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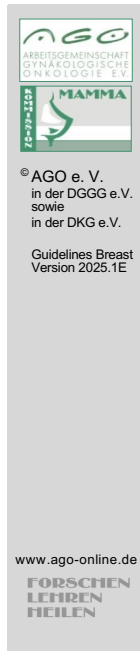
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# Diagnosis and Treatment of Patients with early and advanced Breast Cancer

## 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**

## Screened data bases

Pubmed 2012 – 2024, ASCO 2012 – 2024, SABCS 2012 – 2024, Cochrane data base 2024



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## Risk Factors

- **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>)**

1. White AJ, Fisher JA, Sweeney MR, et al. Ambient fine particulate matter and breast cancer incidence in a large prospective US cohort. J Natl Cancer Inst 2024; 116(1):53-60.
2. Sohi I, Rehm J, Saab M, et al, Alcoholic beverage consumption and female breast cancer risk: A systematic review and meta-analysis of prospective cohort studies. Alcohol Clin Exp Res (Hoboken) 2024 Dec;48(12):2222-2241.
3. Li C, Fan Z, Lin X, et al. Parity and risk of developing breast cancer according to tumor subtype: A systematic review and meta-analysis. Cancer Epidemiol. 2021 Dec;75:102050. doi: 10.1016/j.canep.2021.102050. Epub 2021 Oct 24
4. Coombes,R.C., Tovey, H, Kilburn, L: Effect of Celecoxib vs Placebo as Adjuvant Therapy on Disease-Free Survival Among Patients With Breast Cancer: The REACT Randomized Clinical Trial. JAMA Oncol. 2021 Sep 1;7(9):1291-1301. doi: 10.1001/jamaoncol.2021.2193.
5. Zhou L, Chen B, Sheng L, et al. The effect of vitamin D supplementation on the risk of breast cancer: a trial sequential meta-analysis. Breast Cancer Res Treat. 2020 Jul;182(1):1-8. doi: 10.1007/s10549-020-05669-4. Epub 2020 May 13
6. Wang B, Lu Z, Huang Y et al. Does hypothyroidism increase the risk of breast cancer: evidence from a metaanalysis. . BMC Cancer (2020) 20:733 <https://doi.org/10.1186/s12885-020-07230-4>
7. Puvanesarajah S, Gapstur SM, Gansler T et al. Epidemiologic risk factors for in situ and invasive ductal breast cancer among regularly screened postmenopausal women by grade in the Cancer Prevention Study-II Nutrition Cohort. Cancer Causes Control. 2020

Jan;31(1):95-103. doi: 10.1007/s10552-019-01253-4.

8. Mukama T, Fallah M, Brenner H et al. Risk of invasive breast cancer in relatives of patients with breast carcinoma in situ: a prospective cohort study. *BMC Med.* 2020 Nov 5;18(1):295. doi: 10.1186/s12916-020-01772-x.
9. Peila R, Arthur R, Rohan TE et al. Risk factors for ductal carcinoma in situ of the breast in the UK Biobank cohort study. *Cancer Epidemiol.* 2020 Feb;64:101648. doi: 10.1016/j.canep.2019.101648. Wang B, Lu Z, Huang Y et al. Does hypothyroidism increase the risk of breast cancer: evidence from a metaanalysis. . *BMC Cancer* (2020) 20:733 <https://doi.org/10.1186/s12885-020-07230-4>
10. Yang H, Holowko N, Grassmann F et al. Hyperthyroidism is associated with breast cancer risk and mammographic and genetic risk predictors. *BMC Medicine* (2020) 18:225 <https://doi.org/10.1186/s12916-020-01690-y>
11. 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
12. 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.
13. 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.



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## Protective factors

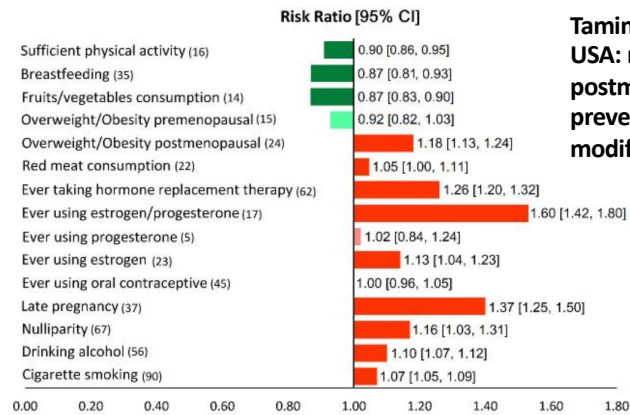
- Full-term pregnancies
- Full-term pregnancies at young age
- Regular physical activity
- Breast feeding

