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Guidelines Breast  
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# Diagnosis and Treatment of Patients with early and advanced Breast Cancer

## Options for Primary Prevention: Modifiable Lifestyle Factors

  
AGG  
ARBEITSGEMEINSCHAFT  
GYNÄKOLOGISCHER  
ONKOLOGEN  
  
MAMMA  
BRUSTKREISLAUFKRAUNKHEITEN

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## Prevention

- **Versions 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.          Guidelines Breast          Version 2022.1E            www.ago-online.de          FORSCHEN          LEHREN          HEILEN       </p>	<h2 style="text-align: center;">Risk Factors for Breast Cancer 1</h2> <ul style="list-style-type: none"> <li>▪ Older age</li> <li>▪ Genetics</li> <li>▪ Family history of cancer</li> <li>▪ Personal history of breast lesions               <ul style="list-style-type: none"> <li>▪ Non-proliferative lesions</li> <li>▪ Proliferative lesions w/o atypia</li> <li>▪ High risk lesions (ADH, LIN)</li> <li>▪ Breast cancer (DCIS, Inv. BC)</li> </ul> </li> <li>▪ Breast density</li> <li>▪ Chest irradiation</li> <li>▪ Type II Diabetes mellitus</li> <li>▪ Hyperthyroidism</li> <li>▪ Lifetime number of menstrual cycles               <ul style="list-style-type: none"> <li>▪ Early menarche, late menopause</li> </ul> </li> <li>▪ Maternal pregnancy factors (e.g. pre-eclampsia) (risk reduction), and low physical activity during pregnancy (risk increase)</li> </ul> <p><b><u>Social risk factors</u></b></p> <ul style="list-style-type: none"> <li>▪ Lower number of births or no pregnancy</li> <li>▪ Advanced age at first full term delivery</li> </ul>
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## Risk Factors for Breast Cancer 2


<ul style="list-style-type: none"> <li>▪ <b>Short duration or absence of breast feeding</b></li> <li>▪ <b>Postmenopausal BMI &lt; 18.5 and &gt; 25 and especially &gt; 40 (obesity)</b></li> <li>▪ <b>Food content</b></li> <li>▪ <b>Steroid hormone therapy</b> <ul style="list-style-type: none"> <li>▪ Recent oral contraceptive use</li> <li>▪ Hormone therapy (estrogen / gestagen combination) in postmenopausal women</li> </ul> </li> <li>▪ <b>Alcohol intake</b></li> <li>▪ <b>Nicotine</b></li> </ul>	<ul style="list-style-type: none"> <li>▪ <b>Light exposure at night (night shifts) <i>contradictory</i></b></li> <li>▪ <b>Low physical activity</b></li> <li>▪ <b>Endocrine disruptors in fetal and early childhood development (e.g. DES, bisphenol-A, DDT)</b></li> <li>▪ <b>Effect of carcinogenic substances / working materials</b></li> <li>▪ <b>Exposition to ionizing radiation</b></li> </ul>
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## Deodorant-use and risk


**Breast Cancer and Deodorants/Antiperspirants: a Systematic Review.**

Allam MF<sup>1</sup>: Cent Eur J Public Health. 2016 Sep;24(3):245-247. doi: 10.21101/cejph.a4475.

**So far there is no evidence of a correlation between aluminum containing deodorants and breast cancer risk**

- 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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Pregnancy Related Factors		
	Oxford	
	LoE	GR
<b>Prevention</b>		
▪ Any full-term pregnancy	2b	B
▪ High number of pregnancies	2b	B
▪ First full-term pregnancy before age of 30 years	2b	B
▪ Breast feeding (protective if total breast-feeding time exceeds 1.5-2 years)	3a	B
▪ Lower birth weight of the first born (3000-3500 vs. > 4500g RR = 1.53)	2b	B
▪ Lower length of pregnancy first born (26-31. WOP vs. 40-41. WOP; HR = 2.38, p = 0.03)	2b	B
<b>No influence</b>		
▪ Polycystic Ovarian Syndrome PCO	3b	C
▪ Assisted reproduction	2b	B
▪ Abortion	2b	B

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## Medical Primary Prevention\*

	Oxford		
	LoE	GR	AGO
■ ASS	2a	B	+/-
■ COX2-Inhibitoren	2a	B	+/-
■ Bisphosphonates	2b	B	+/-
■ Vitamin D	2b	B	+/-
■ Statins	2b	B	-

\* No approval, consider side effects

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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]

Prevention by Changing Lifestyle Factors: Body Mass Index / Diet			
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	LoE	GR	AGO
	2a	B	++
	3a	B	+/-
	2a	B	++
<p>▪ <b>Maintaining normal weight (BMI at 18.5-25 kg/m<sup>2</sup>)*</b></p> <p>▪ Premenopausal</p> <p>▪ Postmenopausal</p> <p>▪ <b>Prevention / screening and treatment of diabetes mellitus type II (reduction of breast cancer incidence and mortality)</b></p>	2b	B	++
* Amount of body fat can be increased in people with normal BMI and correlates with breast cancer risk			


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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]; I<sup>2</sup> = 90 %; 7 studies).**
- **The risk of ovarian cancer was reduced by 53 % [RR: 0.47 (95 % CI [0.27 to 0.81]; I<sup>2</sup> = 0 %; 3 studies).**
- **The risk of endometrial cancer was reduced by 67 % [RR: 0.33 (95 % CI [0.21 to 0.51]; I<sup>2</sup> = 88 %; 7 studies).**

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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.




