Guidelines Breast
Version 2024.1E

FORSCHEN
LEHREN
HEILEN

Options for Primary Prevention: Modifiable Lifestyle Factors

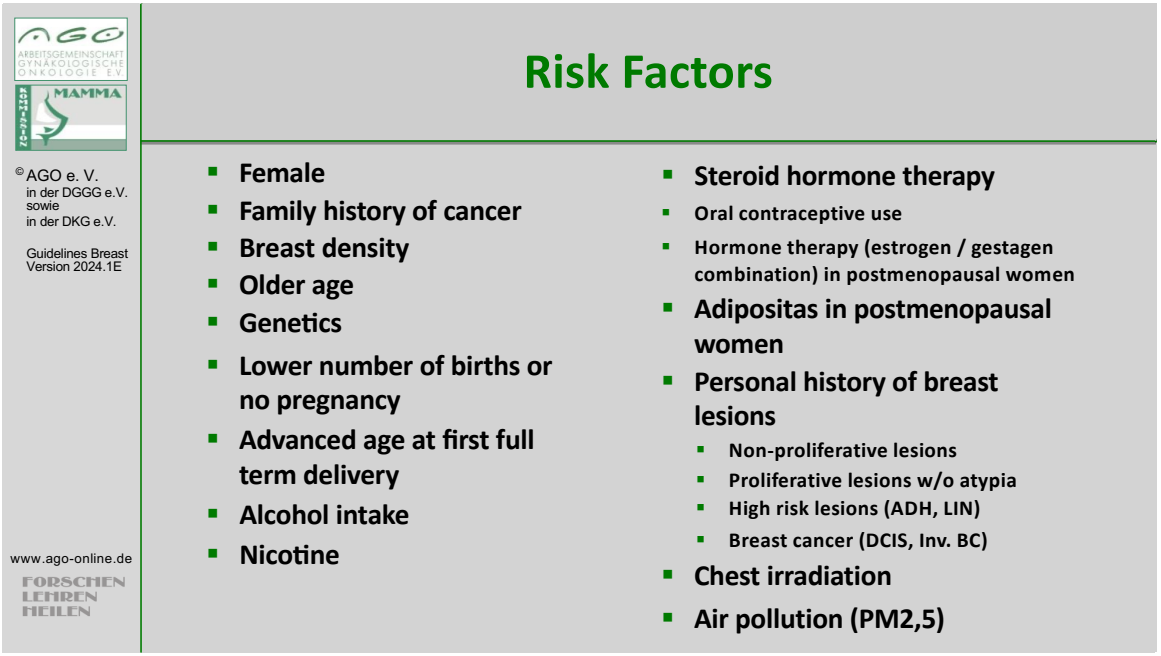
Guidelines Breast
Version 2024.1E

Prevention

- **Versions 2011–2023:**
  Albert / Dall / Diel / Gerber / Hanf / Maass / Mundhenke / Rhiem / Solbach / Solomayer / Thomssen / von Minckwitz / Albert
- **Version 2024:**
  Fasching / Solomayer

