Optionen der primären Prävention:
Veränderbare Lifestyle-Faktoren
Prävention

- **Versionen 2011–2022:**
  Dall / Diel / Gerber / Hanf / Maass / Mundhenke / Rhiem / Solbach / Solomayer / Thomssen / von Minckwitz

- **Version 2023:**
  Albert / Thomssen

**Screened data bases**
Pubmed 2012 – 2022, ASCO 2012 – 2022, SABCS 2012 – 2022, Cochrane data base 2022
1. Li C, Fan Z, Lin X, et al. Parity and risk of developing breast cancer according to tumor subtype: A systematic review and meta-analysis. Cancer Epidemiol. 2021 Dec;75:102050. doi: 10.1016/j.canep.2021.102050. Epub 2021 Oct 24

2. Coombes R.C, Tovey, H, Kilburn, L: Effect of Celecoxib vs Placebo as Adjuvant Therapy on Disease-Free Survival Among Patients With Breast Cancer: The REACT Randomized Clinical Trial. JAMA Oncol. 2021 Sep 1;7(9):1291-1301. doi: 10.1001/jamaoncol.2021.2193.

3. Zhou L, Chen B, Sheng L, et al. The effect of vitamin D supplementation on the risk of breast cancer: a trial sequential meta-analysis. Breast Cancer Res Treat. 2020 Jul;182(1):1-8. doi: 10.1007/s10549-020-05669-4. Epub 2020 May 13

4. Wang B, Lu Z, Huang Y et al. Does hypothyroidism increase the risk of breast cancer: evidence from a metaanalysis. . BMC Cancer (2020) 20:733 https://doi.org/10.1186/s12885-020-07230-4

5. Puvanesarajah S, Gapstur SM, Gansler T et al. Epidemiologic risk factors for in situ and invasive ductal breast cancer among regularly screened postmenopausal women by grade in the Cancer Prevention Study-II Nutrition Cohort. Cancer Causes Control. 2020 Jan;31(1):95-103. doi: 10.1007/s10552-019-01253-4.

6. Mukama T, Fallah M, Brenner H et al. Risk of invasive breast cancer in relatives of patients with breast carcinoma in situ: a prospective cohort study. BMC Med. 2020 Nov 5;18(1):295. doi: 10.1186/s12916-020-01772-x.

7. Peila R, Arthur R, Rohan TE et al. Risk factors for ductal carcinoma in situ of the breast in the UK Biobank cohort study. Cancer Epidemiol. 2020 Feb;64:101648. doi: 10.1016/j.canep.2019.101648. Wang B, Lu Z, Huang Y et al. Does hypothyroidism increase the
risk of breast cancer: evidence from a metaanalysis. . BMC Cancer (2020) 20:733 https://doi.org/10.1186/s12885-020-07230-4

8. Yang H, Holowko N, Grassmann F et al. Hyperthyroidism is associated with breast cancer risk and mammographic and genetic risk predictors. BMC Medicine (2020) 18:225 https://doi.org/10.1186/s12916-020-01690-y

9. Powe CE, Tobias DK, Michels KB et al, History of gestational diabetes mellitus and risk of incident invasive breast cancer among parous women in the Nurses' Health Study II prospective cohort. Cancer Epidemiol Biomarkers Prev. 2017 Mar; 26(3): 321–327

10. Ritte R, Tikk K, Lukanova A et al. Reproductive factors and risk of hormone receptor positive and negative breast cancer: a cohort study. BMC Cancer 2013 Dec 9;13:584.

11. Collaborative Group on Hormonal Factors in Breast Cancer: Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol. 2012 Nov;13(11):1141-51.
1. Poorolajal J, Heidarimoghis F, Karami M, et al. Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies. J Res Health Sci. 2021; 21(3): e00520.

2. Wu Y, Huang R, Wang M: Dairy foods, calcium, and risk of breast cancer overall and for subtypes defined by estrogen receptor status: a pooled analysis of 21 cohort studies. Am J Clin Nutr. 2021 Aug 2;114(2):450-461. doi: 10.1093/ajcn/nqab09

3. Hao Y, Jiang M, Miao Y, et al. Effect of long-term weight gain on the risk of breast cancer across women's whole adulthood as well as hormone-changed menopause stages: A systematic review and dose-response meta-analysis. i J. Obes Res Clin Pract. 2021 Sep-Oct;15(5):439-448. doi: 10.1016/j.orcp.2021.08.004. Epub 2021 Aug 26

4. Kazemi A, Barati-Boldaji R, Soltani S, et al. Intake of Various Food Groups and Risk of Breast Cancer: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies. Adv Nutr. 2021 Jun 1;12(3):809-849. doi: 10.1093/advances/nmaa147

5. Parida S, SharmaD. Microbial Alterations and Risk Factors of Breast Cancer: Connections and Mechanistic Insights. Cells 2020, 9, 1091; doi:10.3390/cells9051091

6. Puvanesarajah S, Gapstur SM, Gansler T et al. Epidemiologic risk factors for in situ and invasive ductal breast cancer among regularly screened postmenopausal women by grade in the Cancer Prevention Study-II Nutrition Cohort. Cancer Causes Control. 2020 Jan;31(1):95-103. doi: 10.1007/s10552-019-01253-4.

7. Mukama T, Fallah M, Brenner H et al. Risk of invasive breast cancer in relatives of patients with breast carcinoma in situ: a prospective cohort study. BMC Med. 2020 Nov 5;18(1):295. doi: 10.1186/s12916-020-01772-x.

8. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet. 2019 Sep 28;394(10204):1159-1168. doi:
9. Peila R, Arthur R, Rohan TE et al. Risk factors for ductal carcinoma in situ of the breast in the UK Biobank cohort study. Cancer Epidemiol. 2020 Feb;64:101648. doi: 10.1016/j.canep.2019.101648

10. American Cancer Society 2019 https://www.cancer.org/cancer/breast-cancer/risk-and-prevention.html

11. Rodgers KM, Udesky JO, Rudel RA et al. Environmental chemicals and breast cancer: An updated review of epidemiological literature informed by biological mechanisms. Environ Res. 2018 Jan;160:152-182. doi: 10.1016/j.envres.2017.08.045. Epub 2017 Oct 6.

