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Guidelines Breast
Version 2021.1D

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LEIPZIG
PREISE

Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Optionen der primären Prävention: Veränderbare Lifestyle-Faktoren

Prävention



- **Versionen 2011–2020:**
Dall / Diel / Gerber / Hanf / Maass / Mundhenke / Solbach / Solomayer / Thomssen / von Minckwitz
- **Version 2021:**
Rhiem / Solomayer

Screened data bases

Pubmed 2005 – 2020, ASCO 2012 – 2020, SABCS 2012 – 2020, Cochrane data base 2020



Risikofaktoren für Brustkrebs 1 → Hintergrund

- **Höheres Alter***
- **Genetisches Risiko**
- **Familiäre Krebsanamnese***
- **Persönliche Brustanamnese***
 - Nicht-proliferative Läsionen
 - Proliferative Läsionen +/- Atypien
 - Hochrisikoläsionen (ADH, LIN)
 - Brustkrebs (DCIS, Inv. MaCa)
- **Brustdichte**
- **Thoraxbestrahlung**
- **Typ II Diabetes mellitus**
- **Hyperthyreose**

* explizit auch für DCIS

- **Anzahl der Menstruationszyklen im Laufe des Lebens**
 - frühe Menarche, späte Menopause
- **Mütterliche Schwangerschaftsfaktoren (z.B. Präeklampsie => Risikoreduktion) und geringe körperliche Aktivität während der Schwangerschaft (Risikoerhöhung)**

Sozial definierte Risikofaktoren


- **Geringe Geburtenzahl oder keine Schwangerschaft**
- **Höheres Alter bei erster Geburt**

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8. 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.



Risikofaktoren für Brustkrebs 2 → Hintergrund

- Keine / kurze Stillperioden
- 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

Legende: * explizit auch für DCIS

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2. 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.
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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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FÜR DEN FORTSCHRITT DER MEDIZIN

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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
25.7%	of postmenopausal breast cancer cases in the Netherlands in 2010 were attributable to lifestyle factors
8.8%	attributed to obesity
6.6%	attributed to alcohol
5.5%	attributed to physical inactivity
3.2%	attributed to low fiber intake
4.6%	attributed to smoking

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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Einfluss durch Reproduktionsfaktoren

	Oxford	
	LoE	GR
Präventiv		
• Hohe Zahl voll ausgetragener Schwangerschaften	2b	B
• Hohe Anzahl der Schwangerschaften	2b	B
• Erste ausgetragene Schwangerschaft \leq 30 Jahre	2b	B
• Stillen (schützt, wenn Gesamtstilldauer 1,5–2 Jahre)	3a	B
• Geringeres Geburtsgewicht des Erstgeborenen (3000–3500g vs. $>$ 4500g, 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

- Li CI, Beaver EF, Tang MT et al.. Reproductive factors and risk of estrogen receptor positive, triple-negative, and HER2-neu overexpressing breast cancer among women 20–44 years of age. *Breast Cancer Res Treat.* 2013;137:579–87.
- 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. doi: 10.26355/eurrev_201811_16434.
- Swerdlow AJ, Wright LB, Schoemaker MJ et al. Maternal breast cancer risk in relation to birthweight and gestation of her offspring. *Breast Cancer Res.* 2018 Oct 5;20(1):110. doi: 10.1186/s13058-018-1035-6.
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- 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. doi: 10.1371/journal.pone.0201097. eCollection 2018.
- 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.
- 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.

Medikamentöse Primärprävention

- **ASS (vor allem bei postmenopausalen Frauen hinsichtlich DCIS und ER pos. Inv. MaCa)**

Siehe Folie 9

- **Bisphosphonate**
- **Statine (kein Effekt)**

Oxford		
LoE	GR	AGO
4d	D	+/-
2b	B	+/-
2b	B	-

1. Peng R, Liang X, Zhang G et al. Association Use of Bisphosphonates with Risk of Breast Cancer: A Meta-Analysis. BioMed Research International Volume 2020, Article ID 5606573, 13 pages <https://doi.org/10.1155/2020/5606573>
2. Cao Y, Tan A. Aspirin might reduce the incidence of breast cancer An updated meta-analysis of 38 observational studies. Medicine (2020) 99:38
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
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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]

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.

1. Cheraghi Z, Poorolajal J, Hashem T et al.. Effect of body mass index on breast cancer during premenopausal and postmenopausal periods: a meta-analysis. PLoS One. 2012;7(12):e51446.
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4. Brinton LA, Cook MB, McCormack V et al.. Anthropometric and hormonal risk factors for male breast cancer: male breast cancer pooling project results. J Natl Cancer Inst. 2014 Mar;106(3):djt46.
5. Chan DS, Vieira AR, Aune D et al. Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. Ann Oncol. 2014 Oct;25(10):1901-14.
6. Jiralerspong S, Goodwin PJ. Obesity and Breast Cancer Prognosis: Evidence, Challenges, and Opportunities JCO 2016, 34:4203-4216.
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8. Pizot C, Boniol M, Mullie P et al. Physical activity, hormone replacement therapy and breast cancer risk: A meta-analysis of prospective studies, Eur J Cancer. 2016; 52:138-54.
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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).**

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UND
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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.



