



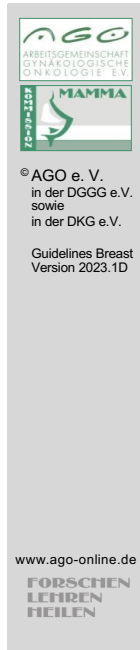
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FORSCHEN
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Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

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



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Risikofaktoren für Brustkrebs 1

<ul style="list-style-type: none"> ▪ Höheres Alter ▪ Genetisches Risiko ▪ Familiäre Krebsanamnese ▪ Persönliche Brustanamnese <ul style="list-style-type: none"> ▪ Nicht-proliferative Läsionen ▪ Proliferative Läsionen +/- Atypien ▪ Hochrisikoläsionen (ADH, LIN) ▪ Brustkrebs (DCIS, Inv. MaCa) ▪ Brustdichte ▪ Thoraxbestrahlung ▪ Typ II Diabetes mellitus ▪ Hyperthyreose 	<ul style="list-style-type: none"> ▪ Anzahl der Menstruationszyklen im Laufe des Lebens <ul style="list-style-type: none"> ▪ frühe Menarche, späte Menopause ▪ Mütterliche Schwangerschaftsfaktoren (z. B. Präeklampsie → Risikoreduktion) und geringe körperliche Aktivität während der Schwangerschaft (Risikoerhöhung) <p><u>Sozial definierte Risikofaktoren</u></p> <ul style="list-style-type: none"> ▪ Geringe Geburtenzahl oder keine Schwangerschaft ▪ Höheres Alter bei erster Geburt
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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.
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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.



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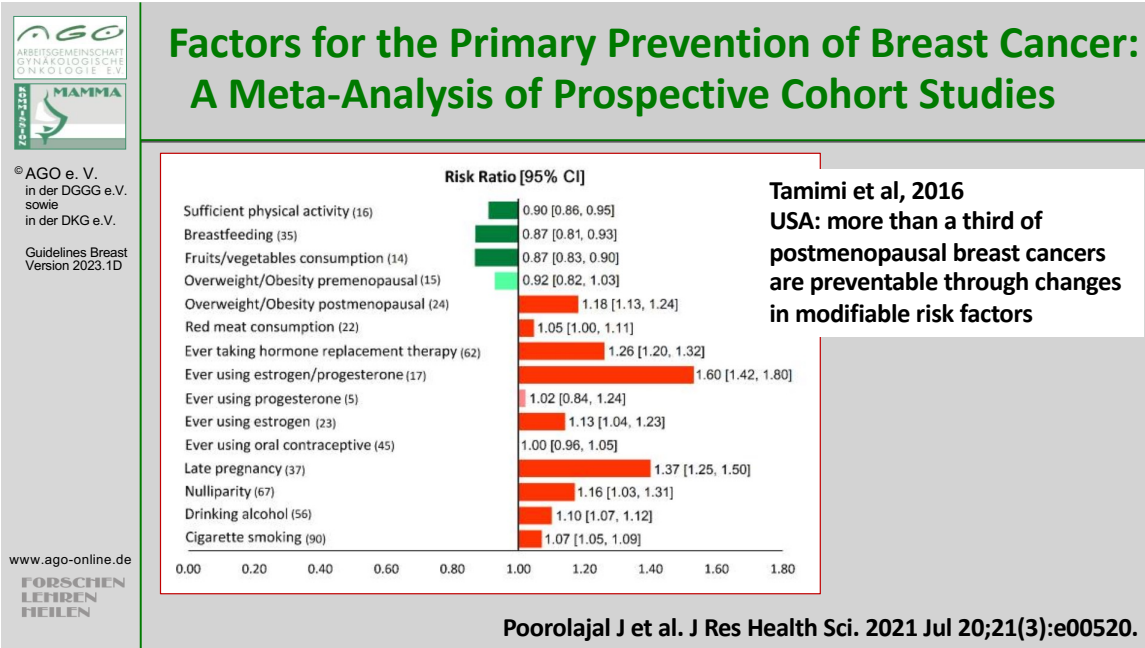
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Risikofaktoren für Brustkrebs 2

- Keine / kurze Stillperioden
- Postmenopausaler BMI < 18,5 und > 25 und besonders > 40 (Adipositas)
- Nahrungszusammensetzung
- Hormontherapie
 - Kürzlicher Gebrauch oraler Kontrazeptiva
 - Hormontherapie (Östrogen / Gestagen-Kombination) in der Postmenopause
- Alkoholkonsum
- Nikotin
- Schlafmangel (Nacht / Schichtarbeit) *widersprüchlich*
- Verminderte körperliche Aktivität
- Endokrine Disruptoren während der fetalen und frühkindlichen Entwicklung (z. B. DES, Bisphenol-A, DDT)
- Einwirkung kanzerogener Substanzen / Arbeitsstoffe
- Exposition gegenüber ionisierender Strahlung

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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.
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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.



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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.