12. Masala G, Bendinelli B, Assedi M et al. Up to one-third of breast cancer cases in post-menopausal Mediterranean women might be avoided by modifying lifestyle habits: the EPIC Italy study. Breast Cancer Res Treat. 2017 Jan;161(2):311-320.

13. Nunez C, Bauman A, Egger S3 et al. Obesity, physical activity and cancer risks: Results from the Cancer, Lifestyle and Evaluation of Risk Study (CLEAR); Cancer Epidemiol 2017: 47: 56-63.

14. Gray JM, Rasanayagam S, Engel C et al. State of the evidence 2017: an update on the connection between breast cancer and the environment. Environ Health. 2017 Sep 2;16(1):94. doi: 10.1186/s12940-017-0287-4.

15. James P, Bertrand KA, Hart JE et al. State of the evidence 2017: an update on the connection between breast cancer and the environment. Environ Health. 2017 Sep 2;16(1):94. doi: 10.1186/s12940-017-0287-4.

16. Nechuta S, Chen WY, Cai H et al. A pooled analysis of post-diagnosis lifestyle factors in association with late estrogen-receptor-positive breast cancer prognosis. Int J Cancer. 2016 May 1;138(9):2088-97.

17. Lin X, Chen W, Wie F et al. Night-shift work increases morbidity of breast cancer and all-cause mortality: a meta-analysis of 16 prospective cohort studies. Sleep Med. 2015 Nov;16(11):1381-1387. doi: 10.1016/j.sleep.2015.02.543. Epub 2015 May 11.

18. Van Germert, Lanting CI, Goldbohm RA et al. The proportion of postmenopausal breast cancer cases in the Netherlands attributable to lifestyle-related risk factors. Breast Cancer Res Treat. 2015 Jul;152(1):155-162.

19. Bao PP, Zhao GM, Shu XO et al. Modifiable Lifestyle Factors and Triple-negative Breast Cancer Survival: A Population-based Prospective Study. Epidemiology. 2015 Nov;26(6):909-16.

20. Willhite CC, Karyakina NA, Yokel RA et al. Systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminium, aluminium oxides, aluminium hydroxide and its soluble salts. Crit Rev Toxicol. 2014;44 Suppl 4:1-80.

21. Gaudet MM, Gapstur SM, Sun J et al. Active smoking and breast cancer risk: original cohort data and meta-analysis. J Natl Cancer Inst. 2013 Apr 17;105(8):515-25.
Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies

1. Poorolajal J, Heidarimoghis F, Karami M et al. Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies. J Res Health Sci. 2021 Jul 20;21(3):e00520.

2. Tamimi RM, Spiegelman D, Smith-Warner SA et al.: Population Attributable Risk of Modifiable and Nonmodifiable Breast Cancer Risk Factors in Postmenopausal Breast Cancer. Am J Epidemiol. 2016 Dec 15;184(12):884-893. Epub 2016 Dec 6.

Tamimi et al, 2016
USA: more than a third of postmenopausal breast cancers are preventable through changes in modifiable risk factors
Einfluss durch Reproduktionsfaktoren

| Präventiv                                                                 | Oxford |
|---------------------------------------------------------------------------|--------|
| Hohe Zahl voll ausgetragener Schwangerschaften                           | 2b     |
| Hohe Anzahl der Schwangerschaften                                         | 2b     |
| Erste ausgetragene Schwangerschaft ≤ 30 Jahre                             | 2b     |
| Stillen (schützt, wenn Gesamtstilldauer 1,5–2 Jahre)                       | 3a     |
| Geringeres Geburtsgewicht des Erstgeborenen (3000–3500 g vs. > 4500 g, RR = 1,53) | 2b     |
| Geringere Schwangerschaftsdauer Erstgeborene (26–31. SSW vs. 40–41. SSW; RR = 2,38, p = 0,03) | 2b     |

Ungünstiger Einfluss möglich

| PCO-Syndrom (Syndrom der Polyzystischen Ovarien)                          | 2b     |

Kein Einfluss

| Assistierte Reproduktion                                                  | 2b     |
| Schwangerschaftsabbruch                                                  | 2b     |

Hohe Zahl voll ausgetragener Schwangerschaften, hohe Anzahl der Schwangerschaften, erste ausgetragene Schwangerschaft ≤ 30 Jahre
1. Li C, Fan Z, Lin X, et al. Parity and risk of developing breast cancer according to tumor subtype: A systematic review and meta-analysis. Cancer Epidemiol. 2021 Dec;75:102050.

Stillen (schützt, wenn Gesamtstilldauer 1,5–2 Jahre)
1. Stordal B. Breastfeeding reduces the risk of breast cancer: A call for action in high-income countries with low rates of breastfeeding. Cancer Med. 2022 Sep 26. doi: 10.1002/cam4.5288. Epub ahead of print. PMID: 36164270.
2. Qiu R, Zhong Y, Hu M et al. Breastfeeding and Reduced Risk of Breast Cancer: A Systematic Review and Meta-Analysis. Comput Math Methods Med. 2022 Jan 28;2022:8500910.
3. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding; collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet. 2002 Jul 20;360(9328):187-95.

Geringeres Geburtsgewicht des Erstgeborenen (3000–3500 g vs. > 4500 g, RR = 1,53), geringere Schwangerschaftsdauer
1. Swerdlow AJ, Wright LB, Schoemaker MJ et al. Maternal breast cancer risk in relation to birthweight and gestation of her offspring.
Syndrom der Polyzystischen Ovarien (PCO-Syndrom)

1. Li Z, Wang YH, Wang L et al. Polycystic ovary syndrome and the risk of endometrial, ovarian and breast cancer: An updated meta-analysis. Scott Med J. 2022 Aug;67(3):109-120.
2. Ding DC, Chen W, Wang JH et al. Association between polycystic ovarian syndrome and endometrial, ovarian, and breast cancer: A population-based cohort study in Taiwan. Medicine (Baltimore). 2018 Sep;97(39):e12608.
3. Wu PF, Li RZ, Zhang W, Hu HY, Wang W, Lin Y. Polycystic ovary syndrome is causally associated with estrogen receptor-positive instead of estrogen receptor-negative breast cancer: a Mendelian randomization study. Am J Obstet Gynecol. 2020 Oct;223(4):583-585.

