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Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Optionen der primären Prävention: Veränderbare Lifestyle-Faktoren



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Prävention

- **Versionen 2011–2021:**
Dall / Diel / Gerber / Hanf / Maass / Mundhenke / Rhiem / Solbach / Solomayer / Thomssen / von Minckwitz
- **Version 2022:**
Dall / Gerber

Screened data bases


Pubmed 2005 – 2021, ASCO 2012 – 2021, SABCS 2012 – 2021, Cochrane data base 2021

 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2022.1D</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<h2 style="text-align: center;">Risikofaktoren für Brustkrebs 1</h2> <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 ▪ 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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11. 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.
12. 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.

 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V. Guidelines Breast Version 2022.1D www.ago-online.de FORSCHEN LEHREN HEILEN</p>	<h2 style="text-align: center;">Risikofaktoren für Brustkrebs 2</h2> <ul style="list-style-type: none"> ▪ Keine / kurze Stillperioden ▪ Postmenopausaler BMI < 18,5 und > 25 und besonders > 40 (Adipositas) ▪ Nahrungszusammensetzung ▪ Hormontherapie <ul style="list-style-type: none"> ▪ Kürzlicher Gebrauch oraler Kontrazeptiva ▪ Hormontherapie (Östrogen / Gestagen-Kombination) in der Postmenopause ▪ Alkoholkonsum ▪ Nikotin ▪ Schlafmangel (Nacht / Schichtarbeit) <i>widersprüchlich</i> ▪ 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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- avoided by modifying lifestyle habits: the EPIC Italy study. *Breast Cancer Res Treat.* 2017 Jan;161(2):311-320.
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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.

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High Proportion of Postmenopausal Breast Cancer Attributable to Lifestyle Factors

population attributable fractions (PAFs) of modifiable risk factors

Risk factors: obesity, physical inactivity, alcohol, low-fiber intake, smoking

Results: retrospective cohort study (Netherlands Cancer Registry)

2000: subpopulations of obese women, inactive women, alcohol drinkers, smokers etc.
2010: breast cancer incidence as compared to background incidence in these subgroups

<p>25.7%</p> <p>8.8%</p> <p>6.6%</p> <p>5.5%</p> <p>3.2%</p> <p>4.6%</p>	<p>of postmenopausal breast cancer cases in the Netherlands in 2010 were attributable to lifestyle factors</p> <p>attributed to obesity</p> <p>attributed to alcohol</p> <p>attributed to physical inactivity</p> <p>attributed to low fiber intake</p> <p>attributed to smoking</p>
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Update 2019: Tamimi et al, 2016
USA: more than a third of postmenopausal breast cancers are preventable through changes in modifiable risk factors

van Germert et al., Int J Cancer 2015; 152: 155-162

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2. Tamini 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.

Einfluss durch Reproduktionsfaktoren		
	Oxford	
	LoE	GR
Präventiv		
▪ Hohe Zahl voll ausgetragener Schwangerschaften	2b	B
▪ Hohe Anzahl der Schwangerschaften	2b	B
▪ Erste ausgetragene Schwangerschaft ≤ 30 Jahre	2b	B
▪ Stillen (schützt, wenn Gesamtstilldauer 1,5–2 Jahre)	3a	B
▪ Geringeres Geburtsgewicht des Erstgeborenen (3000–3500 g vs. > 4500 g, RR = 1,53)	2b	B
▪ Geringere Schwangerschaftsdauer Erstgeborene (26–31. SSW vs. 40–41. SSW; RR = 2,38, p = 0,03)	2b	B
Kein Einfluss		
▪ Polycystic Ovarian Syndrome PCO	3b	C
▪ Assistierte Reproduktion	2b	B
▪ Schwangerschaftsabbruch	2b	B

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7. 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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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

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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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]



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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

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cancer risk factors? Genet Test Mol Biomarkers 2017; 21: 464-470.

