Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2023.1E

Options for Primary Prevention: Modifiable Lifestyle Factors

Prevention

- **Versions 2011–2022:**
  Dall / Diel / Gerber / Hanf / Maass / Mundhenke / Rhiem / Solbach / Solomayer / Thomssen / von Minckwitz

- **Version 2023:**
  Albert / Thomssen

Risk Factors for Breast Cancer 1

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- 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
- Type II Diabetes mellitus
- Hyperthyreoidism
- 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

Risk Factors for Breast Cancer 2

- Short duration or absence of breast feeding
- Postmenopausal 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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Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies

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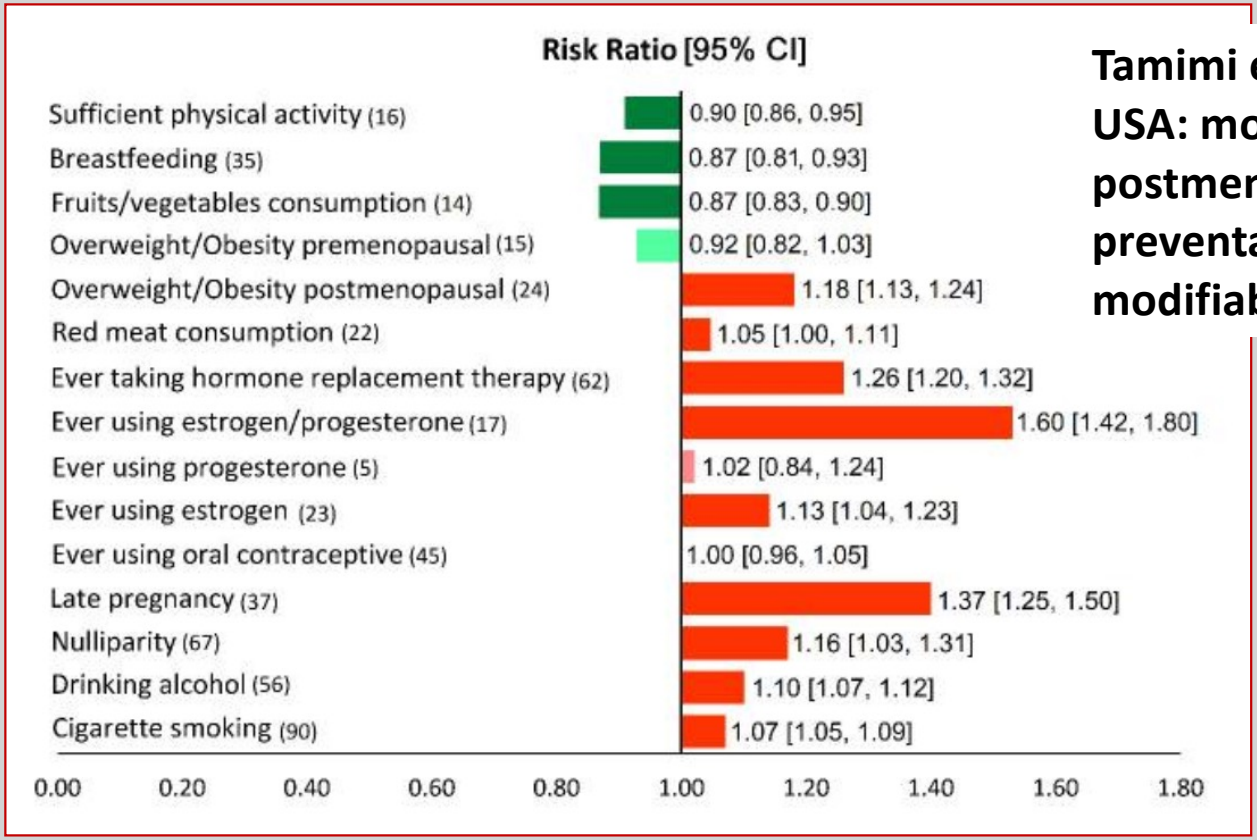

Tamimi et al, 2016
USA: more than a third of postmenopausal breast cancers are preventable through changes in modifiable risk factors

Poorolajal J et al. J Res Health Sci. 2021 Jul 20;21(3):e00520.