Assistierte Reproduktion

1. Al-Ajmi K, Lophatananon A, Ollier W et al. Risk of breast cancer in the UK biobank female cohort and its relationship to anthropometric and reproductive factors. PLoS One. 2018 Jul 26;13(7):e0201097.
2. Del Pup L, Peccatori FA, Levi-Setti PE et al. Risk of cancer after assisted reproduction: a review of the available evidences and guidance to fertility counselors. Eur Rev Med Pharmacol Sci. 2018 Nov;22(22):8042-8059.

Schwangerschaftsabbruch

1. Huang Y, Zhang X, Li W, et al.: A meta-analysis of the association between induced abortion and breast cancer risk among Chinese females. Cancer Causes Control 25 (2): 227-36, 2014.
2. Guo J, Huang Y, Yang L, et al.: Association between abortion and breast cancer: an updated systematic review and meta-analysis based on prospective studies. Cancer Causes Control 26 (6): 811-9, 2015.
Impact of breastfeeding on breast cancer risk

- Breastfeeding reduces the risk of breast cancer by 4.3% for every 12 months of breastfeeding, which is in addition to the 7.0% decrease in risk observed for each birth.
- Breastfeeding has been shown to primarily reduce the risk of Triple-Negative Breast Cancer (20%) as well as in carriers of BRCA1 mutations (22–50%).
- An estimated 4.7% of breast cancer cases in the UK are caused by not breastfeeding.

From: Stordal B. Cancer Med. 2022 Sep 26.

Breastfeeding is protective
1. Stordal B. Breastfeeding reduces the risk of breast cancer: A call for action in high-income countries with low rates of breastfeeding. Cancer Med. 2022 Sep 26.
2. Qiu R, Zhong Y, Hu M et al. Breastfeeding and Reduced Risk of Breast Cancer: A Systematic Review and Meta-Analysis. Comput Math Methods Med. 2022 Jan 28;2022:8500910.
3. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet. 2002 Jul 20;360(9328):187-95.
ASS
1. Cao Y, Tan A. Aspirin might reduce the incidence of breast cancer: An updated meta-analysis of 38 observational studies. Medicine 2020;99:38(e21917).
2. Kehm RD et al. Regular use of aspirin and other non-steroidal anti-inflammatory drugs and breast cancer risk for women at familial or Genetic risk: a cohort study, Breast Cancer Res. 2019 Apr. 18;21(1):52

Cox2
1. Coombes,R.C., Tovey, H, Kilburn, L: Effect of Celecoxib vs Placebo as Adjuvant Therapy on Disease-Free Survival Among Patients With Breast Cancer: The REACT Randomized Clinical Trial. JAMA Oncol. 2021 Sep 1;7(9):1291-1301. doi: 10.1001/jamaoncol.2021.2193.
2. Soley Bayraktar , Sema Baghaki , Jimin Wu.: Biomarker: Modulation Study of Celecoxib for Chemoprevention in Women at Increased Risk for Breast Cancer: A Phase II Pilot Study Cancer Prev Res (Phila). 2020 Sep;13(9):795-802.

Bisphosphonate
1. Peng R, Liang X, Zhang G et al. Association Use of Bisphosphonates with Risk of Breast Cancer: A Meta-Analysis. BioMed Research
Vitamin D
1. Fernandez-Lazaro, CI, Romanos-Nanclares, A, Sánchez-Bayona, R.: Dietary calcium, vitamin D, and breast cancer risk in women: findings from the SUN cohort. Eur J Nutr 2021 Oct;60(7):3783-3797. doi: 10.1007/s00394-021-02549-5. Epub 2021
2. Zhou L, Chen B, Sheng L, Turner A.: The effect of vitamin D supplementation on the risk of breast cancer: a trial sequential meta-analysis. Breast Cancer Res Treat. 2020 Jul;182(1):1-8. doi: 10.1007/s10549-020-05669-4. Epub 2020 May 13
3. Song D, Deng Y, Liu K et al. Vitamin D intake, blood vitamin D levels, and the risk of breast cancer: a dose-response meta-analysis of observational studies. Aging-us.com 2019: 11; 24: 12708 -12732

Statine
1. Zhao G, Ji Y, Ye Q, et al. Effect of statins use on risk and prognosis of breast cancer: a meta-analysis. Anticancer Drug 2022;33 (1): e507-e518
Kehm RD et al. Regular use of aspirin and other non-steroidal anti-inflammatory drugs and breast cancer risk for women at familial or genetic risk: a cohort study. Breast Cancer Res. 2019 Apr. 18;21(1):52

Prospective multinational cohort study, n = 5606, healthy women questionnaire, regular intake of ASS, NSAID, COX2-inhibitors

Regular ASS-intake: HR 0.61, CI 0.33-1.14, breast cancer incidence
Regular COX2-inhibitors: HR 0.39, CI 0.15-0.97, breast cancer incidence other NSAIDs: n. s.
[independent of BRCA-status]
Prävention durch Änderung von Lifestyle-Faktoren: Gewicht / Glucosestoffwechsel

| Oxford | LoE | GR | AGO |
|--------|-----|----|-----|
| Einhaltung Normalgewicht (BMI 18,5-25 kg/m²)* | 2a | B | ++ |
| Prämenopausal | 3a | B | +/- |
| Postmenopausal | 2a | B | ++ |
| Vermeidung bzw. Früherkennung und Einstellung eines Typ II Diabetes mellitus (Reduktion der Brustkrebsinzidenz und -mortalität) | 2b | B | ++ |