1. Li C, Fan Z, Lin X, et al. Parity and risk of developing breast cancer according to tumor subtype: A systematic review and meta-analysis. *Cancer Epidemiol.* 2021 Dec;75:102050. doi: 10.1016/j.canep.2021.102050. Epub 2021 Oct 24
2. Coombes,R.C., Tovey, H, Kilburn, L: Effect of Celecoxib vs Placebo as Adjuvant Therapy on Disease-Free Survival Among Patients With Breast Cancer: The REACT Randomized Clinical Trial. *JAMA Oncol.* 2021 Sep 1;7(9):1291-1301. doi: 10.1001/jamaoncol.2021.2193.
3. Zhou L, Chen B, Sheng L, et al. The effect of vitamin D supplementation on the risk of breast cancer: a trial sequential meta-analysis. *Breast Cancer Res Treat.* 2020 Jul;182(1):1-8. doi: 10.1007/s10549-020-05669-4. Epub 2020 May 13
4. Wang B, Lu Z, Huang Y et al. Does hypothyroidism increase the risk of breast cancer: evidence from a metaanalysis. . *BMC Cancer* (2020) 20:733 <https://doi.org/10.1186/s12885-020-07230-4>
5. Puvanesarajah S, Gapstur SM, Gansler T et al. Epidemiologic risk factors for in situ and invasive ductal breast cancer among regularly screened postmenopausal women by grade in the Cancer Prevention Study-II Nutrition Cohort. *Cancer Causes Control.* 2020 Jan;31(1):95-103. doi: 10.1007/s10552-019-01253-4.
6. Mukama T, Fallah M, Brenner H et al. Risk of invasive breast cancer in relatives of patients with breast carcinoma in situ: a prospective cohort study. *BMC Med.* 2020 Nov 5;18(1):295. doi: 10.1186/s12916-020-01772-x.
7. Peila R, Arthur R, Rohan TE et al. Risk factors for ductal carcinoma in situ of the breast in the UK Biobank cohort study. *Cancer Epidemiol.* 2020 Feb;64:101648. doi: 10.1016/j.canep.2019.101648. Wang B, Lu Z, Huang Y et al. Does hypothyroidism increase the

risk of breast cancer: evidence from a metaanalysis. . BMC Cancer (2020) 20:733 <https://doi.org/10.1186/s12885-020-07230-4>

8. Yang H, Holowko N, Grassmann F et al. Hyperthyroidism is associated with breast cancer risk and mammographic and genetic risk predictors. BMC Medicine (2020) 18:225 <https://doi.org/10.1186/s12916-020-01690-y>
9. 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
10. 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.
11. 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.

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

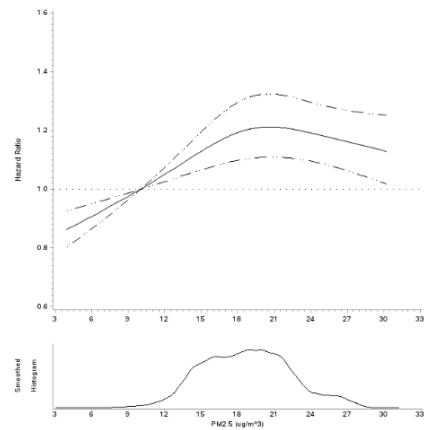


**Tamimi et al, 2016**  
**USA: more than a third of**  
**postmenopausal breast cancers are**  
**preventable through changes in**  
**modifiable risk factors**

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

1. Poorolajal J, Heidarimoghis F, Karami M et al. Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies. J Res Health Sci. 2021 Jul 20;21(3):e00520.
2. Tamimi RM, Spiegelman D, Smith-Warner SA et al.: Population Attributable Risk of Modifiable and Nonmodifiable Breast Cancer Risk Factors in Postmenopausal Breast Cancer. Am J Epidemiol. 2016 Dec 15;184(12):884-893. Epub 2016 Dec 6.

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



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  $\mu\text{g}/\text{m}^3$  increase in PM2.5 (fine particulate matter, i.e. airborne particles < 2.5  $\mu\text{g}$  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).

White AJ et al. JNCI 2024; 116: 53-60

1. White AJ, Fisher JA, Sweeney MR, et al.: Ambient fine particulate matter and breast cancer. J Natl Cancer Inst. 2024 Jan 10;116(1):53-60. doi: 10.1093/jnci/djad170.

## 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

### High number of full-term pregnancies, high number of pregnancies, first full-term pregnancy ≤ 30 years

1. Li C, Fan Z, Lin X, et al. Parity and risk of developing breast cancer according to tumor subtype: A systematic review and meta-analysis. Cancer Epidemiol. 2021 Dec;75:102050.

