

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



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## Options for Primary Prevention: Modifiable Lifestyle Factors

# Prevention

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- **Versions 2011-2024:**  
**Albert / Dall / Diel / Fasching / Gerber / Hanf / Maass / Mundhenke / Rhiem / Solbach / Solomayer / Thomssen / von Minckwitz**
- **Version 2025:**  
**Harbeck / Reimer**

# Risk Factors

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- **Female sex**
- **Family history of cancer**
- **High breast density**
- **Older age**
- **Genetic predisposition**
- **Low number of births or no pregnancy**
- **Later first full-term delivery**
- **Alcohol intake**
- **Nicotine**
- **Steroid hormone therapy**
- **Oral contraceptives**
- **In postmenopausal women (estrogen / gestagen combination)**
- **Obesity in postmenopausal women**
- **Personal history of breast lesions**
  - Non-proliferative lesions
  - Proliferative lesions (+/- atypia)
  - High-risk lesions (ADH, LIN)
  - Breast cancer (DCIS, Inv. BC)
- **Chest irradiation**
- **Air pollution (PM<sub>2,5</sub>)**

# Protective factors

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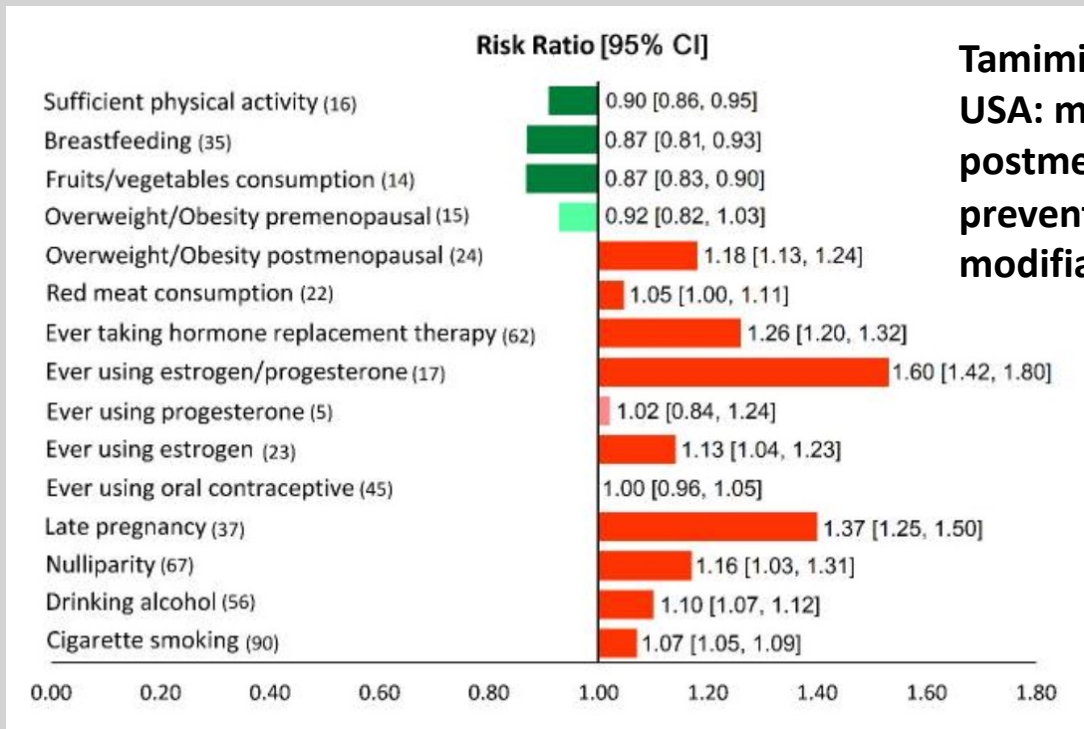
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- **Full-term pregnancies**
- **Full-term pregnancies at young age**
- **Regular physical activity**
- **Breast feeding**

# Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies

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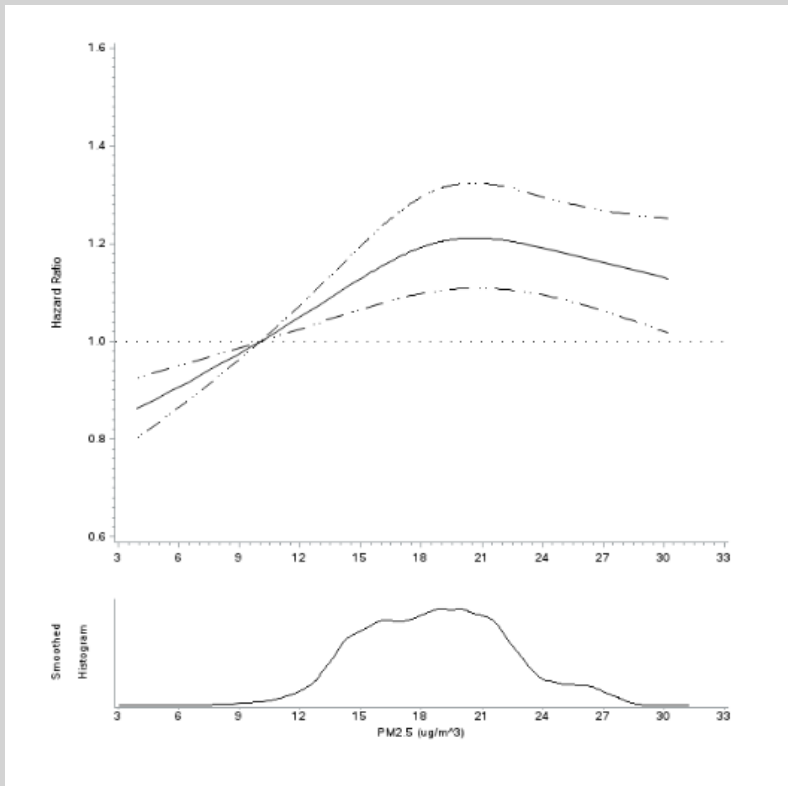
**Tamimi et al, 2016**

**USA: more than a third of  
postmenopausal breast cancers are  
preventable through changes in  
modifiable risk factors**

# Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies

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**196 905 Teilnehmerinnen von denen 15 870 Mammakarzinom hatten. Durchschnittliche PM2.5 Werte in der Wohnregion. Medianes Follow up von 20,7 Jahren**

**A 10 ug/m<sup>3</sup> increase in PM2.5 (fine particulate matter, i.e. airborne particles < 2.5 ug in aerodynamic diameter) was statistically significantly associated with overall breast cancer incidence (HR: 1.08, 95% CI: 1.02 to 1.13). The association was evident for estrogen receptor–positive (H = 1.10, 95% CI: 1.04 to 1.17) but not estrogen receptor–negative tumors (HR: 0.97, 95% CI: 0.84 to 1.13).**

# Pregnancy Related Factors

## List of factors that are still being clarified

### Prevention

- Any full-term pregnancy
- High number of pregnancies
- Young age at first full-term pregnancy
- Breast feeding (protective if total breast-feeding time exceeds 1.5-2 years)
- Lower birth weight of the first born (3000-3500 vs. > 4500g RR = 1.53)
- Lower length of pregnancy first born  
(26-31. WOP vs. 40-41. WOP; HR = 2.38, p = 0.03)

### Oxford

LoE	GR
2b	B
2b	B
2b	B
3a	B
2b	B
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.**

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From: Stordal B, Cancer Med. 2023;12:4616-25.

# Transgender

Corso G, Gandini S, D'Ecclesiis O, et al. (2023)

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**Metaanalysis and systematic review** of six cohort studies (for both female to men and vice versa populations) plus 35 case reports. Incidence and breast cancer risk quantification were the main outcomes considered.

## Results:

- FtM individuals at higher risk for BC in comparison to cisgender men [standardized incidence ratio (SIR) = 63.4; 95% confidence interval (CI), 32.2-124.9], but at lower risk than cisgender women (SIR = 0.42; 95% CI, 0.07-2.41).
- MtF individuals at higher risk of developing breast cancer in comparison to cisgender men (SIR = 22.5; 95% CI, 5.54-91.8) and at lower risk than cisgender women (SIR = 0.30; 95% CI, 0.22-0.42).