* die Menge an Körperfett kann auch bei normalem BMI erhöht sein und korreliert mit dem Brustkrebsrisiko

Einhaltung Normalgewicht
1. Poorolajal J, Heidarimoghis F, Karami M, et al. Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies. J Res Health Sci. 2021; 21(3): e00520
2. Byun D, Hong SE, Ryu S, et al. Early-life body mass index and risks of breast, endometrial, and ovarian cancers: a dose–response meta-analysis of prospective studies British Journal of Cancer (2022) 126:664–672
3. Tao W, Santoni G, von Euler-Chelpin M et al. Cancer Risk After Bariatric Surgery in a Cohort Study from the Five Nordic Countries. Obes Surg. 2020; 30(10): 3761–3767. Published online 2020 Jun 13. doi: 10.1007/s11695-020-04751-6
4. Ishihara BP, Farah D, Fonseca MCM, et al. The risk of developing breast, ovarian, and endometrial cancer in obese women submitted to bariatric surgery: a meta-analysis. Surg Obes Relat Dis. 2020 Oct;16(10):1596-1602.
5. Iyengar NM et al.: Association of Body Fat and Risk of Breast Cancer in Postmenopausal Women with Normal Body Mass Index: A Secondary Analysis of a Randomized Clinical Trial and Observational Study. JAMA Oncol. 2019 Feb 1;5(2):155-163

Typ II Diabetes
Vermeidung, Früherkennung und Einstellung
1. Soltani S, Abdollahi S, Aune D, et al. Body mass index and cancer risk in patients with type 2 diabetes: a dose-response meta-analysis of cohort studies. Sci Rep. 2021 Jan 28;11(1):2479. doi: 10.1038/s41598-021-81671-0
2. Ling S, Brown K, Miksza JK, et al. Risk of cancer incidence and mortality associated with diabetes: A systematic review with trend analysis of 203 cohorts. Nutr Metab Cardiovasc Dis. 2021 Jan 4;31(1):14-22. doi: 10.1016/j.numecd.2020.09.023. Epub 2020 Sep 25
Meta-analysis, of a total of 150,537 patients in the bariatric surgery arm and 1,461,938 women in the control arm.

- The risk of breast cancer was reduced by 49 % [RR: 0.39 (95% CI [0.31 to 0.56]); I² = 90%; 7 studies].
- The risk of ovarian cancer was reduced by 53 % [RR: 0.47 (95% CI [0.27 to 0.81]); I² = 0%; 3 studies].
- The risk of endometrial cancer was reduced by 67 % [RR: 0.33 (95% CI [0.21 to 0.51]); I² = 88%; 7 studies].

Ishihara BP, Farah D, Fonseca MCM, et al. The risk of developing breast, ovarian, and endometrial cancer in obese women submitted to bariatric surgery: a meta-analysis. Surg Obes Relat Dis. 2020 Oct;16(10):1596-1602. doi: 10.1016/j.soard.2020.06.008. Epub 2020 Jun 14. PMID: 32690459.
WHI substudy

Among the 3460 women included in the analysis (mean [SD] age, 63.6 [7.6] years), multivariable-adjusted hazard ratios for the risk of invasive breast cancer were 1.89 (95% CI, 1.21-2.95) for the highest quartile of whole-body fat and 1.88 (95% CI, 1.18-2.98) for the highest quartile of trunk fat mass.

The corresponding adjusted hazard ratios for ER-positive breast cancer were 2.21 (95% CI, 1.23-3.67) and 1.98 (95% CI, 1.18-3.31), respectively.
Bevorzugung einer ausgewogenen Ernährung

1. Kazemi A, Barati-Boldaji R, Soltani S, et al. Intake of Various Food Groups and Risk of Breast Cancer: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies. Adv Nutr. 2021 Jun 1;12(3):809-849
2. Llaha F, Gil-Lespinard M, Unal P, et al. Consumption of Sweet Beverages and Cancer Risk. A Systematic Review and Meta-Analysis of Observational Studies. Nutrients. 2021 Feb 4;13(2):516.
3. Wu Y, Huang R, Wang M, Bernstein L: Dairy foods, calcium, and risk of breast cancer overall and for subtypes defined by estrogen receptor status: a pooled analysis of 21 cohort studies. Am J Clin Nutr. 2021 Feb 4;13(2):516.
4. Petimar J, Park Y-M, Smith-Warner SA et al. Dietary index scores and invasive breast cancer risk among women with a family history of breast cancer. Am J Clin Nutr 2019;109:1393–1401
5. Parida S, SharmaD. Microbial Alterations and Risk Factors of Breast Cancer: Connections and Mechanistic Insights. Cells 2020, 9, 1091; doi:10.3390/cells9051091

Mediterrane Kost

1. Schwinghacker L, Schwedhelm C, Galbete C et al. Adherence to Mediterranean Diet and Risk of Cancer: An Updated Systematic Review and Meta-Analysis. Nutrients. 2017 Sep 26;9(10). pii: E1063. doi: 10.3390/nu9101063.
2. Toledo, E.; Salas-Salvado, J.; Donat-Vargas, C. et al. Mediterranean diet and invasive breast cancer risk among women at high cardiovascular risk in the PREDIMED trial: A randomized clinical trial. JAMA Intern. Med. 2015, 175, 1752–1760.
3. Muscogiuri G, Verde L, Sulu C, Katsiki N, Hassapidou M, Frias-Toral E, Cucalón G, Pazderska A, Yumuk VD, Colao A, Barrea L.
Mediterranean Diet and Obesity-related Disorders: What is the Evidence? Curr Obes Rep. 2022 Dec;11(4):287-304.