Prävention durch Änderung von Lifestyle-Faktoren: Ernährung


- **Bevorzugung einer ausgewogenen Ernährung***
 - **mediterrane Kost**
 - **Nahrungszusammensetzung**
 - Olivenöl (Natives O. extra) i. Rahmen mediterr. Diät
 - Fettreduzierte Nahrung
 - Verminderter Konsum an rotem Fleisch
 - Ergänzung von Vitaminen, Mineralien, Spurenelem.
 - Vitamin-D-Substitution zur Prävention (MaCa RRI,02)
 - Gemüse / Obst **
 - Phytoöstrogene / Soja
 - Ballaststoffreiche Ernährung
 - Vegetarische/Vegane Diät (keine sign. Risikoreduktion)
 - Kaffee (keine signifikante Risikoreduktion)
 - Nüsse/Erdnüsse (> 10g/d) (Erdnussbutter ohne Effekt)
- * s. Empfehlungen der Dt. Gesellschaft f. Ernährung (DGE)
 ** Empfohlen als Bestandteil einer gesunden Ernährung

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


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11. 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.
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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

1. 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.

Prävention durch Änderung von Lifestyle-Faktoren: Alkohol

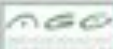
- Reduktion des Alkoholkonsums vermindert Brustkrebsrisiko (ideal < 10g/d, class II evidence)

Insbesondere für


- ER+/PR+ Tumoren
- Invasiv lobuläre Tumoren

Oxford		
LoE	GR	AGO
2a	B	+
2a	B	
2a	B	

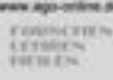
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- Rainey L, Eriksson M, Trinh T et al. The impact of alcohol consumption and physical activity on breast cancer: The role of breast cancer risk. *Int. J. Cancer:* 147, 931–939 (2020)

 **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} , $I^2 = 26\%$,
 $P_{\text{small effect bias}} = 0.184$, $P_{\text{excess significance bias}} = 4 \times 10^{-6}$)


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1. 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 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)**

1. 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.
2. Bjerkaas E, Parajuli R, Weiderpass E et al. Smoking duration before first childbirth: an emerging risk factor for breast cancer? Results from 302,865 Norwegian women. *Cancer Causes Control.* 2013 Jul;24(7):1347-56.
3. Dossus L, Boutron-Ruault MC, Kaaks R et al. Active and passive cigarette smoking and breast cancer risk: results from the EPIC cohort. *Int J Cancer.* 2014 Apr 15;134(8):1871-88.
4. Jones ME, Schoemaker MJ, Wright LB, Ashworth A, Swerdlow AJ. 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.
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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; $P = 0.22$).

1. 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	++

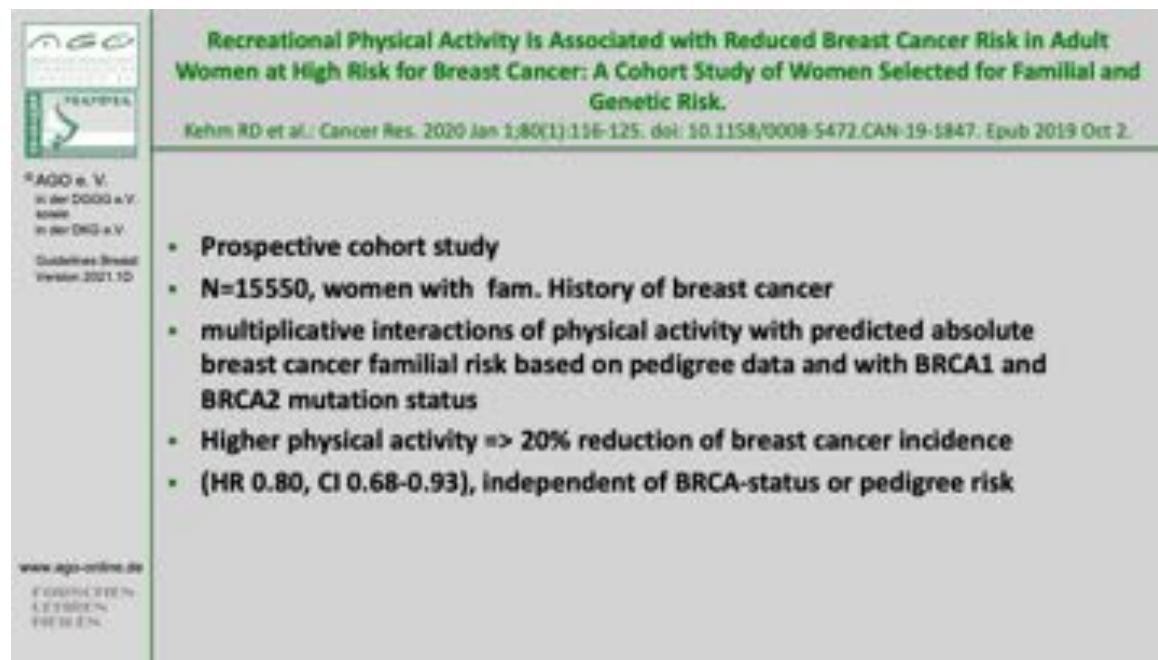
• Körperliche Aktivität

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.