### Breast feeding (protective if total duration 1.5–2 years)

1. Stordal B. Breastfeeding reduces the risk of breast cancer: A call for action in high-income countries with low rates of breastfeeding. Cancer Med. 2022 Sep 26. doi: 10.1002/cam4.5288. Epub ahead of print. PMID: 36164270.
2. Qiu R, Zhong Y, Hu M et al. Breastfeeding and Reduced Risk of Breast Cancer: A Systematic Review and Meta-Analysis. Comput Math Methods Med. 2022 Jan 28;2022:8500910.
3. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet. 2002 Jul 20;360(9328):187-95.

### Low birth weight of first born (3000–3500 g vs. > 4500 g, RR = 1,53), short pregnancy duration

1. 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.

### Polycystic Ovary Syndrom (PCO-Syndrom)

1. Li Z, Wang YH, Wang Llet al. Polycystic ovary syndrome and the risk of endometrial, ovarian and breast cancer: An updated meta-analysis. *Scott Med J*. 2022 Aug;67(3):109-120.
2. Ding DC, Chen W, Wang JH et al. Association between polycystic ovarian syndrome and endometrial, ovarian, and breast cancer: A population-based cohort study in Taiwan. *Medicine (Baltimore)*. 2018 Sep;97(39):e12608.
3. Wu PF, Li RZ, Zhang W, Hu HY, Wang W, Lin Y. Polycystic ovary syndrome is causally associated with estrogen receptor-positive instead of estrogen receptor-negative breast cancer: a Mendelian randomization study. *Am J Obstet Gynecol*. 2020 Oct;223(4):583-585.

### Assisted reproduction

1. Al-Ajmi K, Lophatananon A, Ollier W et al. Risk of breast cancer in the UK biobank female cohort and its relationship to anthropometric and reproductive factors. *PLoS One*. 2018 Jul 26;13(7):e0201097.
2. Del Pup L, Peccatori FA, Levi-Setti PE et al. Risk of cancer after assisted reproduction: a review of the available evidences and guidance to fertility counselors. *Eur Rev Med Pharmacol Sci*. 2018 Nov;22(22):8042-8059.

### Induced abortion

1. Huang Y, Zhang X, Li W, et al.: A meta-analysis of the association between induced abortion and breast cancer risk among Chinese females. *Cancer Causes Control* 25 (2): 227-36, 2014.
2. Guo J, Huang Y, Yang L, et al.: Association between abortion and breast cancer: an updated systematic review and meta-analysis based on prospective studies. *Cancer Causes Control* 26 (6): 811-9, 2015.



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## Impact of Breastfeeding on Breast Cancer Risk

- **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. 2023;12:4616-25.

### Breast feeding is protective

1. Stordal B. Breastfeeding reduces the risk of breast cancer: A call for action in high-income countries with low rates of breastfeeding. Cancer Med. 2022 Sep 26.
2. Qiu R, Zhong Y, Hu M et al. Breastfeeding and Reduced Risk of Breast Cancer: A Systematic Review and Meta-Analysis. Comput Math Methods Med. 2022 Jan 28;2022:8500910.
3. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet. 2002 Jul 20;360(9328):187-95.

## 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.**

1. Corso G, Gandini S, D'Ecclesiis O, et al.: Risk and incidence of breast cancer in transgender individuals: a systematic review and meta-analysis. Eur J Cancer Prev. 2023 May 1;32(3):207-214. doi: 10.1097/CEJ.0000000000000784.

## Medical endocrine Prevention for Women at Increased Risk

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>▪ <b>Tamoxifen for women &gt; 35 years:</b> Risk reduction of invasive BC, DCIS and LN</li> </ul>	1a	A	+*
<ul style="list-style-type: none"> <li>▪ <b>Raloxifen for postmenopausal women:</b> Risk reduction of invasive BC only</li> </ul>	1b	A	+*
<ul style="list-style-type: none"> <li>▪ <b>AI for postmenopausal women</b></li> </ul>	1b	A	+**

\* Risk situation as defined in NSABP P1-trial (1.66% in 5 years) or according to #Tyrer-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.

1. Cuzick J, Sestak I, Cawthorn S, et al. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. *Lancet Oncol.* 2015;16(1):67-75.
2. Cuzick J, Sestak I, Forbes JF, et al. Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial. *Lancet.* 2020;395(10218):117–122. doi:10.1016/S0140-6736(19)32955-1
3. Forbes JF, Sestak I, Howell A, et al. Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial. *Lancet.* 2016;387(10021):866-73.
4. Goss PE, Ingle JN, Ales-Martinez JE, et al. Exemestane for breast-cancer prevention in postmenopausal women. *N Engl J Med.* 2011;364(25):2381-91.
5. King MC, Wieand S, Hale K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. *JAMA.* 2001;286(18):2251-6.
6. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA.* 2006;295(23):2727-41.