**Olivenöl**
1. Markellos C, Ourailidou M-E, Gavriatopoulou M, et al. Olive oil intake and cancer risk: A systematic review and meta-analysis. PLoS ONE 2022; 17(1): e0261649.
2. Sealy N, Hanking SE, Houghton SC. Olive oil and risk of breast cancer: a systematic review and dose-respond meta-analysis of observational studies. Brit J Nutrition 2021;125:1148-1156
3. Guasch-Ferré M, Li Y, Willett WC, Sun Q, Sampson L, Salas-Salvadó J, Martínez-González MA, Stampfer MJ, Hu FB. Consumption of Olive Oil and Risk of Total and Cause-Specific Mortality Among U.S. Adults. J Am Coll Cardiol. 2022 Jan 18;79(2):101-112.

**Fettreduzierte Nahrung**
1. Buja A, Pierbon M, Lago L et al. Breast Cancer Primary Prevention and Diet: An Umbrella Review. Int J Environ Res Public Health. 2020 Jul 1;17(13):4731. doi: 10.3390/ijerph17134731. PMID: 32630215; MCID: PMC7369836

**Weniger rotes Fleisch**
1. Poorolajal J, Heidarimoghis F, Karami M, et al. Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies. J Res Health Sci. 2021; 21(3): e00520.

**Nüsse**
1. van den Brandt PA, Nieuwenhuis L. Tree nut, peanut, and peanut butter intake and risk of postmenopausal breast cancer: The Netherlands Cohort Study. Cancer Causes Control. 2018 Jan;29(1):63-75.

**Ballaststoffreiche Ernährung**
1. Key TJ, Angela B, Bradbury KE et al. Foods, macronutrients and breast cancer risk in postmenopausal women: a large UK cohort. Chiropr Med. 2018 Jun; 17(2): 90–96. Published online 2018 Jun 14. doi: 10.1016/j.jcm.2017.12.001
2. Marc P. McRae. The Benefits of Dietary Fiber Intake on Reducing the Risk of Cancer: An Umbrella Review of Meta-analyses. Nutr J. 2018 Sep 21;17(1):87. doi: 10.1186/s12937-018-0394-2.
3. Xiao Y, Ke Y, Wu S et al. Association between whole grain intake and breast cancer risk: a systematic review and meta-analysis of observational studies. Asian Pac J Cancer Prev. 2017 Sep 27;18(9):2309-2328.

**Vitamin D**

1. Song D, Deng Y, Liu K et al. Vitamin D intake, blood vitamin D levels, and the risk of breast cancer: a dose-response meta-analysis of observational studies. Aging-us.com 2019: 11; 24: 12708 -12732
2. Jiang X, Dimou NL, Al-Dabhani K et al. Circulating vitamin D concentrations and risk of breast and prostate cancer: a Mendelian randomization study. N Engl J Med. 2019 Jan 3;380(1):33-44.
3. Manson JE, Cook NR, Lee IM et al; VITAL Research Group. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. Int J Epidemiol. 2018 Nov 8. doi: 10.1093/ije/dyy238. [Epub ahead of print]

**Gemüse / Obst**

1. Farvid MS, Barnett JB, Spence ND. Fruit and vegetable consumption and incident breast cancer: a systematic review and meta-analysis of prospective studies. British Journal of Cancer (2021) 125:284–298;
2. Darooghegi Mofrad M, Mozaffari H, et al. Potato Consumption and Risk of Site-Specific Cancers in Adults: A Systematic Review and Dose-Response Meta-Analysis of Observational Studies. Adv Nutr. 2021 Oct 1;12(5):1705-1722.

**Phytoöstrogene/Soja**

1. Boutas I, Kontogeorgi A, Dimitrakakis C, et al. Soy Isoflavones and breast cancer risk: A meta-analysis. In vivo 2022;36:556-562
2. Finkeldey,L.;Schmitz,E.; Ellinger, S. Effect of the Intake of Isoflavones on Risk Factors of Breast Cancer—A Systematic Review of Randomized Controlled Intervention Studies. Nutrients 2021, 13, 2309.
3. Sak K. Epidemiological Evidences on Dietary Flavonoids and Breast Cancer Risk: A Narrative Review. Asian Pac J Cancer Prev. 2017 Sep 27;18(9):2309-2328.

**Vegetarisch / Vegan**

1. Watling CZ, Schmidt JA, Dunneram Y, et al. Risk of cancer in regular and low meat-eaters, fish-eaters, and vegetarians: a prospective analysis of UK Biobank Participants. BMC Medicine 2022,20 73-8
2. Chang-Claude J, Herman S, Eiber U, et al. Lifestyle Determinants and Mortality in German Vegetarians and Health-Conscious Persons: Results of a 21-Year Follow-up. Epidemiol Biomarker Prev 2005; 14(4)963-8

**Kaffee**
1. Wang S, Li X, Yang Y, et al. Does Coffee, tea and caffein consumption reduce the risk of incident breast cancer risk? A systemativ review and meta-analysis. Public Health Nutrition 2021;24(8): 6377-6389
2. Li Y, Ma L. The association between coffee intake and breast cancer risk: a meta-analysis and dose-response analysis using recent evidence. Ann Palliat Med 2021;10(4):3804-3816.
3. Gapstur SM, Gaudet MM, Wang Y et al. Coffee Consumption and Invasive Breast Cancer Incidence among Postmenopausal Women in the Cancer Prevention Study-II Nutrition Cohort. Cancer Epidemiol Biomarkers Prev. 2020 Nov;29(11):2383-2386. doi: 10.1158/1055-9965.EPI-20-1051. Epub 2020 Aug 14. PMID: 32817071.
4. Poole R, Kennedy OJ, Roderick P et al. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. BMJ 2017 Nov 22;359:j5024. doi: 10.1136/bmj.j5024.
5. Grosso G, Godos J, Galvano F et al. Coffee, Caffeine, and Health Outcomes: An Umbrella Review. Annu Rev Nutr. 2017 Aug 21;37:131-156. doi: 10.1146/annurev-nutr-071816-064941.
6. Li XJ, Ren ZJ, Qin JW, et al. Coffee consumption and risk of breast cancer: an up-to-date meta-analysis. PLoS One2013;8:e52681 doi:10.1371/journal.pone.0052681

**Vitamine, Mineralien, Spurenelemente**
1. Cadeau C, Farvid MS, Rosner BA, et al. Dietary and Supplemental Vitamin C Intake and Risk of Breast Cancer: Results from the Nurses’ Health Studies. J Nutr 2022;152:835–843.
2. Fernandez-Lazaro C.I., Martínez-González, M.Á.; Aguilera-Buenosvinos, I.; Gea, A.; Ruiz-Canela, M.; Romanos-Nanclares, A.; Toledo, E. Dietary Antioxidant Vitamins and Minerals and Breast Cancer Risk: Prospective Results from the SUN Cohort. Antioxidants 2021, 10, 340.
Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease

Manson JE, Cook NR, Lee IM, et al. VITAL Research Group. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. N Engl J Med. 2019 Jan 3;380(1):33-44. doi: 10.1056/NEJMoA1809944. Epub 2018 Nov 10.