→ **FtM and MtF individuals are at substantially higher risk of developing BC in comparison to cisgender men, though at lower risk than cisgender women.**

# Medical endocrine Prevention for Women at Increased Risk

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	Oxford		
	LoE	GR	AGO
■ Tamoxifen for women > 35 years: Risk reduction of invasive BC, DCIS and LN	1a	A	+*
■ Raloxifen for postmenopausal women: Risk reduction of invasive BC only	1b	A	+*
■ AI for postmenopausal women	1b	A	+**

\* Risk situation as defined in NSABP P1-trial (1.66% in 5 years) or according to #Tyrrer-Cuzick model (IBIS-II)

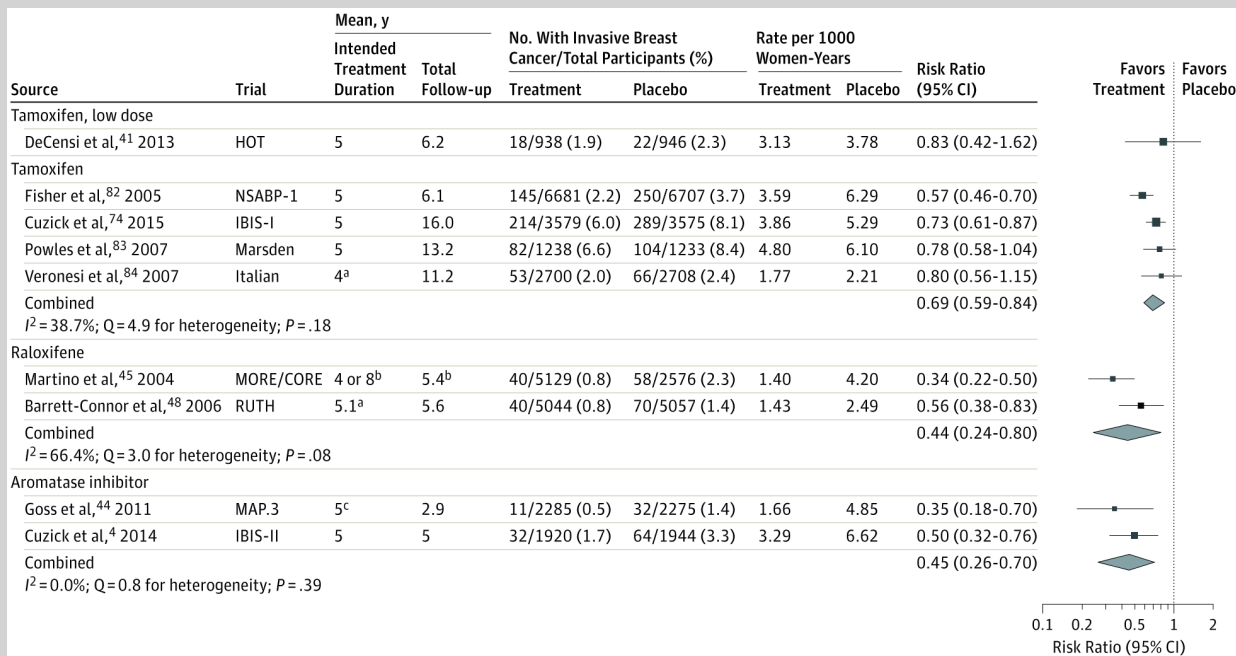
\*\* Significant risk reduction was seen for anastrozole for ovarian and endometrial cancer, as well as skin, colorectal, hematologic, thyroid and urinary tract cancers. Chemopreventive regimes should only be offered after individual and comprehensive counseling. The net benefit strongly depends on risk status, age and pre-existing risk factors for side effects.