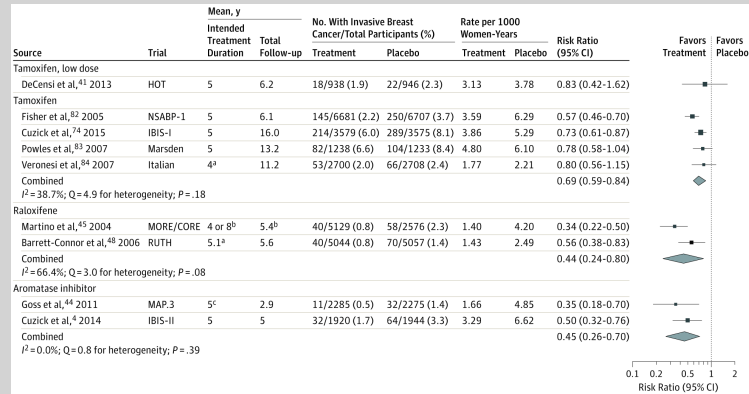


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# Medical Endocrine Prevention

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



Nelson et al. JAMA. 2019;322(9):868-886. doi:10.1001/jama.2019.5780

1. 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

## Medical Primary non-hormonally Prevention\*

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

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

\* No approval, consider side effects

### ASS

1. Cao Y, Tan A. Aspirin might reduce the incidence of breast cancer: An updated meta-analysis of 38 observational studies. *Medicine* 2020;99:38(e21917).
2. 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

### Cox2

1. Coombes,R.C., Tovey, H, Kilburn, L: Effect of Celecoxib vs Placebo as Adjuvant Therapy on Disease-Free Survival Among Patients With Breast Cancer: The REACT Randomized Clinical Trial. *JAMA Oncol.* 2021 Sep 1;7(9):1291-1301. doi: 10.1001/jamaoncol.2021.2193.
2. Soley Bayraktar , Sema Baghaki , Jimin Wu.: Biomarker: Modulation Study of Celecoxib for Chemoprevention in Women at Increased Risk for Breast Cancer: A Phase II Pilot Study *Cancer Prev Res (Phila).* 2020 Sep;13(9):795-802.

### Bisphosphonates

1. Peng R, Liang X, Zhang G et al. Association Use of Bisphosphonates with Risk of Breast Cancer: A Meta-Analysis. *BioMed Research International* Volume 2020, Article ID 5606573, 13 pages <https://doi.org/10.1155/2020/5606573>

#### Vitamin D

1. Fernandez-Lazaro, CI, Romanos-Nanclares, A, Sánchez-Bayona, R.: Dietary calcium, vitamin D, and breast cancer risk in women: findings from the SUN cohort. *Eur J Nutr* 2021 Oct;60(7):3783-3797. doi: 10.1007/s00394-021-02549-5. Epub 2021
2. Zhou L, Chen B, Sheng L, Turner A.: The effect of vitamin D supplementation on the risk of breast cancer: a trial sequential meta-analysis. *Breast Cancer Res Treat.* 2020 Jul;182(1):1-8. doi: 10.1007/s10549-020-05669-4. Epub 2020 May 13
3. Song D, Deng Y, Liu K et al. Vitamin D intake, blood vitamin D levels, and the risk of breast cancer: a dose-response meta-analysis of observational studies. *Aging-us.com* 2019: 11; 24: 12708 -12732

#### Statins

1. Zhao G, Ji Y, Ye Q, et al. Effect of statins use on risk and prognosis of breast cancer: a meta-analysis. *Anticancer Drug* 2022;33 (1): e507-e518



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## Medical non-endocrine 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]

1. 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

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

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>■ <b>Maintaining normal weight (BMI at 18.5-25 kg/m<sup>2</sup>)*</b> <ul style="list-style-type: none"> <li>■ Premenopausal</li> <li>■ Postmenopausal</li> </ul> </li> <li>■ <b>Prevention / screening and treatment of diabetes mellitus type II (reduction of breast cancer incidence and mortality)</b></li> </ul>	<b>2a</b>	<b>B</b>	<b>++</b>
	<b>3a</b>	<b>B</b>	<b>+/-</b>
	<b>2a</b>	<b>B</b>	<b>++</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

### Maintaining normal weight

1. Poorolajal J, Heidarimoghis F, Karami M, et al. Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies. J Res Health Sci. 2021; 21(3): e00520
2. Byun D, Hong SE, Ryu S, et al. Early-life body mass index and risks of breast, endometrial, and ovarian cancers: a dose–response meta-analysis of prospective studies British Journal of Cancer (2022) 126:664–672
3. Tao W, Santoni G, von Euler-Chelpin M et al. Cancer Risk After Bariatric Surgery in a Cohort Study from the Five Nordic Countries. Obes Surg. 2020; 30(10): 3761–3767. Published online 2020 Jun 13. doi: 10.1007/s11695-020-04751-6
4. Ishihara BP, Farah D, Fonseca MCM, et al. The risk of developing breast, ovarian, and endometrial cancer in obese women submitted to bariatric surgery: a meta-analysis. Surg Obes Relat Dis. 2020 Oct;16(10):1596-1602.
5. Iyengar NM et al.: 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. JAMA Oncol. 2019 Feb 1;5(2):155-163