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Pregnancy Related Factors

	Oxford	
	LoE	GR
Prevention		
▪ 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
Unfavourable influence possible		
▪ Polycystic Ovarian Syndrome (PCOS)	2b	C
No influence		
▪ Assisted reproduction	2b	B
▪ Abortion	2b	B

Impact of breastfeeding on breast cancer risk

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- **Breastfeeding reduces the risk of breast cancer by 4.3% for every 12 months of breastfeeding, which is in addition to the 7.0% decrease in risk observed for each birth.**
- **Breastfeeding has been shown to primarily reduce the risk of Triple- Negative Breast Cancer (20%) as well as in carriers of BRCA1 mutations (22– 50%).**
- **An estimated 4.7% of breast cancer cases in the UK are caused by not breastfeeding.**

From: Stordal B. Cancer Med. 2022 Sep 26.

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Medical Primary Prevention*

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

* No approval, consider side effects

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 questionaire, 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

	Oxford		
	LoE	GR	AGO
▪ **Maintaining normal weight (BMI at 18.5-25 kg/m²)***	2a	B	++
▪ **Premenopausal**	3a	B	+/-
▪ **Postmenopausal**	2a	B	++
▪ **Prevention / screening and treatment of diabetes mellitus type II (reduction of breast cancer incidence and mortality)**	2b	B	++

* Amount of body fat can be increased in people with normal BMI and correlates with breast cancer risk

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

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

	Oxford		
	LoE	GR	AGO
▪ Preference of a balanced diet*	2b	B	+
▪ Mediterranean Diet	2a	B	+
▪ Dietary components			
▪ 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	-

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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Randomized, placebo-controlled trial, with a two-by-two factorial design, of vitamin D_3 (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

Olive oil consumption and breast cancer risk

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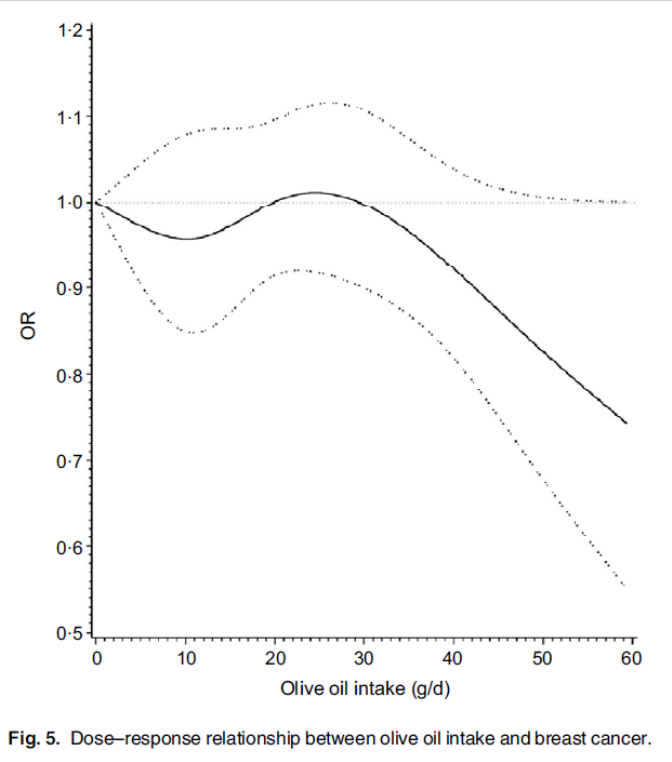

Fig. 5. Dose–response relationship between olive oil intake and breast cancer.

Table 3. Subgroup analyses for case–control studies of olive oil and breast cancer

Group	Number of studies	OR	95 % CI	I^2 (%)	$P_{for\ heterogeneity}$
Location					
Italy, Spain, Greece	4	0·60	0·39, 0·95	85	<0·001
Other countries	4	1·06	0·72, 1·57	58	0·07
Source of controls					
Hospital based	5	0·94	0·69, 1·28	65	0·02
Population based	3	0·57	0·28, 1·19	90	<0·001
Number of cases					
<500 cases	5	0·71	0·37, 1·39	89	<0·001
≥500 cases	3	0·80	0·67, 0·95	0	0·47
Exposure assessment					
Assessed amount consumed	5	0·75	0·48, 1·15	88	<0·001
Assessed frequency consumed	3	0·77	0·39, 1·51	69	0·04
Adjustment for total energy					
Adjusts for total energy	5	0·67	0·46, 0·98	83	<0·001
No adjustment for total energy	3	0·98	0·50, 1·91	69	0·04

