7. Ghazanfarpour M, Sadeghi R, Roudsari RL. The application of soy isoflavones for subjective symptoms and objective signs of vaginal atrophy in menopause: A systematic review of randomised controlled trials. J Obstet Gynaecol. 2016;36(2):160-71.
8. Ribeiro AE, Monteiro NES, Moraes AVG et al. Can the use of probiotics in association with isoflavone improve the symptoms of genitourinary syndrome of menopause? Results from a randomized controlled trial. Menopause. 2018 Dec 10. doi: 10.1097/GME.0000000000001279. [Epub ahead of print]

<u>Flaxseed</u>

1. Flower G: Flax and Breast Cancer: A Systematic Review. Integr Cancer Ther. 2013 8;13(3):181-192.
2. Pruthi S: A phase III, randomized, placebo-controlled, double-blind trial of flaxseed for the treatment of hot flashes:

North Central Cancer Treatment Group N08C7.Menopause 2012: 19:48-53.

Black cohosh (Cimicifuga racemosa) nor St John's Wort nor Ginseng root

1. Leach MJ: Black cohosh (Cimicifuga spp.) for menopausal symptoms. Cochrane Database Syst Rev. 2012; 9:CD007244.
2. Caraci F: Metabolic drug interactions between antidepressants and anticancer drugs: focus on selective serotonin reuptake inhibitors and hypericum extract. Curr Drug Metab. 2011 Jul 1;12(6):570-7.
3. Kim MS: Ginseng for managing menopause symptoms: a systematic review of randomized clinical trials. J Ginseng Res. 2013 Mar;37(1):30-6.
4. Mehrpooya M1, Rabiee S2, Larki-Harchegani A3, Fallahian AM1, Moradi A4, Ataei S1, Javad MT5. A comparative study on the effect of "black cohosh" and "evening primrose oil" on menopausal hot flashes. J Educ Health Promot. 2018 Mar 1;7:36. doi: 10.4103/jehp.jehp_81_17. eCollection 2018.

Sodium selenite, proteolytic plant enzymes (bromelaine and papain), and Lens culinaris lectin

1. Beuth J, van Leendert R, Schneider B et al.: Complementary medicine on side-effects of adjuvant hormone therapy in patients with breast cancer**.** In Vivo. 2013 Nov-Dec;27(6):869-71.


1. Duncan M, Moschopoulou E, Herrington E et al.: Review of systematic reviews of non-pharmacological interventions to improve quality of life in cancer survivors. BMJ Open. 2017 Nov 28;7(11):e015860. doi: 10.1136/bmjopen-2017-015860.

Physical exercise

1. Duijts SF: Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: results of a randomized, controlled, multicenter trial. J Clin Oncol. 2012 Nov 20;30(33):4124-33.
2. Hartman SJ, Nelson SH, Myers E et al.: Randomized controlled trial of increasing physical activity on objectively measured and self-reported cognitive functioning among breast cancer survivors: The memory & motion study. Cancer. 2018 Jan 1;124(1):192-202. doi: 10.1002/cncr.30987. Epub 2017 Sep 19.

Mind Body Medicine

1. Mann E: Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial. Lancet Oncol. 2012 Mar;13(3):309-18.
2. Buffart LM: Physical and psychosocial benefits of yoga in cancer patients and survivors, a systematic review and meta-analysis of randomized controlled trials. BMC Cancer. 2012 Nov 27;12:559.
3. Cramer H: Characteristics of randomized controlled trials of yoga: a bibliometric analysis. BMC Complement Altern Med. 2014 Sep 2;14:328.
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5. Goldstein KM, Shepherd-Banigan M, Coeytaux RR et al.: Use of mindfulness, meditation and relaxation to treat vasomotor symptoms. Climacteric. 2017;20(2):178-82.
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7. Tao WW, Tao XM, Song CL. Effects of non-pharmacological supportive care for hot flushes in breast cancer: a meta-analysis. Support Care Cancer. 2017;25(7):2335-47
8. van Driel CM, Stuursma A, Schroevers MJ et al. Mindfulness, cognitive behavioural and behaviour-based therapy for natural and treatment-induced menopausal symptoms: a systematic review and meta-analysis. BJOG. 2019 Feb;126(3):330-339. doi: 10.1111/1471-0528.15153. Epub 2018 Mar 15.