### Typ II Diabetes - Prevention/ screening and treatment

1. Soltani S, Abdollahi S, Aune D, et al. Body mass index and cancer risk in patients with type 2 diabetes: a dose-response meta-analysis of cohort studies. Sci Rep. 2021 Jan 28;11(1):2479. doi: 10.1038/s41598-021-81671-0
2. Ling S, Brown K, Miksza JK, et al. Risk of cancer incidence and mortality associated with diabetes: A systematic review with trend analysis of 203 cohorts. Nutr Metab Cardiovasc Dis. 2021 Jan 4;31(1):14-22. doi: 10.1016/j.numecd.2020.09.023. Epub 2020 Sep 25



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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).**

1. Ishihara BP, Farah D, Fonseca MCM, et al. The risk of developing breast, ovarian, and endometrial cancer in obese women submitted to bariatric surgery: a meta-analysis. Surg Obes Relat Dis. 2020 Oct;16(10):1596-1602. doi: 10.1016/j.soard.2020.06.008. Epub 2020 Jun 14. PMID: 32690459.

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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

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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.**

1. Iyengar NM, Manson JE, Chlebowski RT et al. 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 JAMA Oncol. 2019 Feb 1;5(2):155-163

## Prevention by Changing Lifestyle Factors: Diet

	Oxford		
	LoE	GR	AGO
* As recommended by German Society of Nutrition (DGE)			
** Recommended as a part of healthy nutrition			
▪ 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	-

### Preference of a balanced diet

1. Kazemi A, Barati-Boldaji R, Soltani S, et al. Intake of Various Food Groups and Risk of Breast Cancer: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies. *Adv Nutr.* 2021 Jun 1;12(3):809-849
2. Llahi F, Gil-Lespinaud M, Unal P, et al. Consumption of Sweet Beverages and Cancer Risk. A Systematic Review and Meta-Analysis of Observational Studies. *Nutrients.* 2021 Feb 4;13(2):516.
3. Wu Y, Huang R, Wang M, Bernstein L: Dairy foods, calcium, and risk of breast cancer overall and for subtypes defined by estrogen receptor status: a pooled analysis of 21 cohort studies. *Am J Clin Nutr.* 2021 Aug 2;114(2):450-461.
4. Petimar J, Park Y-M, Smith-Warner SA et al. Dietary index scores and invasive breast cancer risk among women with a family history of breast cancer. *Am J Clin Nutr* 2019;109:1393–1401
5. Parida S, Sharma D. Microbial Alterations and Risk Factors of Breast Cancer: Connections and Mechanistic Insights. *Cells* 2020, 9, 1091; doi:10.3390/cells9051091

### Mediterranean Diet

1. Schwingshackl L, Schwedhelm C, Galbete C et al. Adherence to Mediterranean Diet and Risk of Cancer: An Updated Systematic Review and Meta-Analysis. *Nutrients.* 2017 Sep 26;9(10). pii: E1063. doi: 10.3390/nu9101063.
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3. Muscogiuri G, Verde L, Sulu C, Katsiki N, Hassapidou M, Frias-Toral E, Cucalón G, Pazderska A, Yumuk VD, Colao A, Barrea L. Mediterranean Diet and Obesity-related Disorders: What is the Evidence? *Curr Obes Rep.* 2022 Dec;11(4):287-304.

#### Olive oil

1. Markellos C, Ourailidou M-E, Gavriatopoulou M, et al. Olive oil intake and cancer risk: A systematic review and meta-analysis. *PLoS ONE* 2022; 17(1): e0261649.
2. Sealy N, Hanking SE, Houghton SC. Olive oil and risk of breast cancer: a systematic review and dose-response meta-analysis of observational studies. *Brit J Nutrition* 2021;125:1148-1156
3. Guasch-Ferré M, Li Y, Willett WC, Sun Q, Sampson L, Salas-Salvadó J, Martínez-González MA, Stampfer MJ, Hu FB. Consumption of Olive Oil and Risk of Total and Cause-Specific Mortality Among U.S. Adults. *J Am Coll Cardiol.* 2022 Jan 18;79(2):101-112.