Randomized, placebo-controlled trial, with a two-by-two factorial design, of vitamin D₃ (cholecalciferol) at a dose of 2000 IU per day and marine n-3 (also called omega-3) fatty acids at a dose of 1 g per day

Primary end points were invasive cancer of any type and major cardiovascular events

25,871 participants

median follow-up of 5.3 years

124 breast cancers (Vit D group) vs. 122 (placebo group) Hazard Ratio: 1.02
Olive oil consumption and breast cancer risk

1. Amount of olive oil consumption correlates to breast cancer risk (not significant)
2. The source/quality of the olive oil (mediterranean vs others) seems to be relevant (or the origin of the data)
3. It is difficult to separate between use of olive oil and general adherence to a mediterranean diet.

Sealy N et al. British Journal of Nutrition (2021), 125, 1148–1156.
1. Poorolajal J, Heidarimoghis F, Karami M et al. Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies. J Res Health Sci. 2021 Jul 20;21(3):e00520.
2. Rainey L, Eriksson M, Trinh T et al. The impact of alcohol consumption and physical activity on breast cancer: The role of breast cancer risk. Int. J. Cancer: 147, 931–939 (2020).
3. Zhang YB, Pan XF, Chen J, et al. Combined lifestyle factors, incident cancer, and cancer mortality: a systematic review and meta-analysis of prospective cohort studies. Br J Cancer. 2020 Mar;122(7):1085-1093.
4. Sun Q, Xie W, Wang Y, et al. Alcohol Consumption by Beverage Type and Risk of Breast Cancer: A Dose-Response Meta-Analysis of Prospective Cohort Studies. Alcohol Alcohol. 2020 Apr 16;55(3):246-253.
5. Key TJ, Angela B, Bradbury KE et al. Foods, macronutrients and breast cancer risk in postmenopausal women: a large UK cohort. Int J Epidemiol. 2018 Nov 8.
6. Theodoratou, E.; Timofeeva, M.; Li, X.; et al. Nature, Nurture, and Cancer Risks: Genetic and Nutritional Contributions to Cancer. Annu. Rev. Nutr. 2017, 37, 293–320.
No association was classified as convincing (class I). The association between alcohol intake and ER+ breast cancer was classified as highly suggestive (class II) based on a meta-analysis of 20 prospective studies (≥ 30 g/d of alcohol consumption versus non-drinkers).

RR (95% CI): 1.35 (1.23, 1.48), p-value = 5.2 x 10^{-10}, I^2 = 26%, P_{small effect bias} = 0.184, P_{excess significance bias} = 4 x 10^{-8}
Prävention durch Änderung von Lifestyle-Faktoren: Rauchen

- Frauen, die nie geraucht haben, haben ein verringertes Lebenszeitrisko für einen Brustkrebs (~ 15-24 % Reduktion)
- Junge Frauen haben ein 60 % höheres Risiko für ein Mammakarzinom, wenn sie > 10 Jahre vor der Geburt des ersten Kindes geraucht haben (vs. Nichtraucherinnen)

1. Poorolajal J, Heidarimoghis F, Karami M, et al. Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies. J Res Health Sci. 2021 Jul 20;21(3):e00520. doi: 10.34172/jrhs.2021.57
2. Zhang YB, Pan XF, Chen J, et al. Combined lifestyle factors, incident cancer, and cancer mortality: a systematic review and meta-analysis of prospective cohort studies. Br J Cancer. 2020 Mar;122(7):1085-1093. doi: 10.1038/s41416-020-0741-x. Epub 2020 Feb 10
3. Jones ME, Schoemaker MJ, Wright LB, et al. Smoking and risk of breast cancer in the Generations Study cohort. Breast Cancer Res. 2017 Nov 22;19(1):118. doi: 10.1186/s13058-017-0908-4.
4. Macacu A, Autier P, Boniol M, et al. Active and passive smoking and risk of breast cancer: a meta-analysis. Breast Cancer Res Treat. 2015 Nov;154(2):213-24. doi: 10.1007/s10549-015-3628-4. Epub 2015 Nov 6.
Jones ME, Schoemaker MJ, Wright LB et al. Smoking and risk of breast cancer in the Generations Study cohort. Breast Cancer Res. 2017 Nov 22;19(1):118. doi: 10.1186/s13058-017-0908-4.