Cognitive behavioral therapy

1. Mewes JC, Steuten LM, Duijts SF et al.: Cost-effectiveness of cognitive behavioral therapy and physical exercise for alleviating treatment-induced menopausal symptoms in breast cancer patients. J Cancer Surviv. 2015 Mar;9(1):126-35.

doi: 10.1007/s11764-014-0396-9. Epub 2014 Sep 2.

2. Desautels C, Savard J, Ivers H et al.: Treatment of Depressive Symptoms in Patients with Breast Cancer: A Randomized Controlled Trial Comparing Cognitive Therapy and Bright Light Therapy. Health Psychol. 2017 Nov 27. doi: 10.1037/hea0000539. [Epub ahead of print]

Acupuncture

1. Chiu HY1, Shyu YK, Chang PC et al.: Effects of Acupuncture on Menopause-Related Symptoms in Breast Cancer Survivors: A Meta-analysis of Randomized Controlled Trials. Cancer Nurs. 2016 May-Jun;39(3):228-37.
2. Garland SN1, Xie SX, Li Q et al.: Comparative effectiveness of electro-acupuncture versus gabapentin for sleep disturbances in breast cancer survivors with hot flashes: a randomized trial. Menopause. 2017 May;24(5):517-523. doi: 10.1097/GME.0000000000000779.
3. Chen L, Lin CC, Huang TW et al.: Effect of acupuncture on aromatase inhibitor-induced arthralgia in patients with breast cancer: A meta-analysis of randomized controlled trials. Breast. 2017;33:132-8.
4. Chien TJ, Hsu CH, Liu CY et al.: Effect of acupuncture on hot flush and menopause symptoms in breast cancer- A systematic review and meta-analysis. PLoS One. 2017;12(8):e0180918.
5. Hershman DL, Unger JM, Greenlee H et al.: Randomized blinded sham- and waitlist-controlled trial of acupuncture for joint symptoms related to aromatase inhibitors in women with early stage breast cancer (S1200). San Antonio Breast Cancer Conference 2017; Abstract GS4-04.
6. Hershman DL, Unger JM, Greenlee H et al. Effect of Acupuncture vs Sham Acupuncture or Waitlist Control on Joint Pain Related to Aromatase Inhibitors Among Women With Early-Stage Breast Cancer: A Randomized Clinical Trial. JAMA. 2018 Jul 10;320(2):167-176. doi: 10.1001/jama.2018.8907.
7. Wang W, Liu Y, Sun S et al. Electroacupuncture for postmenopausal women with stress urinary incontinence: secondary analysis of a randomized controlled trial. World J Urol. 2018 Oct 13. doi: 10.1007/s00345-018-2521-2. [Epub ahead of print]
8. Befus D, Coeytaux RR, Goldstein KM et al. Management of Menopause Symptoms with Acupuncture: An Umbrella Systematic Review and Meta-Analysis. J Altern Complement Med. 2018 Apr;24(4):314-323. doi:

10.1089/acm.2016.0408. Epub 2018 Jan 3.


Ovarian function protection


1. Gerber B, von Minckwitz G, Stehle H et al.: Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: the GBG 37 ZORO study. J Clin Oncol. 2011 Jun 10;29(17):2334-41.
2. Del Mastro L, Ceppi M, Poggio F et al.: Gonadotropin-releasing hormone analogues for the prevention of chemotherapy-induced premature ovarian failure in cancer women: systematic review and meta-analysis of randomized trials. Cancer Treat Rev. 2014 Jun;40(5):675-83.
3. Del Mastro L, Rossi G, Lambertini M et al.: New insights on the role of luteinizing hormone releasing hormone agonists in premenopausal early breast cancer patients. Cancer Treat Rev. 2016 Jan;42:18-23.
4. Munholz RR, et al: Gonadotropin-Releaseing hormone agonists for ovarian function preservation in premenopausal women undergoing chemotherapy for early stage breast cancer- A systematic Review and Meta Analysis. JAMA Oncol 2016;2:65-73
5. Munster PN, Moore AP, Ismail-Khan R et al.: Randomized Trial Using Gonadotropin-Releasing

Hormone Agonist Triptorelin for the Preservation of Ovarian Function During (Neo)Adjuvant Chemotherapy for Breast Cancer. J Clin Oncol. 2012;30(5):533–8.