Breast feeding 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.
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Medikamentöse Primärprävention*

- ASS
- COX2-Inhibitoren
- Bisphosphonate
- Vitamin D
- Statine

Oxford		
LoE	GR	AGO
2a	B	+/-
2a	B	+/-
2b	B	+/-
2b	B	+/-
2b	B	-

* Keine Zulassung, Nebenwirkungsprofil muss berücksichtigt werden

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).
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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.
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Bisphosphanate


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
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Statine

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Medical Prevention

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]

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

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

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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
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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

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
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The Risk of Breast, Ovarian and Endometrial Cancer in Obese Women Submitted to Bariatric Surgery: a Meta-Analysis


B Ishihara, D Farah, M Fonseca and A Nazário, Surg Obes Relat Dis 2020;16(10):1596-1602

- **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.



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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

Iyengar NM et al.: JAMA Oncol. 2019 Feb 1;5(2):155-163

- **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.**

Iyengar NM, Manson JE, Chlebowski RT 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

Prävention durch Änderung von Lifestyle-Faktoren: Ernährung

* s. Empfehlungen der Dt. Gesellschaft f. Ernährung (DGE)
 ** Empfohlen als Bestandteil einer gesunden Ernährung

Bevorzugung einer ausgewogenen Ernährung*

mediterrane Kost

Nahrungszusammensetzung

- Olivenöl (natives O. extra) i. Rahmen mediterraner Diät
- Fettreduzierte Nahrung
- Verminderter Konsum an rotem Fleisch
- Nüsse / Erdnüsse (> 10g/d) (Erdnussbutter ohne Effekt)
- Ballaststoffreiche Ernährung
- Vitamin-D-Substitution zur Prävention (MaCa RR1,02)
- Gemüse / Obst **
- Phytoöstrogene / Soja
- Vegetarische / Vegane Diät (keine sign. Risikoreduktion)
- Kaffee (keine signifikante Risikoreduktion)
- Ergänzung von Vitaminen, Mineralien, Spurenelementen

Oxford

LoE	GR	AGO
2b	B	+
2a	B	+
2b	B	+
2a	B	+
2b	C	+
2b	B	+
2a	B	+
1b	B	+/-
2a	B	+/-
2a	B	+/-
2b	C	+/-
2a	B	+/-
2a	B	-

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. Llahi F, Gil-Lespinaud 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 Aug 2;114(2):450-461.
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Mediterrane Kost

1. Schwingshackl 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-response 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

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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

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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
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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;
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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.

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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 caffeine consumption reduce the risk of incident breast cancer risk? A systematic 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.
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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.
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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.




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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

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.

Olive oil consumption and breast cancer risk

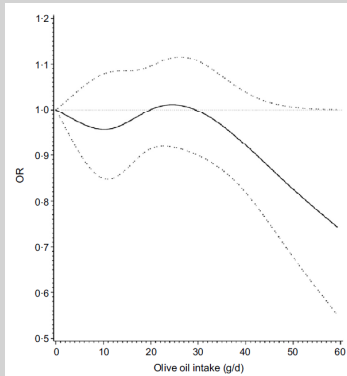


Fig. 5. Dose-response relationship between olive oil intake and breast cancer.

Table 3. Subgroup analyses for case-control studies of olive oil and breast cancer

Group	Number of studies	OR	95 % CI	I^2 (%)	P for heterogeneity
Location					
Italy, Spain, Greece	4	0.60	0.39, 0.95	85	<0.001
Other countries	4	1.06	0.72, 1.57	58	0.07
Source of controls					
Hospital based	5	0.94	0.69, 1.28	65	0.02
Population based	3	0.57	0.28, 1.19	90	<0.001
Number of cases					
<500 cases	5	0.71	0.37, 1.39	89	<0.001
≥500 cases	3	0.80	0.67, 0.95	0	0.47
Exposure assessment					
Assessed amount consumed	5	0.75	0.48, 1.15	88	<0.001
Assessed frequency consumed	3	0.77	0.39, 1.51	69	0.04
Adjustment for total energy					
Adjusts for total energy	5	0.67	0.46, 0.98	83	<0.001
No adjustment for total energy	3	0.98	0.50, 1.91	69	0.04

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

Sealy N, Hankinson SE, Houghton SC. Olive oil and risk of breast cancer: a systematic review and dose-response meta-analysis of observational studies. Br J Nutr. 2021 May 28;125(10):1148-1156.


