


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

## Options for Primary Prevention: Modifiable Lifestyle Factors




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## Prevention

- **Version 2011–2018**  
Dall / Diel / Gerber / Maass / Mundhenke /  
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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## Risk Factors for Breast Cancer 1


- Older age
- Genetics
- Family history of cancer
- Personal history of breast lesions
  - Non-proliferative lesions
  - Proliferative lesions w/o atypia
  - High risk lesions (ADH, LIN)
  - Breast cancer (DCIS, Inv. BC)
- Breast density
- Chest irradiation
- Typ II Diabetes mellitus

- Lifetime number of menstrual cycles
  - Early menarche, late menopause
- Maternal pregnancy factors (e.g. pre-eclampsia) (risk reduction), and low physical activity during pregnancy (risk increase)

**Social risk factors**

- Lower number of births or no pregnancy
- Advanced age at first full term delivery

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## Risk Factors for Breast Cancer 2

- **Short duration or absence of breast feeding**
- **BMI < 18.5 and > 25 and especially > 40 (obesity)**
- **Food content**
- **Steroid hormone therapy**
  - Recent oral contraceptive use
  - Hormone therapy (estrogen/gestagen combination) in postmenopausal women
- **Alcohol intake**
- **nicotine**

- **Light exposure at night (night shifts) *contradictory***
- **Low physical activity**
- **Endocrine disruptors in fetal and early childhood development (e.g. DES, bisphenol-A, DDT)**
- **Effect of carcinogenic substances / working materials**
- **Exposition to ionizing radiation**


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## Deodorant-use and risk

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 MF<sup>1</sup>.

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)**

<p>2000: subpopulations of obese women, inactive women, alcohol drinkers, smokers etc.</p> <p>2010: breast cancer incidence as compared to background incidence in these subgroups</p> <p>25.7% of postmenopausal breast cancer cases in the Netherlands in 2010 were attributable to lifestyle factors</p> <p>8.8% attributed to obesity</p> <p>6.6% attributed to alcohol</p> <p>5.5% attributed to physical inactivity</p> <p>3.2.% attributed to low fiber intake</p> <p>4.6% attributed to smoking</p>	<p>Update 2019: Tamimi et al, 2016 USA: more than a third of postmenopausal breast cancers are preventable through changes in modifiable risk factors</p>
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van Germert et al., Int J Cancer 2015; 152: 155-162

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Prevention through by Pregnancy Related Factors			
	Oxford		
	LoE	GR	AGO
■ Any full term pregnancy	2b	B	
■ 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	
■ Assisted reproduction (no influence)	2b	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	
■ Polycystic Ovarian Syndrome PCO (no influence on BC)	3b	C	




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## Prevention by Changing Lifestyle Factors: Body Mass Index / Diet

Oxford		
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2a	B	++
3a	B	++
2a	B	++
2b	B	++

- **Maintaining normal weight  
(BMI at 18.5 – 25 kg/m<sup>2</sup>)**
  - Premenopausal
  - Postmenopausal
- **Prevention/Screening and treatment of  
diabetes mellitus type II  
(reduction of breast cancer incidence and mortality)**

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prospective studies, Eur J Cancer. 2016; 52:138-54.

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## 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  $\geq 30$  > BMI 25–29 > BMI 25 kg/m<sup>2</sup> (p < 0.001 resp.)**

**postmenopausal > premenopausal (p = 0.046)**

**[multivariate analysis]**

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



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## 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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# Prevention by Changing Lifestyle Factors: Diet

\* As recommended by German Society of Nutrition (DGE)

\*\* Recommended as a part of healthy nutrition

## ■ Preference of a balanced diet\*

## ■ Mediterranean Diet

## ■ Dietary components

■ Olive oil (extra virgin olive oil), as part of mediterr. diet

■ Fat reduced food

■ Reduced consumption of red meat

■ Supplementation of vitamins, minerals, trace elements

■ Vitamin D substitution for prevention (MaCa HR1,02)

■ Vegetables / fruits \*\*

■ Phytoestrogens / soy

■ Fiber containing food

■ Vegetarian/vegan diet (no significant risk reduction)

■ Coffee reduces the BC risk (esp. receptor neg.)