6. Lambertini M, Boni L, Michelotti A et al.: Ovarian Suppression With Triptorelin During Adjuvant Breast Cancer Chemotherapy and Long-term Ovarian Function, Pregnancies, and Disease-Free Survival: A Randomized Clinical Trial. JAMA. 2015 Dec 22-29;314(24):2632-40. doi: 10.1001/jama.2015.17291.
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8. Sun X, Dongol S, Jiang J et al.: Protection of ovarian function by GnRH agonists during chemotherapy: a meta-analysis. Int J Oncol. 2014;44(4):1335–40.

Pregnancy rates

1. Lambertini M, Ceppi M, Poggio F et al.: Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies. Ann Oncol 2015; 26(12):2408-19.
2. Moore HCF, Unger JM, Phillips K-A et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Med. 2015;372(10):923–32.
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Fertility preservation counselling

1. Loren AW, Mangu PB, Beck LN et al. Fertility Preservation for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2013;31(19):2500–10.
2. Peccatori FA, Azim Jr HA, Orecchia R et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi160–70.

3. Abe A, Kuwahara A, Iwasa T et al.: A survey on fertility management in young women of reproductive age treated with chemotherapy. Int J Clin Oncol. 2016 Dec;21(6):1183-1190.

Fertility preservation with assisted reproduction therapy

1. Dittrich R, Hackl J, Lotz L et al.: Pregnancies and live births after 20 transplantations of cryopreserved ovarian tissue in a single center. Fertil Steril. 2015 Feb;103(2):462-8.
2. Gamzatova Z, Komlichenko E, Kostareva A et al.: Autotransplantation of cryopreserved ovarian tissue--effective method of fertility preservation in cancer patients. Gynecol Endocrinol. 2014 Oct;30 Suppl 1:43-7.
3. Luke B, Brown MB, Missmer SA et al.: Assisted reproductive technology use and outcomes among women with a history of cancer. Hum Reprod. 2016 Jan;31(1):183-9.
4. Goldrat O, Kroman N, Peccatori FA et al.: Pregnancy following breast cancer using assisted reproduction and its effect on long-term outcome. Eur J Cancer. 2015;51(12):1490–6.
5. Oktay K, Turan V, Bedoschi G et al.: Fertility Preservation Success Subsequent to Concurrent Aromatase Inhibitor Treatment and Ovarian Stimulation in Women With Breast Cancer. J Clin Oncol. 2015;33(22):2424–9.


| | ZORO | PROMISE | Munster et al. - US | POEMS | Option |
|---|---|---|---|---|---|
| **Patient number** | 60 (60 HR-) | 281 (50 HR-) | 49 (13 HR-) of 124 | 218 (218 HR-) | 227 (126 HR-) |
| **Age median** | 38 years | 39 years | 39 years | Premenop. < 50 years | premenopausal |
| **Treatment** | goserelin | triptorelin | triptorelin | goserelin | goserelin |
| **Start of treatment** | >2 weeks prior to cht | >1 week prior to cht | > 1 week prior to cht | > 1 week prior to cht | > 1 week prior to cht |
| **Primary Endpoint** | menstruation at month 6 after chemotherapy | rate of early menopause at month 12 after cht | menstruation rate within 2 years after cht | Ovarian failure at 2 yrs after cht | Amenorrhea with elevated FSH levels between 12 and 24 months |
| **Primary objective** | to detect 30% absolute increase of menstruation rate | to detect at least 20% absolute reduction in early menopause | to detect 20% difference in amenorrhea rate – from 10% to 30% | | To detect 20%-25% absolute reduction in early menopause |
| **Multivar. analysis** | age as only independent predictive factor | treatment as only independent predictive factor | n.d. | Treatment as only Independent predictive factor | Age, total cyclophosphamide dose and baseline AMH |
| **Resumption of menses at month 12** | 83% with LHRH vs. 80% w/o | 93% with LHRHa vs. 74% w/o | 74% with LHRH vs. 68% w/o | 78% with LHRH vs. 75% w/o; at 2 years; 22% with LHRH vs. 8% | 78% with LHRHa vs. 62% amnorrhea rate between month 12 and 24 |
| **Median time to restoration of menses (months)** | 6.1 with LHRHa vs. 6.8 w/o; p=0.30 | not reached with LHRH vs. 6.7 w/o; p=0.07 | 5.8 with LHRH vs. 5.0 w/o; p=0.58 | n.d. | n.d. |
| **Cyclophosph. dose** | 4600 vs. 4700mg | 4080 vs. 4008 mg | n.r. | n.a. | 5940 vs. 5940mg |