# Medical Endocrine Prevention

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## Risk Reduction of Invasive Breast Cancer: Meta-analysis of Primary Prevention Trials





# Medical Primary non-hormonally Prevention\*

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- **ASS**
- **COX2-Inhibitors**
- **Bisphosphonates**
- **Vitamin D**
- **Statins**

Oxford		
LoE	GR	AGO
2a	B	+/-
2a	B	+/-
2b	B	+/-
2b	B	+/-
2b	B	-

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\* No approval, consider side effects

# Medical non-endocrine 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]

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

## Oxford

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

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- **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).**

# 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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# 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

	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 RR: 1,02)	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.

**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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# Olive Oil Consumption and Breast Cancer Risk

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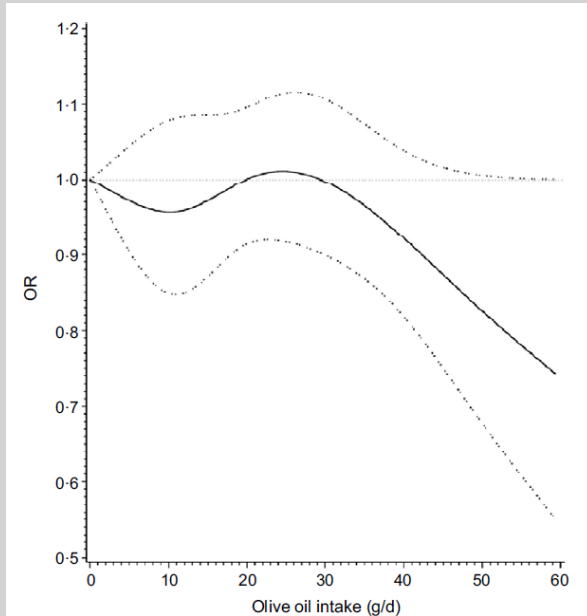


Fig. 5. Dose–response relationship between olive oil intake and breast cancer.

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

Group	Number of studies	OR	95% CI	I <sup>2</sup> (%)	P <sub>for heterogeneity</sub>
<b>Location</b>					
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
<b>Source of controls</b>					
Hospital based	5	0.94	0.69, 1.28	65	0.02
Population based	3	0.57	0.28, 1.19	90	<0.001
<b>Number of cases</b>					
<500 cases	5	0.71	0.37, 1.39	89	<0.001
≥500 cases	3	0.80	0.67, 0.95	0	0.47
<b>Exposure assessment</b>					
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
<b>Adjustment for total energy</b>					
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.

# Prevention by Modifying Lifestyle Risk Factors: Alcohol

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

Oxford		
LoE	GR	AGO
2a	B	+

## Particularly for

- ER+ / PR+ tumors
- Invasive lobular tumors

2a	B
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

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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 =  $5.2 \times 10^{-10}$ ,  $I^2 = 26\%$ ,**

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



# 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)**

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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	B	++

- 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.



# 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 = 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**
- **(HR 0.80, CI 0.68-0.93), independent of BRCA-status or pedigree risk**

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



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- **Avoiding hormonal therapy in postmenopausal women**
  - **Avoiding estrogen / progestin combinations**
  - **Avoiding estrogens only**  
(no increased, possibly reduced breast cancer risk, but increased risk for endometrial cancer, if not hysterectomized)

Oxford		
LoE	GR	AGO
1b	A	+
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: ELEE (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  $Q < 0.05$ )**

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# Prevention of Hormones in Postmenopausal Patients

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	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 +

# Prevention of Hormones (EGC) in Postmenopausal Patients

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	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
		2.62 (1.56-4.38)	E/P combination
		1.80 (1.21-2.68)	E only
<b>Case-Control-Study, retrospect. Australia</b>			

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

Oxford

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LoE

1a

- OC does not increase the risk of mortality from breast cancer
- Risk of breast cancer slightly increased, risk of ovarian, endometrial cancer is decreased

1a<sup>(-)</sup>

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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**

**Additional preventive effect by**

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

**Oxford**

<b>LoE</b>	<b>GR</b>	<b>AGO</b>
<b>1a</b>	<b>A</b>	<b>+</b>
<b>1a</b>	<b>A</b>	<b>+</b>
<b>1b</b>	<b>B</b>	<b>+</b>

# Risk Reduction for Ipsi- and Contralateral Second Breast Cancers (“Second Primaries”)

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	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	-	