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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).**

1. 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.**

	Oxford		
	LoE	GR	AGO
Bevorzugung einer ausgewogenen Ernährung*	2b	B	+
mediterrane Kost	2a	B	+
Nahrungszusammensetzung			
▪ Olivenöl (natives O. extra) i. Rahmen mediterraner Diät	2b	B	+
▪ Fettreduzierte Nahrung	2a	B	+
▪ Verminderter Konsum an rotem Fleisch	2b	C	+
▪ Nüsse / Erdnüsse (> 10g/d) (Erdnussbutter ohne Effekt)	2b	B	+
▪ Ballaststoffreiche Ernährung	2a	B	+
▪ Vitamin-D-Substitution zur Prävention (MaCa RR1,02)	1b	B	+/-
▪ Gemüse / Obst **	2a	B	+/-
▪ Phytoöstrogene / Soja	2a	B	+/-
▪ Vegetarische / Vegane Diät (keine sign. Risikoreduktion)	2b	C	+/-
▪ Kaffee (keine signifikante Risikoreduktion)	2a	B	+/-
▪ Ergänzung von Vitaminen, Mineralien, Spurenelementen	2a	B	-


* s. Empfehlungen der Dt. Gesellschaft f. Ernährung (DGE)

** Empfohlen als Bestandteil einer gesunden Ernährung


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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

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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) Insbesondere für <ul style="list-style-type: none"> ▪ ER+ / PR+ Tumoren ▪ Invasiv lobuläre Tumoren 	2a	B	+
	2a	B	
	2a	B	


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

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Prävention durch Änderung von Lifestyle-Faktoren: Rauchen


Oxford		
LoE	GR	AGO
2a	B	++

- **Frauen, die nie geraucht haben, haben ein verringertes Lebenszeitrisiko 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)**

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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; $P = 0.22$).

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Prävention durch Änderung von Lifestyle-Faktoren: Körperliche Aktivität

	Oxford	LoE	GR	AGO
<p>■ Körperliche Aktivität</p> <p>Metabolisches Equivalent zu 3–5 Std. Spaziergänge pro Woche mit moderater Schrittgeschwindigkeit</p> <p>Diese Effekte gelten auch für <i>BRCA1/2</i>-Mutationsträgerinnen und für Frauen mit erhöhtem familiärem Risiko.</p>	2a	B	++	

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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**

We examined associations of adult and adolescent recreational physical activity (quintiles of age-adjusted total metabolic equivalents per week) with breast cancer risk using multivariable Cox proportional hazards regression, adjusted for demographics, lifestyle factors, and body mass index. We tested for multiplicative interactions of physical activity with predicted absolute breast cancer familial risk based on pedigree data and with BRCA1 and BRCA2 mutation status. Baseline recreational physical activity level in the highest four quintiles compared with the lowest quintile was associated with a 20% lower breast cancer risk (HR, 0.80; 95% confidence interval, 0.68-0.93). The association was not modified by familial risk or BRCA mutation status (P interactions >0.05). No overall association was found for adolescent recreational physical activity. Recreational physical activity in adulthood may lower breast cancer risk for women across the spectrum of familial risk.



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Prävention durch Lifestyle-Faktoren: Hormontherapie in der Postmenopause

	Oxford		
	LoE	GR	AGO
<p>■ Vermeidung von Hormontherapie in der Postmenopause</p> <ul style="list-style-type: none"> ▪ Vermeidung von Östrogen- / Gestagen-Kombination ▪ Vermeidung von alleiniger Östrogentherapie (kein erhöhtes, evtl. sogar verringertes Brustkrebsrisiko bei alleiniger Östrogentherapie, aber erhöhtes EM Ca Risiko) 	1b 1b	A A	+ +/-

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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 = 3×10^{-12}) in EPIC-Italy.
694 CpG sites were associated with ELEE (FDR Q < 0.05)**



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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 ²⁹
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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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 et al., Int J Cancer. 2016;138(8):1905-14

	<h2>Prävention durch Änderung von Lifestyle-Faktoren: Orale Kontrazeption (OC)</h2>	
© AGO e. V. in der DGGG e.V. sowie in der DKG e.V. Guidelines Breast Version 2022.1D www.ago-online.de FORSCHEN LEHREN HEILEN	<ul style="list-style-type: none"> ■ Insgesamt erhöht die OC <u>nicht</u> das Risiko an Brustkrebs zu versterben. ■ Risiko für Mammakarzinom leicht erhöht, Risiko für Ovarial- und Endometriumkarzinom wird erniedrigt. 	Oxford
		LoE
		1a
		1a ⁽⁻⁾

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Risikoreduktion für das ipsi- und kontralaterale Mammakarzinom

**Frauen nach Brustkrebs haben ein erhöhtes Risiko für ein
kontralaterales Zweitkarzinom.**

- Tamoxifen*
- Aromatasehemmer*
- GnRHa + Tamoxifen*

Oxford		
LoE	GR	AGO
1a	A	+
1a	A	+
1b	B	+

* Nur für das HR positive sporadische MaCa belegt

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