■ nuts/peanuts (> 10g/d) (peanut butter without effect)

## Oxford

### LoE GR AGO

2b B +

2a B +

2b B +

2a B +

2b C +

2a B -

1b B +/-

2a B +/-

2a B +/-

2a B +

2b C +/-

2a B +/-

2b B +

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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.




 <p>ARBEITSGEMEINSCHAFT GYNAKOLOGISCHE ONKOLOGIE e.V.</p>  <p>MAMMA</p> <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2019.1</p>  <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<h2 style="text-align: center;">Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease</h2> <p style="text-align: center;"><u>N Engl J Med.</u> 2019 Jan 3;380(1):33-44. doi: 10.1056/NEJMoa1809944. Epub 2018 Nov 10.</p> <p><b>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</b></p> <p><b>Primary end points were invasive cancer of any type and major cardiovascular events</b></p> <p><b>25,871 participants</b></p> <p><b>median follow-up of 5.3 years</b></p> <p><b>124 breast cancers (Vit D group) vs. 122 (placebo group) Hazard Ratio: 1,02</b></p>
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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 women ....compared 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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## Prevention by Modifying Lifestyle Risk Factors: Alcohol


	Oxford LoE	GR	AGO
<ul style="list-style-type: none"> <li>■ <b>Reduction of alcohol intake reduces risk of breast cancer (ideal &lt;10g/d, class II evidence)</b></li> </ul>	2a	B	
Particularly for			
<ul style="list-style-type: none"> <li>■ ER+/PgR+ tumors</li> </ul>	2a	B	
<ul style="list-style-type: none"> <li>■ Invasive lobular tumors</li> </ul>	2a	B	

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

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
2a	B	++

- **Never smoking reduces risk of breast cancer  
(~ 15-24% reduction of lifetime risk)**
- **Young women smoking have a 60% increased risk of bc,  
when smoking > 10 years before the first childbirth  
(vs. never smokers)**

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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## Prevention by Modifying Lifestyle Risk Factors: Physical Activity

Oxford		
LoE	GR	AGO
2a <sup>(-)</sup>	B	++


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

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## Prevention by Modifying Lifestyle Risk Factors: Hormone Therapy in Postmenopausal Women

	Oxford LoE	GR	AGO
<ul style="list-style-type: none"> <li>■ <b>Avoiding hormonal therapy in postmenopausal women</b></li> <li> <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> </li> </ul>	1b	A	+
	1b	A	+/-

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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.
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## 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 J <b>II 2321</b> open-label, 2.7J	<b>1.2</b> (0.95-1.5)	med. age 67 J 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 +

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
<b>CLEAR-study (NSW)</b>	<b>1236 BC cases</b>	2.09 (1.57-2.78)	current user
		1.03 (0.82-1.28)	past user
<b>Case-Control-Study, retrospect. Australia</b>		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

 <small>ARBEITSGEMEINSCHAFT GYNAKOLOGISCHE ONKOLOGIE e.V.</small>  <small>100-117</small>	<h2 style="text-align: center;">Prevention by Modifying Lifestyle Risk Factors: Oral Contraception (OC)</h2>	
<small>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.  Guidelines Breast Version 2019.1          www.ago-online.de  FORSCHEN LEHREN HEILEN</small>	<ul style="list-style-type: none"> <li>OC does <u>not</u> increase the risk of mortality from breast cancer</li> </ul>	<div>Oxford LoE</div> <hr/> <div>1a</div>
	<ul style="list-style-type: none"> <li><u>Risk</u> of breast cancer slightly increased, risk of ovarian, endometrial cancer is decreased</li> </ul>	<div>1a<sup>(-)</sup></div>

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