#### Fat reduced food

1. Buja A, Pierbon M, Lago L et al. Breast Cancer Primary Prevention and Diet: An Umbrella Review. *Int J Environ Res Public Health.* 2020 Jul 1;17(13):4731. doi: 10.3390/ijerph17134731. PMID: 32630215; MCID: PMC7369836

#### Reduced consumption of red meat

1. Poorolajal J, Heidaramoghis F, Karami M, et al. Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies. *J Res Health Sci.* 2021; 21(3): e00520.

#### Nuts

1. van den Brandt PA, Nieuwenhuis L. Tree nut, peanut, and peanut butter intake and risk of postmenopausal breast cancer: The Netherlands Cohort Study. *Cancer Causes Control.* 2018 Jan;29(1):63-75.

#### Fiber containing food

1. 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
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3. Xiao Y, Ke Y, Wu S et al. Association between whole grain intake and breast cancer risk: a systematic review and meta-analysis of observational studies. *Asian Pac J Cancer Prev*. 2017 Sep 27;18(9):2309-2328.

#### Vitamin D

1. Song D, Deng Y, Liu K et al. Vitamin D intake, blood vitamin D levels, and the risk of breast cancer: a dose-response meta-analysis of observational studies. *Aging-us.com* 2019; 11; 24: 12708 -12732
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1. Farvid MS, Barnett JB, Spence ND. Fruit and vegetable consumption and incident breast cancer: a systematic review and meta-analysis of prospective studies. *British Journal of Cancer* (2021) 125:284–298;
2. Darooghegi Mofrad M, Mozaffari H, et al. Potato Consumption and Risk of Site-Specific Cancers in Adults: A Systematic Review and Dose-Response Meta-Analysis of Observational Studies. *Adv Nutr*. 2021 Oct 1;12(5):1705-1722.

#### Phytoestrogens/soy

1. Boutas I, Kontogeorgi A, Dimitrakakis C, et al. Soy Isoflavones and breast cancer risk: A meta-analysis. *In vivo* 2022;36:556-562
2. Finkeldey, L.; Schmitz, E.; Ellinger, S. Effect of the Intake of Isoflavones on Risk Factors of Breast Cancer—A Systematic Review of Randomized Controlled Intervention Studies. *Nutrients* 2021, 13, 2309.
3. 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.

#### Vegetarian/ vegan diet

1. Watling CZ, Schmidt JA, Dunneram Y, et al. Risk of cancer in regular and low meat-eaters, fish-eaters, and vegetarians: a prospective analysis of UK Biobank Participants. *BMC Medicine* 2022,20 73-8


2. Chang-Claude J, Herman S, Eiber U, et al. Lifestyle Determinants and Mortality in German Vegetarians and Health-Conscious Persons: Results of a 21-Year Follow-up. *Epidemiol Biomarker Prev* 2005; 14(4):963-8


### Coffee

1. Wang S, Li X, Yang Y, et al. Does Coffee, tea and caffeine consumption reduce the risk of incident breast cancer risk? A systematic review and meta-analysis. *Public Health Nutrition* 2021;24(8): 6377-6389
2. Li Y, Ma L. The association between coffee intake and breast cancer risk: a meta-analysis and dose-response analysis using recent evidence. *Ann Palliat Med* 2021;10(4):3804-3816.
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### Supplementation of vitamins, minerals, trace elements


1. Cadeau C, Farvid MS, Rosner BA, et al. Dietary and Supplemental Vitamin C Intake and Risk of Breast Cancer: Results from the Nurses' Health Studies. *J Nutr* 2022;152:835–843.
2. Fernandez-Lazaro C.I., Martínez-González, M.Á.; Aguilera-Buenosvinos, I.; Gea, A.; Ruiz-Canela, M.; Romanos-Nanclares, A.; Toledo, E. Dietary Antioxidant Vitamins and Minerals and Breast Cancer Risk: Prospective Results from the SUN Cohort. *Antioxidants* 2021, 10, 340.

  
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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**

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

# Olive Oil Consumption and Breast Cancer Risk

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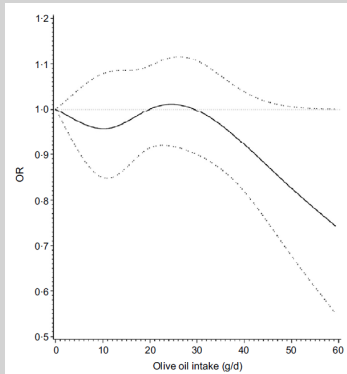


Fig. 5. Dose-response relationship between olive oil intake and breast cancer.

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>
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

1. Sealy N, Hankinson SE, Houghton SC. Olive oil and risk of breast cancer: a systematic review and dose-response meta-analysis of observational studies. Br J Nutr. 2021 May 28;125(10):1148-1156.

