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Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Optionen der primären Prävention: Veränderbare Lifestyle-Faktoren



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Prävention

- **Versionen 2011–2018:**
Dall / Diel / Gerber / Maass / Mundhenke /
Solbach / Thomssen / von Minckwitz
- **Version 2019:**
Hanf / Solomayer

Screened data bases

Pubmed 2005 – 2018, ASCO 2012 – 2018, SABCS 2012 – 2018, Cochrane data base 2018



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Risikofaktoren für Brustkrebs 1

- **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



1. 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.
2. 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.
3. Powe CE, Tobias DK, Michels KB et al, History of gestational diabetes mellitus and risk of incident invasive breast cancer among parous women in the Nurses' Health Study II prospective cohort. Cancer Epidemiol Biomarkers Prev. 2017 Mar; 26(3): 321–327

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


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.
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Deodorant-Gebrauch und Risiko

Cent Eur J Public Health. 2016 Sep;24(3):245-247. doi: 10.21101/cejph.a4475.
Breast Cancer and Deodorants/Antiperspirants: a Systematic Review.
Allam MF¹.

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.

1. 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.



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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

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

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3. 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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Prävention durch Änderung von Lifestyle-Faktoren: Gewicht / Glucosestoffwechsel

	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 ■ Vermeidung bzw. Früherkennung und Einstellung eines Typ II Diabetes mellitus (Reduktion der Brustkrebsinzidenz und -mortalität) 	2a 3a 2a 2b	B B B B	++ ++ ++ ++

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.
2. Pierobon M, Frankenfeld CL. Obesity as a risk factor for triple-negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat. 2013 Jan;137(1):307-14.
3. Simpson ER, Brown KA. Obesity and breast cancer: role of inflammation and aromatase. J Mol Endocrinol. 2013 Nov 26;51(3):T51-9.
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.
7. Penniecook-Sawyers JA, Jaceldo-Siegl K, Fan J et al. Vegetarian dietary patterns and the risk of breast cancer in a low-risk population, Br J Nutr. 2016; 115(10): 1790-1797.
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.

9. Daraei A, Izadi P, Khorasani G et al. Epigenetic changes of the ESR1 gene in breast tissue of healthy women: A missing link with breast cancer risk factors? Genet Test Mol Biomarkers 2017; 21: 464-470.

BMI and Epigenetics

Link between Obesity and Breast Cancer?

Changing the ESR1-promoter activity by methylation of CpG-islands

n = 120 breast tissue samples of cancer free patients

ESR1-promoter methylation

BMI ≥ 30 > BMI 25–29 > BMI 25 kg/m² (p < 0.001 resp.)

postmenopausal > premenopausal (p = 0.046)

[multivariate analysis]


Daraei A., Genet Test Mol Biomarkers 2017, 21:464-470

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

Walker, CL, SABCS 2011



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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	+

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3. Chlebowski RT. Nutrition and physical activity influence on breast cancer incidence and outcome. *Breast.* 2013 Aug;22 Suppl 2:S30-7.
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):djt465.
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13. Jiang X, Dimou NL, Al-Dabhani K et al. Circulating vitamin D concentrations and risk of breast and prostate cancer: a Mendelian randomization study. *N Engl J Med.* 2019 Jan 3;380(1):33-44. doi: 10.1056/NEJMoa1809944. Epub 2018 Nov 10.
14. 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]
15. Key TJ, Angela B, Bradbury KE et al. Foods, macronutrients and breast cancer risk in postmenopausal women: a large UK cohort. *Chiropr Med.* 2018 Jun; 17(2): 90–96. Published online 2018 Jun 14. doi: 10.1016/j.jcm.2017.12.001
16. Marc P. McRae. The Benefits of Dietary Fiber Intake on Reducing the Risk of Cancer: An Umbrella Review of Meta-analyses. *Nutr J.* 2018 Sep 21;17(1):87. doi: 10.1186/s12937-018-0394-2.
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18. 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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Coffee Consumption and Risk of Breast Cancer: An Up- To-Date Meta-Analysis


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

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.




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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.



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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.”

1. 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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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

1. McDonald JA, Goyal A, Terry MB. Alcohol Intake and Breast Cancer Risk: Weighing the Overall Evidence. Curr Breast Cancer Rep. 2013 Sep;5(3). doi: 10.1007/s12609-013-0114-z.
2. Bagnardi V, Rota M, Botteri E et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer. 2015 Feb 3;112(3):580-93.
3. 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. doi: 10.1093/ije/dyy238. [Epub ahead of print]
4. 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.
5. Bagnardi V, Rota M, Botteri E et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer. 2015;112:580–93.

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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} , I² = 26%,
Psmall effect bias = 0.184, P excess significance bias = 4×10^{-8})

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



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Prävention durch Änderung von Lifestyle-Faktoren: Rauchen


	Oxford		
	LoE	GR	AGO
■ Frauen, die nie geraucht haben, haben ein verringertes Lebenszeitrisko für einen Brustkrebs (~ 15–24% Reduktion)	2a	B	++
■ 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.
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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
2a ⁽⁻⁾	B	++

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

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Prävention durch Lifestyle-Faktoren: Hormontherapie in der Postmenopause

	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	+/-

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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 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 +

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

	N	MC-RR (95% CI)	Further statements
CLEAR-study (NSW)	1236 BC cases	2.09 (1.57-2.78)	current user
		1.03 (0.82-1.28)	past user
Case-Control-Study, retrospect. Australia		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



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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
■ Risiko für Mammakarzinom leicht erhöht, Risiko für Ovarial- und Endometriumkarzinom wird erniedrigt	1a ⁽⁻⁾

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