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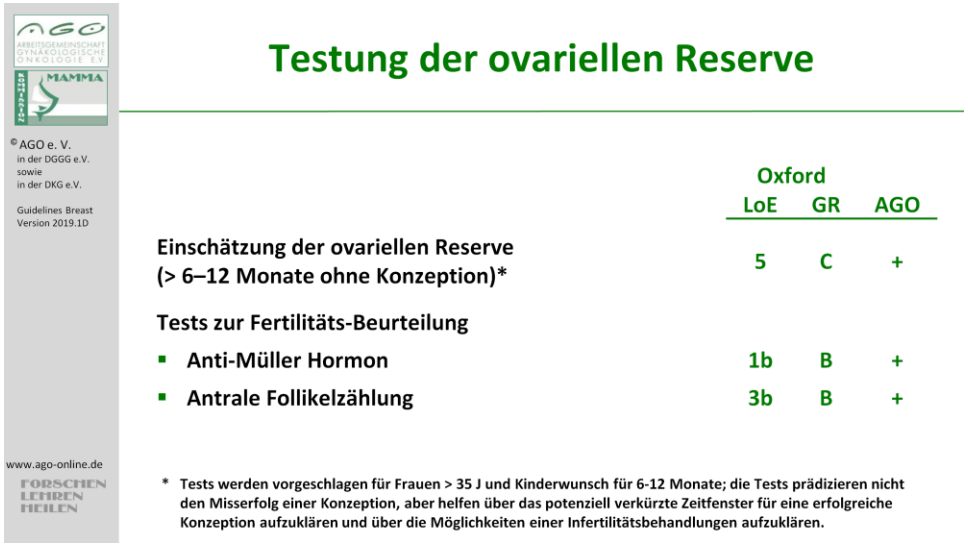



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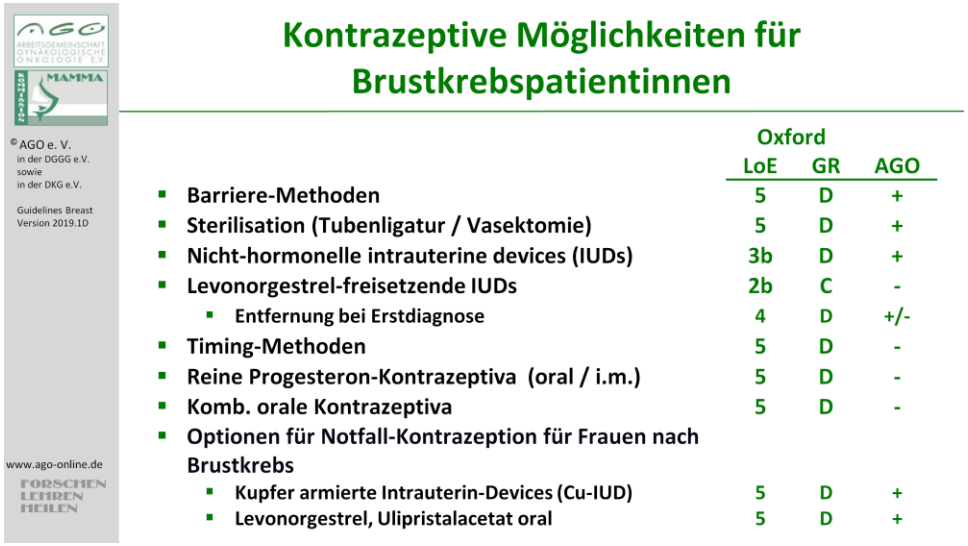