## Prevention by Modifying Lifestyle Risk Factors: Alcohol

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

1. Poorolajal J, Heidarimoghis F, Karami M et al. Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies. J Res Health Sci. 2021 Jul 20;21(3):e00520.
2. Rainey L , Eriksson M , Trinh T et al. The impact of alcohol consumption and physical activity on breast cancer: The role of breast cancer risk. Int. J. Cancer: 147, 931–939 (2020)
3. Zhang YB, Pan XF, Chen J, et al. Combined lifestyle factors, incident cancer, and cancer mortality: a systematic review and meta-analysis of prospective cohort studies. Br J Cancer. 2020 Mar;122(7):1085-1093.
4. Sun Q, Xie W, Wang Y, et al. Alcohol Consumption by Beverage Type and Risk of Breast Cancer: A Dose-Response Meta-Analysis of Prospective Cohort Studies. Alcohol Alcohol. 2020 Apr 16;55(3):246-253.
5. 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.
6. 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 ( $\geq 30$  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

## 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. Poorolajal J, Heidarimoghis F, Karami M, et al. Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies. J Res Health Sci. 2021 Jul 20;21(3):e00520. doi: 10.34172/jrhs.2021.57
2. Zhang YB, Pan XF, Chen J, et al. Combined lifestyle factors, incident cancer, and cancer mortality: a systematic review and meta-analysis of prospective cohort studies. Br J Cancer. 2020 Mar;122(7):1085-1093. doi: 10.1038/s41416-020-0741-x. Epub 2020 Feb 10
3. 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.
4. Macacu A, Autier P, Boniol M, et al. Active and passive smoking and risk of breast cancer: a meta-analysis. Breast Cancer Res Treat. 2015 Nov;154(2):213-24. doi: 10.1007/s10549-015-3628-4. Epub 2015 Nov 6.



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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).**

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.

## 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.

### Physical activity

1. Poorolajal J, Heidarimoghis F, Karami M, et al. Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies. *J Res Health Sci.* 2021 Jul 20;21(3):e00520.
2. Orange ST, Hicks KM, Saxton JM.: Effectiveness of diet and physical activity interventions amongst adults attending colorectal and breast cancer screening: a systematic review and meta-analysis. *Cancer Causes Control.* 2021 Jan;32(1):13-26.
3. Kerr J, Anderson C, Lippman SM. Physical activity, sedentary behavior, diet and cancer: an update and emerging new evidence. *Lancet Oncol.* 2017 Aug;18(8):e457-e471.
4. Boyne DJ, O'Sullivan DE, Olij BF et al. Physical Activity, Global DNA Methylation, and Breast Cancer Risk: A Systematic Literature Review and Meta-analysis. *Cancer Epidemiol Biomarkers Prev.* 2018 Nov;27(11):1320-1331.
5. Neilson HK, Farris MS, Stone CR et al. Moderate-vigorous recreational physical activity and breast cancer risk, stratified by menopause status: a systematic review and meta-analysis. *Menopause.* 2017 Mar;24(3):322-344.

### Physical activity in the interval between menarche and first pregnancy

1. Lin D, Liu Y, Tobias DK, Sturgeon K. Physical activity from menarche-to-first pregnancy and risk of breast cancer: the California teachers study. *Cancer Causes Control.* 2022 Nov;33(11):1343-1353. doi: 10.1007/s10552-022-01617-3. Epub 2022 Aug 20. PMID:

35987978.

All these effects are valid also for women with germline BRCA1/2 mutation and hereditary risk for breast cancer



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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 = 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**

1. Kehm RD et al.: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 Cancer Res. 2020 Jan 1;80(1):116-125.

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


### ■ 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	+/-

1. Poorolajal J, Heidarimoghis F, Karami M: Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies. *J Res Health Sci.* 2021 Jul 20;21(3):e00520. doi: 10.34172/jrhs.2021.57.
2. Saeai N, Peeyananjarassri K, Liabsuetrakul T, et al. Hormone replacement therapy after surgery for epithelial ovarian cancer. *Cochrane Database Syst Rev.* 2020 Jan 28;1(1):CD012559. doi: 10.1002/14651858.CD012559.pub2
3. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *Lancet.* 2019 Sep 28;394(10204):1159-1168. doi: 10.1016/S0140-6736(19)31709-X. Epub 2019 Aug 29.
4. Chlebowski RT, Aragaki AK, Anderson GL. Menopausal Hormone Therapy Influence on Breast Cancer Outcomes in the Women's Health Initiative. *J Natl Compr Canc Netw.* 2015 Jul;13(7):917-24.
5. Salagame U, Banks E, Sitas F et al. Menopausal hormone therapy use and breast cancer risk in Australia: Findings from the New South Wales Cancer, Lifestyle and Evaluation of Risk study. *Int J Cancer.* 2016 Apr 15;138(8):1905-14.
6. Manson JE, Aragaki AK, Rossouw JE et al. Menopausal hormone therapy and long-term all-cause and cause-specific mortality, the women's health initiative randomized trials. *JAMA* 2017; 318: 927-938.



