

Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome



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Optionen der primären Prävention: Veränderbare Lifestyle-Faktoren

Prävention

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- **Versionen 2011–2019:**
Dall / Diel / Gerber / Hanf / Maass / Mundhenke / Solbach / Solomayer / Thomssen / von Minckwitz
- **Version 2020:**
Dall / Mundhenke

Risikofaktoren für Brustkrebs 1

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- **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**
- **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**

Risikofaktoren für Brustkrebs 2

- 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 frühkindl. Entwicklung (z.B. DES, Bisphenol-A, DDT)
- Einwirkung kanzerogener Substanzen / Arbeitsstoffe
- Exposition gegenüber ionisierender Strahlung



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.

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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
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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Präventiver Einfluss durch Reproduktionsfaktoren

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	Oxford		
	LoE	GR	AGO
▪ Zahl voll ausgetragener Geburten	2b	B	
▪ Anzahl der Schwangerschaften	2b	B	
▪ Erste ausgetragene Schwangerschaft ≤ 30 Jahre	2b	B	
▪ Stillen (schützt, wenn Gesamtstilldauer 1,5–2 Jahre)	3a	B	
▪ Assistierte Reproduktion (keinen Einfluss)	2b	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	
▪ Polycystic Ovarian Syndrome PCO (keinen Einfluss auf MaCa)	3b	C	

Medical Prevention

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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

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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ■ Einhaltung Normalgewicht (BMI 18,5 – 25 kg/m²)* <ul style="list-style-type: none"> ▪ Prämenopausal ▪ Postmenopausal 	2a	B	++
	3a	B	++
	2a	B	++
<ul style="list-style-type: none"> ■ 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.

The risk of breast, ovarian and endometrial cancer in obese women submitted to bariatric surgery: A meta-analysis

SABCS 2019, B Ishihara, D Farah, M Fonseca and A Nazário.

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- **Meta-analysis, of a total of 150,528 patients in the bariatric surgery arm and 1,461,938 women in the control arm.**
- **The risk of breast cancer was reduced by 61% [RR: 0.39 (95%CI [0.24 to 0.64]; I2= 90%; 6 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).**

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



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- **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.**

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BMI and Epigenetics

Link between Obesity and Breast Cancer?

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- **Changing the ESR1-promoter activity by methylation of CpG-islands**
- **n = 120 breast tissue samples of cancer free patients**
- **ESR1-promoter methylation**
- **BMI \geq 30 > BMI 25–29 > BMI 25 kg/m² (p < 0.001 resp.)**
- **postmenopausal > premenopausal (p = 0.046)**
- **[multivariate analysis]**



BMI and Epigenetics

Link between Obesity and Breast Cancer?

- **The epigenetic code (methyl marks) determines how the genome functions, dictating which genes are turned on and which genes are turned off**
- **Development is the critical period when this programming occurs, directing cell and organ development**

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Walker, CL, SABCS 2011

Prävention durch Änderung von Lifestyle-Faktoren: Ernährung

* 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 RR1,02)	1b	B	+
■ Gemüse / Obst **	2a	B	+/-
■ Phytoöstrogene / Soja	2a	B	+/-
■ Ballaststoffreiche Ernährung	2a	B	+
■ Vegetarische/Vegane Diät (keine sign. Risikoreduktion)	2b	C	+/-
■ Kaffee reduziert das MaCa Risiko (bes. Rezeptor-neg)	2a	B	+/-
■ Nüsse/Erdnüsse (> 10g/d) (Erdnussbutter ohne Effekt)	2b	B	+

■ **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 RR1,02)**

 ■ **Gemüse / Obst ****

 ■ **Phytoöstrogene / Soja**

 ■ **Ballaststoffreiche Ernährung**

 ■ **Vegetarische/Vegane Diät (keine sign. Risikoreduktion)**

 ■ **Kaffee reduziert das MaCa Risiko (bes. Rezeptor-neg)**

 ■ **Nüsse/Erdnüsse (> 10g/d) (Erdnussbutter ohne Effekt)**

Coffee Consumption and Risk of Breast Cancer: An Up- To-Date Meta-Analysis

Xiu Juan Li: PlosOne, January 2013 | Volume 8 | Issue 1 | e52681



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49497 breast cancer cases

26 studies (16 cohort and 10 case–control studies)

The pooled RR showed a borderline significant influence of highest coffee consumption (RR = 0.96; 95% CI 0.93–1.00), low-to moderate coffee consumption (RR = 0.99; 95% CI 0.95–1.04), or an increment of 2 cups/ day of coffee consumption (RR = 0.98; 95% CI 0.97–1.00) on the risk of breast cancer.

In stratified analysis, a significant inverse association was observed in ER-negative subgroup. However, no significant association was noted in the others.

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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Epidemiological Evidences on Dietary Flavonoids and Breast Cancer Risk: A Narrative Review

Sak, K.: [Asian Pac J Cancer Prev.](#) 2017 Sep 27;18(9):2309-2328.

Conclusions and further perspectives

...probably the most apparent relationship prevails for consumption of isoflavones, whereas beneficial effects seem to be expressed only at high intake levels typical to Asian womencompared to Western countries where the intake of soy products is remarkably low.

protective activities of isoflavones might appear only in females consuming soy foods since their early age as childhood and adolescence can be crucial periods of exposure

At present: “recommendations for consumption of high-dose isoflavones ... to reduce the individual susceptibility towards breast carcinogenesis are still premature and can also be not completely without .. risks.”



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Prävention durch Änderung von Lifestyle-Faktoren: Alkohol

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

- **Reduktion des Alkoholkonsums vermindert Brustkrebsrisiko (ideal < 10g/d, class II evidence)**
Insbesondere für
 - ER+/PgR+ Tumoren
 - Invasiv lobuläre Tumoren

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



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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} , I² = 26%,

P_{small effect bias} = 0.184, P_{excess significance bias} = 4×10^{-8})

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Prävention durch Änderung von Lifestyle-Faktoren: Rauchen

Oxford		
LoE	GR	AGO

- 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)**

2a	B	++
----	---	----



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.

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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
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.



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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- **Prospective cohort study**
- **N=15550, women with fam. Hx 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**
- **(HR0.80, CI 0.68-0.93), independent of BRCA-status or pedigree risk**

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Prävention durch Lifestyle-Faktoren: Hormontherapie in der Postmenopause

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Oxford		
LoE	GR	AGO

■ Vermeidung von Hormontherapie in der Postmenopause

- | | | | |
|--|-----------|----------|------------|
| <ul style="list-style-type: none"> Vermeidung von Östrogen-/Gestagen-Kombinat. | 1b | A | + |
| <ul style="list-style-type: none"> Vermeidung von alleiniger Östrogentherapie
(kein erhöhtes, evt. sogar verringertes Brustkrebsrisiko bei
alleiniger Östrogentherapie, aber erhöhtes EM Ca Risiko) | 1b | A | +/- |



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.

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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

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	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 J II 2321 open-label, 2.7J	1.2 (0.95-1.5)	med. age 67 J 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 +

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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

Prevention of Hormones (EGC) in Postmenopausal Patients

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	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 (1.21-2.68)	E only



Prävention durch Änderung von Lifestyle-Faktoren: Orale Kontrazeption (OC)

Oxford
LoE

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

1a

1a⁽⁻⁾

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