1. Wu Y, Zhang D, Kang S. Physical activity and risk of breast cancer: a meta-analysis of prospective studies. *Breast Cancer Res Treat.* 2013 Feb;137(3):869-82.
2. Chlebowski RT. Nutrition and physical activity influence on breast cancer incidence and outcome. *Breast.* 2013 Aug;22 Suppl 2:S30-7.
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.
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7. de Boer MC, Wörner EA, Verlaan D et al. The Mechanisms and Effects of Physical Activity on Breast Cancer. *Clin Breast Cancer.* 2017 Jul;17(4):272-278. doi: 10.1016/j.clbc.2017.01.006. Epub 2017 Jan 24.

8. Pizot C, Boniol M, Mullie P et al. Physical activity, hormone replacement therapy and breast cancer risk: A meta-analysis of prospective studies. *Eur J Cancer*. 2016 Jan;52:138-54. doi: 10.1016/j.ejca.2015.10.063. Epub 2015 Dec 11.



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.

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10115 BERLIN

- **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.

Prävention durch Lifestyle-Faktoren: Hormontherapie in der Postmenopause

Vermeidung von Hormontherapie in der Postmenopause

- Vermeidung von Östrogen-/Gestagen-Kombination
- Vermeidung von alleiniger Östrogen-therapie
(kein erhöhtes, evtl. sogar verringertes Brustkrebsrisiko bei
alleiniger Östrogen-therapie, aber erhöhtes EM Ca Risiko)

Oxford		
LoE	GR	AGO
1b	A	+
1b	A	+/-

1. Beral V; Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003; 362: 419 – 27.
2. Chlebowski RT, Hendrix SL, Langer RD et al.. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 2003; 289: 3243–3253.
3. Reeves GK, Beral V, Green J et al. Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. Lancet Oncol 2006; 7: 910–918.
4. De P, Neutel CI, Olivotto I et al. Breast cancer incidence and hormone replacement therapy in Canada. J Natl Cancer Inst 2010; 102: 1489 – 95.
5. Chlebowski RT, Anderson GL, Gass M et al. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA 2010;304: 1684–1692.
6. Sæther S, Bakken K, Lund E. The risk of breast cancer linked to menopausal hormone therapy. Tidsskr Nor Laegeforen 2012;132: 1330–1334.
7. Marjoribanks J, Farquhar C, Roberts H et al. Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev. 2012 Jul 11;7:CD004143.
8. Manson JE, Chlebowski RT, Stefanick ML et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA. 2013 Oct 2;310(13):1353-68.
9. Chlebowski RT, Anderson GL, Prentice RL et al. Reliable evidence from placebo-controlled, randomized, clinical trials for menopausal hormone therapy's influence on incidence and deaths from breast cancer. Climacteric. 2015 Jun;18(3):336-8.
10. 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.

11. 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.
12. 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: 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%)	Further information
WHI WHI: JAMA 2002, JAMA 2017	~ 27 000	1.3 (0.9-1.6)	2.3 (2.1-2.6) coronary events 2.4 (2.1-2.8) stroke 2.1 (1.8-2.5) pulmonary embolism 2.1 (1.5-2.9) deep vein thrombosis
HERS Hulley S: JAMA 2002	I 2763 RCT, med. 4.1 J II 2321 open label, 3.7J	1.2 (0.90-1.5)	med. age 67 J no secondary prevention side effects as comp. to WHI + cholesterostats [®]
Million Women Beral V: Lancet 2005	1.084 110 ~ 50% HRT 4.1 J follow-up	1.66 (1.4-1.8)	EPC + E mode of applic. not relevant duration > 5 yrs. Tibolon RR 1.40 (1.2-1.7)
EPIC Int J Cancer 2005	1.153 747 persec-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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Fortschritt

Prevention of Hormones (EGC) in Postmenopausal Patients

	N	MC-RR (95% CI)	Further statements
CLEAR-study (NSW)	1236 BC cases	2.09 (1.57-2.76)	current user
		1.03 (0.80-1.26)	past user
Case-Control-Study, retrospect. Australia		2.62 (1.94-4.36)	E/P combination
		1.80 (1.25-2.48)	E only

Salagame et al., Int J Cancer. 2016;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. 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.
2. 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.
3. Mørch LS, Skovlund CW, Hannaford PC et al. Contemporary hormonal contraception and the risk of breast cancer. *N Engl J Med.* 2017 Dec 7;377(23):2228-2239.
4. 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