**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: 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 x 10<sup>-12</sup>) in EPIC-Italy. 694 CpG sites were associated with ELEE (FDR Q < 0.05)**

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1. Johansson A et al. Epigenome-Wide Association Study for Lifetime Estrogen Exposure Identifies an Epigenetic Signature Associated with Breast Cancer Risk. Clin Epigenetics 2019; Apr 30;11(1):66.



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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 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. Tibolone 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

1. Chlebowski RT, Aragaki AK, Anderson GL. Menopausal Hormone Therapy Influence on Breast Cancer Outcomes in the Women's Health Initiative. J Natl Compr Canc Netw. 2015 Jul;13(7):917-24.
2. Manson JE, Aragaki AK, Rossouw JE et al. Menopausal hormone therapy and long-term all-cause and cause-specific mortality, the women's health initiative randomized trials. JAMA 2017; 318: 927-938.



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## 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
<b>Case-Control-Study, retrospect. Australia</b>		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

1. Salagame U, Banks E, Sitas F et al. Menopausal hormone therapy use and breast cancer risk in Australia: Findings from the New South Wales Cancer, Lifestyle and Evaluation of Risk study. Int J Cancer. 2016 Apr 15;138(8):1905-14.

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

	Oxford
<ul style="list-style-type: none"> <li>▪ <b>OC does <u>not</u> increase the risk of mortality from breast cancer</b></li> <li>▪ <b><u>Risk</u> of breast cancer slightly increased, risk of ovarian, endometrial cancer is decreased</b></li> </ul>	<p><b>LoE</b></p> <p><b>1a</b></p> <p><b>1a<sup>(-)</sup></b></p>

1. Baranska,A.Oral Contraceptive Use and Assessment of Breast Cancer Risk among Premenopausal Women via Molecular Characteristics: Systematic Review with Meta-Analysis. Int. J. Environ. Res. Public Health 2022, 19, 15363.
2. Kanadys W, Barańska A, Malm M, et al. Use of Oral Contraceptives as a Potential Risk Factor for Breast Cancer: A Systematic Review and Meta-Analysis of Case-Control Studies Up to 2010. Int J Environ Res Public Health. 2021 Apr 27;18(9):4638. doi: 10.3390/ijerph18094638.
3. Nur U,El Reda D, Hashim D, Weiderpass E. A prospective investigation of oral contraceptive use and breast cancer mortality: findings from the Swedish women ´s lifestyle and health cohort. BMC Cancer 2019, 19:807
4. Gierisch JM, Coeytaux RR, Urrutia RP et al. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. Cancer Epidemiol Biomarkers Prev. 2013 Nov;22(11):1931-43.
5. 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.

## 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	GR	AGO
▪ Tamoxifen	1a	A	+
▪ Aromatase inhibitors	1a	A	+
▪ Suppression of ovarian function + Tamoxifen	1b	B	+

### Tamoxifen (HR<sub>total</sub>=0.71; HR<sub>ER+</sub>=0.62)


1. Early Breast Cancer Trialists' Collaborative G. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365(9472):1687-717.

### Aromatase inhibitors (HR=0.62 vs Tam)

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.
2. Early Breast Cancer Trialists' Collaborative G, Dowsett M, Forbes JF, et al. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet*. 2015;386(10001):1341-52.

### GnRH-agonists + Tamoxifen (HR=0.56 vs Tam)

1. Bui KT, Willson ML, Goel S, Beith J, Goodwin A. Ovarian suppression for adjuvant treatment of hormone receptor-positive early breast cancer. *Cochrane Database Syst Rev*. 2020 Mar 6;3(3):CD013538.

 <b>Risk Reduction for Ipsi- and Contralateral Second Breast Cancers (“Second Primaries”)</b>					
	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	-	

Tamoxifen (HR<sub>total</sub>=0.71; HR<sub>ER+</sub>=0.61)

1. Early Breast Cancer Trialists' Collaborative G. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365(9472):1687-717.

Aromatase inhibitors (HR=0.62 vs Tam)

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.
2. Early Breast Cancer Trialists' Collaborative G, Dowsett M, Forbes JF, et al. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015;386(10001):1341-52.

GnRHa + Tamoxifen (HR=0.56 vs Tam)

1. Bui KT, Willson ML, Goel S, Beith J, Goodwin A. Ovarian suppression for adjuvant treatment of hormone receptor-positive early breast cancer. Cochrane Database Syst Rev. 2020 Mar 6;3(3):CD013538.