1. **Amount of olive oil consumption correlates to breast cancer risk (not significant)**
2. **The source / quality of the olive oil (mediterranean vs others) seems to be relevant (or the origin of the data)**
3. **It is difficult to separate between use of olive oil and general adherence to a mediterranean diet.**

Sealy N et al. British Journal of Nutrition (2021), 125, 1148–1156

Prevention by Modifying Lifestyle Risk Factors: Alcohol

	Oxford		
	LoE	GR	AGO
▪ **Reduction of alcohol intace reduces risk of breast cancer (ideal < 10g/d, class II evidence)**	2a	B	+
Particularly for			
▪ **ER+ / PR+ tumors**	2a	B	
▪ **Invasive lobular tumors**	2a	B	

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}, $I^2 = 26$ %,
$P_{\text{small effect bias}} = 0.184$, $P_{\text{excess significance bias}} = 4 \times 10^{-8}$)

Prevention by Modifying Lifestyle Risk Factors: Smoking

	Oxford		
	LoE	GR	AGO
▪ Never smoking reduces risk of breast cancer (~ 15-24 % reduction of lifetime risk)	2a	B	++

- Young women smoking have a 60 % increased risk of BC, when smoking > 10 years before the first childbirth (vs. never smokers)

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).

Prevention by Modifying Lifestyle Risk Factors: Physical Activity

	Oxford		
	LoE	GR	AGO
▪ Physical exercise (Metabolic equivalents to 3–5 hrs moderate pace walking per week)	2a	B	++

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

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 = 15 550, 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**

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

	Oxford		
	LoE	GR	AGO
Avoiding hormonal therapy in postmenopausal women			
Avoiding estrogen / progestin combinations	1b	A	+
Avoiding estrogens only (no increased, possibly reduced breast cancer risk, but increased risk for endometrial cancer, if not hysterectomized)	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.

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 = $3x10^{-12}$) in EPIC-Italy.
694 CpG sites were associated with ELEE (FDR Q < 0.05)

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 yrs. II 2321 open-label, 2.7 yrs.	1.2 (0.95-1.5)	med. age 67 yrs. no secondary prevention side effects as comp. to WHI + cholcystectomy↗
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) **Case-Control-Study, retrospect. Australia**	**1236 BC cases**	2.09 (1.57-2.78)	current user
		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

Prevention by Modifying Lifestyle Risk Factors: Oral Contraception (OC)

	Oxford LoE
▪ OC does <u>not</u> increase the risk of mortality from breast cancer	1a
▪ <u>Risk</u> of breast cancer slightly increased, risk of ovarian, endometrial cancer is decreased	1a$^{(-)}$

Risk Reduction for Ipsi- and Contralateral Breast Cancer

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

Additional preventive effect by	Oxford LoE	Oxford GR	Oxford AGO
▪ Tamoxifen	1a	A	+
▪ Aromatase inhibitors	1a	A	+
▪ Suppression of ovarian function + Tamoxifen	1b	B	+

Risk reduction for ipsi- and contralateral second breast cancers (“second primaries”)

	Locali-zation	HR / RR	95% CI	p-value	ref.
Tamoxifen (vs nil)	ipsilat.	0.47	SE 0.08	0.00001	EBCTCG 2005
	contralat.	0.71	SE 0.06	< 0.00001	
Tamoxifen (vs nil) ER+ or unknown	ipsilat.	n.d.	n.d.	-	EBCTCG 2005
	contralat.	0.61	0.50–0.73	-	
Aromatase inhibitor (vs Tam)	ipsilat.	0.74	0.58 - 0.95	0.020	EBCTCG 2015
	contralat.	0.62	0.48 - 0.80	0.0003	
GnRH-agonist + tamoxifen (vs Tam)	ipsilat.		11.8 vs 16.7%	-	Cochrane 2020
	contralat.	0.56	0.29- 1.07	-	

Deodorant-use and risk

Breast Cancer and Deodorants/Antiperspirants: a Systematic Review.

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

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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.**