102,927 women recruited 2003–2013

average of 7.7 years of follow-up

The HR (reference group was never smokers) was
1.14 (95% CI 1.03–1.25; \( P = 0.010 \)) for ever smokers,
1.24 (95% CI 1.08–1.43; \( P = 0.002 \)) for starting smoking at ages < 17 years
1.23 (1.07–1.41; \( P = 0.004 \)) for starting smoking 1–4 years after menarche

Women with a family history of breast cancer (ever vs. never smokers HR 1.35; 95% CI 1.12–1.62; \( P = 0.002 \)) had a significantly larger HR ... than women without (ever smoker vs. never smoker HR 1.07; 95% CI 0.96–1.20; \( P = 0.22 \)).
Körperliche Aktivität

1. Poorolajal J, Heidarimoghis F, Karami M, et al. Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies. J Res Health Sci. 2021 Jul 20;21(3):e00520.
2. Orange ST, Hicks KM, Saxton JM.: Effectiveness of diet and physical activity interventions amongst adults attending colorectal and breast cancer screening: a systematic review and meta-analysis. Cancer Causes Control. 2021 Jan;32(1):13-26.
3. Kerr J, Anderson C, Lippman SM. Physical activity, sedentary behavior, diet and cancer: an update and emerging new evidence. Lancet Oncol. 2017 Aug;18(8):e457-e471.
4. Boyne DJ, O'Sullivan DE, Olij BF et al. Physical Activity, Global DNA Methylation, and Breast Cancer Risk: A Systematic Literature Review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2018 Nov;27(11):1320-1331.
5. Neilson HK, Farris MS, Stone CR et al. Moderate-vigorous recreational physical activity and breast cancer risk, stratified by menopause status: a systematic review and meta-analysis. Menopause. 2017 Mar;24(3):322-344.

Körperliche Aktivität im Intervall zwischen Menarche und erster Schwangerschaft

1. Lin D, Liu Y, Tobias DK, Sturgeon K. Physical activity from menarche-to-first pregnancy and risk of breast cancer: the California teachers study. Cancer Causes Control. 2022 Nov;33(11):1343-1353. doi: 10.1007/s10552-022-01617-3. Epub 2022 Aug 20. PMID: 35987978.
Diese Effekte gelten auch für BRCA1/2-Mutationsträgerinnen und für Frauen mit erhöhtem familiärem Risiko.
Kehm RD et al.: Recreational Physical Activity is Associated with Reduced Breast Cancer Risk in Adult Women at High Risk for Breast Cancer: A Cohort Study of Women Selected for Familial and Genetic Risk

Cancer Res. 2020 Jan 1;80(1):116-125. doi: 10.1158/0008-5472.CAN-19-1847. Epub 2019 Oct 2.

- Prospective cohort study
- N = 15550, women with fam. history of breast cancer
- Multiplicative interactions of physical activity with predicted absolute breast cancer familial risk based on pedigree data and with BRCA1 and BRCA2 mutation status
- Higher physical activity → 20% reduction of breast cancer incidence
- (HR 0.80, CI 0.68-0.93), independent of BRCA-status or pedigree risk
Prävention durch Lifestyle-Faktoren: Hormontherapie in der Postmenopause

1. Poorolajal J, Heidarimoghis F, Karami M: Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies. J Res Health Sci. 2021 Jul 20;21(3):e00520. doi: 10.34172/jrhs.2021.57.
2. Saeaib N, Peeyananjarassri K, Liabsuetrakul T, et al. Hormone replacement therapy after surgery for epithelial ovarian cancer. Cochrane Database Syst Rev. 2020 Jan 28;1(1):CD012559. doi: 10.1002/14651858.CD012559.pub2
3. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet. 2019 Sep 28;394(10204):1159-1168. doi: 10.1016/S0140-6736(19)31709-X. Epub 2019 Aug 29.
4. Chlebowski RT, Aragaki AK, Anderson GL. Menopausal Hormone Therapy Influence on Breast Cancer Outcomes in the Women's Health Initiative. J Natl Compr Canc Netw. 2015 Jul;13(7):917-24.
5. Salagame U, Banks E, Sitas F et al. Menopausal hormone therapy use and breast cancer risk in Australia: Findings from the New South Wales Cancer, Lifestyle and Evaluation of Risk study. Int J Cancer. 2016 Apr 15;138(8):1905-14.
6. Manson JE, Aragaki AK, Rosssouw JE et al. Menopausal hormone therapy and long-term all-cause and cause-specific mortality, the women’s health initiative randomized trials. JAMA 2017; 318: 927-938.
Epigenome-Wide Association Study for Lifetime Estrogen Exposure Identifies an Epigenetic Signature Associated with Breast Cancer Risk

Johansson A et al.: Clin Epigenetics. 2019 Apr 30;11(1):66.

Epidemiological data from EPIC-Italy (n = 31,864)
Study: ELEE (estimated lifetime estrogen exposure)

Method: epigenome-wide association study, blood DNA samples, N = 216, and 440 healthy controls

Results: an estimated 5% increase in breast cancer risk per 1-year longer ELEE (OR = 1.05, 95% CI 1.04-1.07, P = 3 x 10^{-12}) in EPIC-Italy. 694 CpG sites were associated with ELEE (FDR Q < 0.05)
### Prevention of Hormones in Postmenopausal Patients

| Study | N | MC-RR (95% CI) | Further information |
|-------|---|----------------|---------------------|
| WHI   | ~27,000 | 1.3 (1.0-1.6) | 1.3 [1.1-1.4] coronary events  
1.4 [1.1-1.8] strokes  
2.1 [1.5-2.9] pulmonary embolism  
2.1 [1.5-2.9] deep vein thrombosis |
| HERS  | 2,763 | 1.2 (0.95-1.5) | med. age 67 yrs.  
no secondary prevention  
side effects as compared to WHI + cholecystectomy |
| Million Women | 1,084,110 | 1.66 (1.4-1.9) | EPC > E  
mode of application not relevant  
duration > 5 yrs.  
Tibolon RR 1.45 (1.2-1.7) |
| EPIC  | 1,153,747 person-years | 1.4 (1.2-1.6) 1.8 (1.4-2.2) | E-Mono  
EPC > E |
| Metanalysis | 16 Studies | 1.21-1.40 | side effects as compared to WHI + |

1. Chlebowski RT, Aragaki AK, Anderson GL. Menopausal Hormone Therapy Influence on Breast Cancer Outcomes in the Women's Health Initiative. J Natl Compr Canc Netw. 2015 Jul;13(7):917-24.
2. Manson JE, Aragaki AK, Rossouw JE et al. Menopausal hormone therapy and long-term all-cause and cause-specific mortality, the women's health initiative randomized trials. JAMA 2017; 318: 927-938.
## Prevention of Hormones (EGC) in Postmenopausal Patients

| Study                  | N        | MC-RR (95% CI)       | Further statements |
|------------------------|----------|----------------------|--------------------|
| CLEAR-study (NSW)      | 1236 BC cases | 2.09 [1.57-2.78]     | current user       |
| Case-Control-Study, retrospect. Australia | 1.03 [0.82-1.28] | past user            |
|                        | 2.62 [1.56-4.38] | E/P combination      |
|                        | 1.80 [1.31-2.44] | E only               |