Prevention by Changing Lifestyle Factors: Diet			
	Oxford		
	LoE	GR	AGO
■ <b>Preference of a balanced diet*</b>	2b	B	+
■ <b>Mediterranean Diet</b>	2a	B	+
■ <b>Dietary components</b>			
■ Olive oil (extra virgin olive oil), as part of mediterranean diet	2b	B	+
■ Fat reduced food	2a	B	+
■ Reduced consumption of red meat	2b	C	+
■ Nuts / peanuts (> 10g/d) (peanut butter without effect)	2b	B	+
■ Fiber containing food	2a	B	+
■ Vitamin D substitution for prevention (MaCa HR1,02)	1b	B	+/-
■ Vegetables / fruits **	2a	B	+/-
■ Phytoestrogens / soy	2a	B	+/-
■ Vegetarian / vegan diet (no significant risk reduction)	2b	C	+/-
■ Coffee (no significant reduction)	2a	B	+/-
■ Supplementation of vitamins, minerals, trace elements	2a	B	-

\* As recommended by German Society of Nutrition (DGE)  
 \*\* Recommended as a part of healthy nutrition

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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 D<sub>3</sub> (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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# Prevention by Modifying Lifestyle Risk Factors: Alcohol

- Reduction of alcohol intake reduces risk of breast cancer (ideal < 10g/d, class II evidence)



## Particularly for

- ER+ / PR+ tumors
- Invasive lobular tumors

Oxford		
LoE	GR	AGO
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

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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 ( $\geq 30$  g/d of alcohol consumption versus non-drinkers**  
**RR (95 % CI): 1.35 (1.23, 1.48, p-value =  $5.2 \times 10^{-10}$ ,  $I^2 = 26$  %,  $P_{\text{small effect bias}} = 0.184$ ,  $P_{\text{excess significance bias}} = 4 \times 10^{-8}$ )**

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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## Prevention by Modifying Lifestyle Risk Factors: Smoking


	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>▪ <b>Never smoking reduces risk of breast cancer ~ 15-24 % reduction of lifetime risk)</b></li>   <li>▪ <b>Young women smoking have a 60 % increased risk of BC, when smoking &gt; 10 years before the first childbirth (vs. never smokers)</b></li> </ul>	2a	B	++

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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.

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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;  $P = 0.22$ ).**

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.



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## Prevention by Modifying Lifestyle Risk Factors: Physical Activity

■ **Physical exercise**

**(Metabolic equivalents to 3–5 hrs  
moderate pace walking per week)**


**These effects also apply to *BRCA1/2* mutation carriers and for women  
with an increased family risk.**

Oxford		
LoE	GR	AGO
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. 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**

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.

Prevention by Modifying Lifestyle Risk Factors: Hormone Therapy in Postmenopausal Women			
	Oxford		
	LoE	GR	AGO
<p>■ <b>Avoiding hormonal therapy in postmenopausal women</b></p> <ul style="list-style-type: none"> <li>■ Avoiding estrogen / progestin combinations</li> <li>■ Avoiding estrogens only (no increased, possibly reduced breast cancer risk, but increased risk for endometrial cancer, if not hysterectomized)</li> </ul>	1b	A	+
	1b	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: 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 =  $3 \times 10^{-12}$ ) in EPIC-Italy.  
694 CpG sites were associated with ELEE (FDR Q < 0.05)**

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



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## 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
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

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



 	<h2>Prevention by Modifying Lifestyle Risk Factors: Oral Contraception (OC)</h2>	Oxford
© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.  Guidelines Breast Version 2022.1E	<ul style="list-style-type: none"> <li>OC does <u>not</u> increase the risk of mortality from breast cancer</li> <li><u>Risk</u> of breast cancer slightly increased, risk of ovarian, endometrial cancer is decreased</li> </ul>	<hr/> LoE 1a  1a <sup>(-)</sup>
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3. 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.
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## Risk Reduction for Ipsi- and Contralateral Breast Cancer

**Rationale: Women with breast cancer have an increased risk for a second primary**

- Tamoxifen\*
- Aromatase inhibitors\*
- Suppression of ovarian function\* + Tamoxifen

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

\* Only proven for ER / PgR-positive primary sporadic BC

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.
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