Prävention durch Änderung von Lifestyle-Faktoren: Alkohol

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Reduktion des Alkoholkonsums vermindert Brustkrebsrisiko (ideal < 10g/d, class II evidence) 	2a	B	+
Insbesondere für			
<ul style="list-style-type: none"> ER+ / PR+ Tumoren 	2a	B	
<ul style="list-style-type: none"> Invasiv lobuläre Tumoren 	2a	B	

1. Poorolajal J, Heidaramoghis 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.




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Nature, Nurture and Cancer Risks: Genetic and Nutritional Contributions to Cancer

Theodoratou, E.: Annu Rev Nutr. 2017 August 21; 37: 293–320.
doi:10.1146/annurev-nutr-071715-051004

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 = 5.2×10^{-10} , $I^2 = 26\%$, $P_{\text{small effect bias}} = 0.184$, $P_{\text{excess significance bias}} = 4 \times 10^{-8}$)


Theodoratou, E. Nature, Nurture and cancer risks: Genetic and nutritional contributions to cancer. Annu Rev Nutr. 2017 August 21; 37: 293–320. doi:10.1146/annurev-nutr-071715-051004

Prävention durch Änderung von Lifestyle-Faktoren: Rauchen

Oxford		
LoE	GR	AGO
2a	B	++


- **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.



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Smoking and Risk of Breast Cancer in the Generations Study Cohort

Jones, M.E.:[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; $P = 0.22$).

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.

Prävention durch Änderung von Lifestyle-Faktoren: Körperliche Aktivität

Oxford		
LoE	GR	AGO
2a	B	++

- Körperliche Aktivität**
Metabolisches Equivalent zu 3–5 Std.
Spaziergänge pro Woche mit moderater
Schrittgeschwindigkeit

Diese Effekte gelten auch für *BRCA1/2*-Mutationsträgerinnen und für Frauen mit erhöhtem familiärem Risiko.


Körperliche Aktivität

- 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.
- 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.
- 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.
- 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.
- 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

- 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.



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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

Kehm RD et al.: 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**


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.

Prävention durch Lifestyle-Faktoren: Hormontherapie in der Postmenopause


		Oxford		
		LoE	GR	AGO
bei Risiko)	■ Vermeidung von Hormontherapie in der Postmenopause			
	■ Vermeidung von Östrogen- / Gestagen-Kombination	1b	A	+
	■ Vermeidung von alleiniger Östrogentherapie (kein erhöhtes, evtl. sogar verringertes Brustkrebsrisiko	1b	A	+/-

bei
Risiko)
alleiniger Östrogentherapie, aber erhöhtes EM Ca

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. Saeai 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, 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.



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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)**

Johansson A et al. Epigenome-Wide Association Study for Lifetime Estrogen Exposure Identifies an Epigenetic Signature Associated with Breast Cancer Risk
Clin Epigenetics. 2019 Apr 30;11(1):66.

Prevention of Hormones in Postmenopausal Patients			
	N	MC-RR (95 % CI)	Further information
WHI WHI: JAMA 2002, JAMA 2017	~ 27 000	1.3 (1.0-1.6)	1.3 (1.1-1.6) coronary events 1.4 (1.1-1.9) insults 2.1 (1.4-3.3) pulmonary embolism 2.1 (1.5-2.9) deep vein thrombosis
HERS Hulley S: JAMA 2002	I 2763 RCT, med. 4.1 yrs. II 2321 open-label, 2.7 yrs.	1.2 (0.95-1.5)	med. age 67 yrs. no secondary prevention side effects as comp. to WHI + cholecystectomy
Million Women Beral V: Lancet 2003	1.084 110 ~ 50% HRT 4.1 J. follow-up	1.66 (1.6-1.8)	EPC > E mode of applic. not relevant duration > 5 yrs. Tibolon RR 1.45 (1.2-1.7)
EPIC Int J Cancer 2010	1.153 747 person-years	1.4 (1.2-1.6) 1.8 (1.4-2.2)	E-Mono EPC > E
Metaanalyse Nelson HD: JAMA 2002	16 Studies	1.21-1.40	side effects as compared to WHI +

Chlebowski et al., Climacteric 2015, 18:336-8
Chlebowski et al., J Natl Compr Canc Netw 2015, 13:917-24
Manson JE et al., JAMA 2017; 318: 927-938



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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			
	N	MC-RR (95 % CI)	Further statements
CLEAR-study (NSW) Case-Control-Study, retrospect. Australia	1236 BC cases	2.09 (1.57-2.78)	current user
		1.03 (0.82-1.28)	past user
		2.62 (1.56-4.38)	E/P combination
		1.80 (1.21-2.68)	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)

	Oxford
	LoE
■ Insgesamt erhöht die OC <u>nicht</u> das Risiko an Brustkrebs zu versterben.	1a
■ <u>Risiko</u> für Mammakarzinom leicht erhöht, Risiko für Ovarial- und Endometriumkarzinom wird erniedrigt.	1a(-)

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
1a	A	+
1a	A	+
1b	B	+

Tamoxifen ($HR_{total}=0.71$; $HR_{ER+}=0.62$)

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”)


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

Tamoxifen ($HR_{total}=0.71$; $HR_{ER+}=0.61$)

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.


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: meta-analysis of individual patient data from randomised trials. Lancet. 2015;385(9981):1827-38.



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FORSCHEN
LEHREN
HEILEN

Deodorant-Gebrauch und Risiko

Breast Cancer and Deodorants/Antiperspirants: a Systematic Review.

Allam MF¹: 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.

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.