Salagame U, Banks E, Sitas F et al. Menopausal hormone therapy use and breast cancer risk in Australia: Findings from the New South Wales Cancer, Lifestyle and Evaluation of Risk study. Int J Cancer. 2016 Apr 15;138(8):1905-14.
Prävention durch Änderung von Lifestyle-Faktoren: Orale Kontrazeption (OC)

- Insgesamt erhöht die OC nicht das Risiko an Brustkrebs zu versterben.  
- Risiko für Mammakarzinom leicht erhöht, Risiko für Ovarial- und Endometriumkarzinom wird erniedrigt.

1. Baranska,A. Oral Contraceptive Use and Assessment of Breast Cancer Risk among Premenopausal Women via Molecular Characteristics: Systematic Review with Meta-Analysis. Int. J. Environ. Res. Public Health 2022, 19, 15363.
2. Kanadys W, Barańska A, Malm M, et al. Use of Oral Contraceptives as a Potential Risk Factor for Breast Cancer: A Systematic Review and Meta-Analysis of Case-Control Studies Up to 2010. Int J Environ Res Public Health. 2021 Apr 27;18(9):4638. doi: 10.3390/ijerph18094638.
3. Nur U, El Reda D, Hashim D, Weiderpass E. A prospective investigation of oral contraceptive use and breast cancer mortality: findings from the Swedish women’s lifestyle and health cohort. BMC Cancer 2019, 19:807
4. Gierisch JM, Coeytaux RR, Urrutia RP et al. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. Cancer Epidemiol Biomarkers Prev. 2013 Nov;22(11):1931-43.
5. Moorman PG, Havrilesky LJ, Gierisch JM et al. Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis. J Clin Oncol. 2013 Nov 20;31(33):4188-98.
Risikoreduktion für ipsi- und kontralaterale Zweitkarzinome

Frauen nach Brustkrebs haben ein erhöhtes Risiko für ein ipsi- oder kontralaterales Zweitkarzinom.

Präventiver Zusatznutzen durch

- Tamoxifen
- Aromatasehemmer
- GnRH-Agonist + Tamoxifen

Oxford

|               | LoE | GR | AGO |
|---------------|-----|----|-----|
| Tamoxifen     | 1a  | A  | +   |
| Aromatasehemmer | 1a  | A  | +   |
| GnRH-Agonist + Tamoxifen | 1b  | B  | +   |

**Tamoxifen** (HR\text{total}=0.71; HR\text{ER+}=0.62)
1. Early Breast Cancer Trialists' Collaborative G. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365(9472):1687-717.

**Aromatasehemmer** (HR=0.62 vs Tam)
1. Breast International Group 1-98 Collaborative Group, Thurlimann B, Keshaviah A, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med. 2005;353(26):2747-57.
2. Early Breast Cancer Trialists' Collaborative G, Dowsett M, Forbes JF, et al. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015;386(10001):1341-52.

**GnRHa + Tamoxifen** (HR=0.56 vs Tam)
1. Bui KT, Willson ML, Goel S, Beith J, Goodwin A. Ovarian suppression for adjuvant treatment of hormone receptor-positive early breast cancer. Cochrane Database Syst Rev. 2020 Mar 6;3(3):CD013538.
### Risk reduction for ipsi- and contralateral second breast cancers ("second primaries")

| Localisation          | HR / RR | 95% CI  | p-value | ref.       |
|-----------------------|---------|---------|---------|-----------|
| Tamoxifen (vs nil)    |         |         |         |           |
| ipsilat.              | 0.47    | SE 0.08 | 0.00001 | EBCTCG    |
| contralat.            | 0.71    | SE 0.06 | < 0.0001| 2005      |
| Tamoxifen (vs nil) ER+ or unknown | |         |         |           |
| ipsilat.              | n.d.    | n.d.    | -       | EBCTCG    |
| contralat.            | 0.61    | 0.50–0.73| -       | 2005      |
| Aromatase inhibitor (vs Tam) | |         |         |           |
| ipsilat.              | 0.74    | 0.58 - 0.95| 0.020  | EBCTCG    |
| contralat.            | 0.62    | 0.48 - 0.80| 0.0003 | 2015      |
| GnRH-agonist + tamoxifen (vs Tam) | |         |         |           |
| ipsilat.              |         | 11.8 vs 16.7% | -     | Cochrane  |
| contralat.            | 0.56    | 0.29 - 1.07 | -     | 2020      |

**Tamoxifen (HR\textsubscript{total}=0.71; HR\textsubscript{ER+}=0.61)**

1. Early Breast Cancer Trialists' Collaborative G. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365(9472):1687-717.

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2. Early Breast Cancer Trialists' Collaborative G, Dowsett M, Forbes JF, et al. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015;386(10001):1341-52.
Allam MF. Breast Cancer and Deodorants/Antiperspirants: a Systematic Review. Cent Eur J Public Health. 2016 Sep;24(3):245-247. doi: 10.21101/cejph.a4475.

Bisher gibt es keine Evidenz für eine Korrelation zwischen Aluminium-enthaltenden Deodorants und Brustkrebsrisiko.

- All observational studies that evaluated the association between breast cancer risk and deodorants / antiperspirants use were reviewed. We have only identified two case-control studies, carried out between 2002 and 2006.
- There was no risk of antiperspirants use in the pooled risk (odds ratio 0.40, 95% confidence interval 0.35-0.46).
- Our comprehensive search has identified an insufficient number of studies to conduct a quantitative review and obtain reliable results. Further prospective studies are strongly needed.