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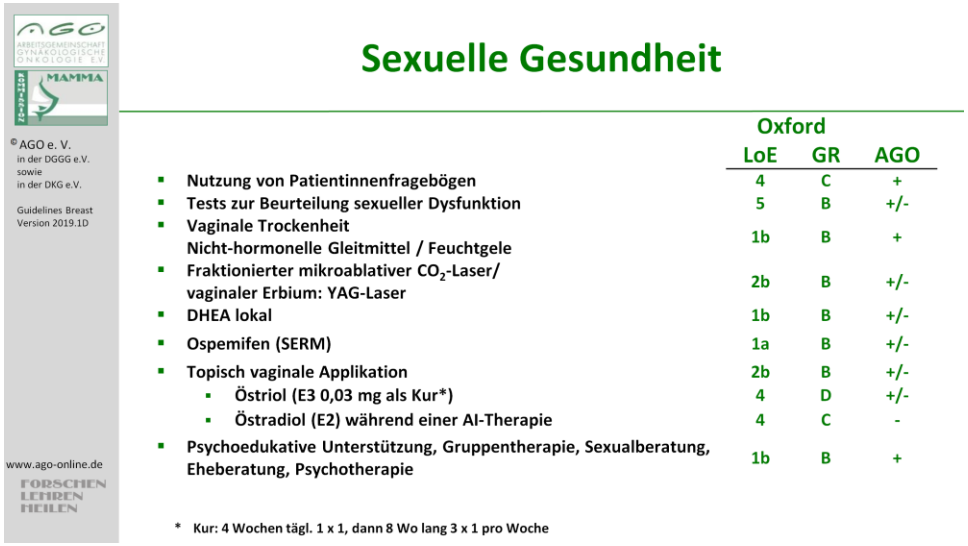


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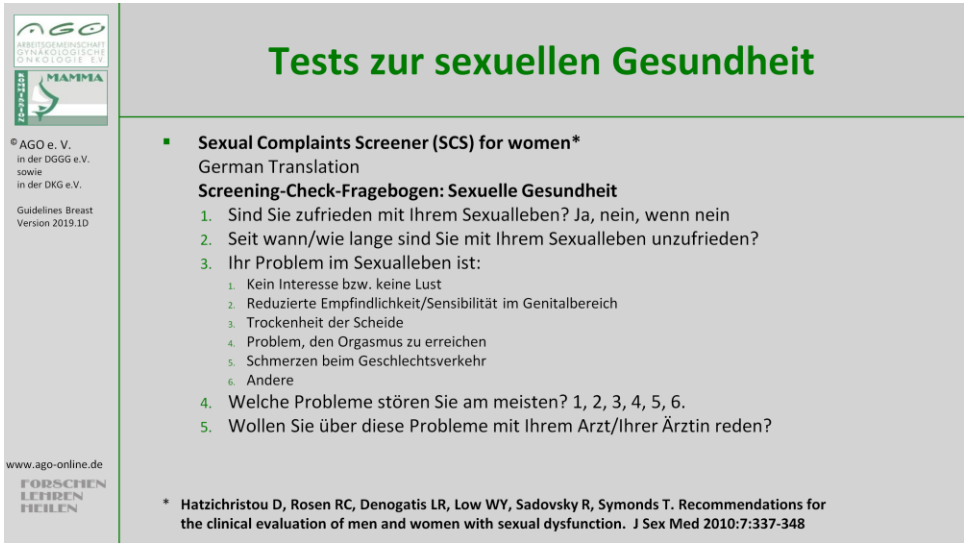


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