Screened data bases

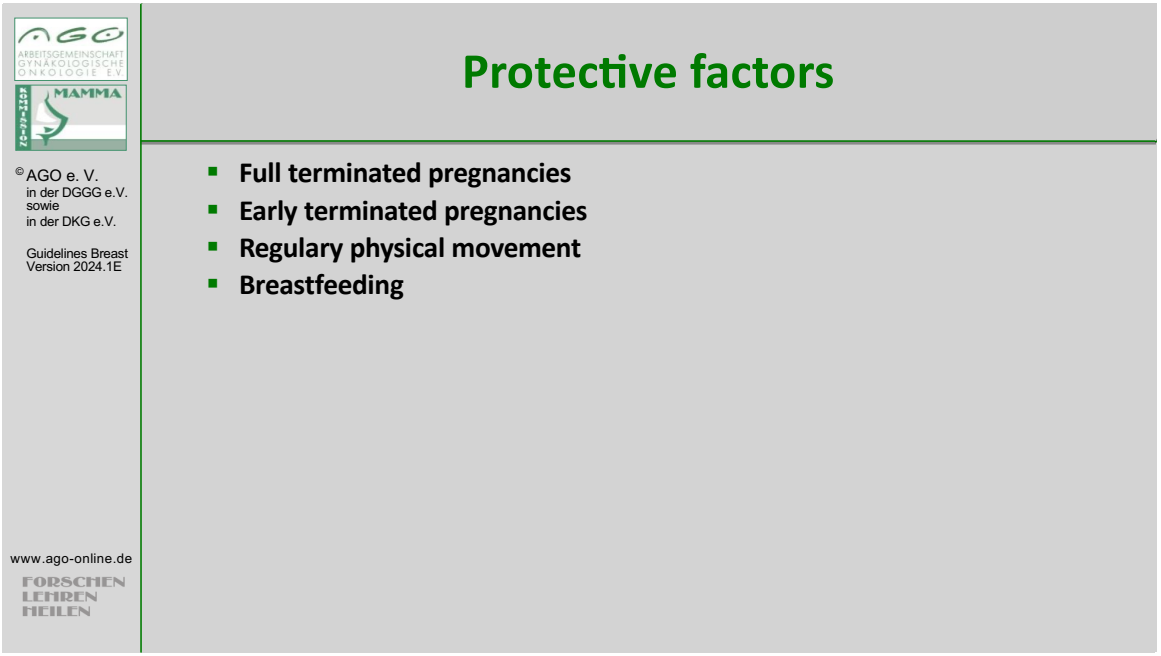
Pubmed 2012 – 2023, ASCO 2012 – 2023, SABCS 2012 – 2023, Cochrane data base 2023



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.

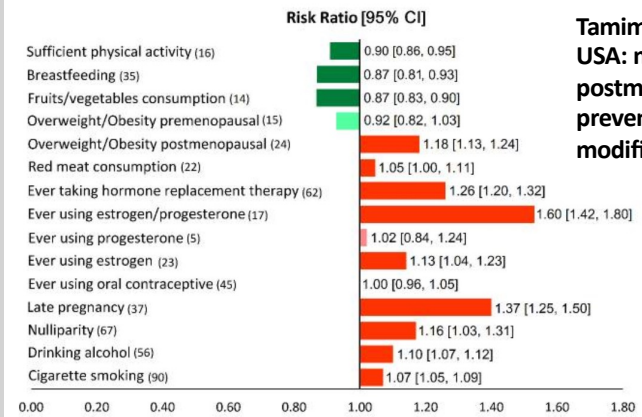


1. Li C, Fan Z, Lin X, et al. Parity and risk of developing breast cancer according to tumor subtype: A systematic review and meta-analysis. Cancer Epidemiol. 2021 Dec;75:102050. doi: 10.1016/j.canep.2021.102050. Epub 2021 Oct 24
2. Coombes,R.C., Tovey, H, Kilburn, L: Effect of Celecoxib vs Placebo as 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



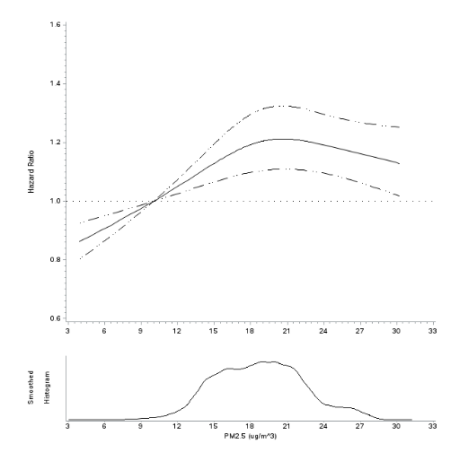
Tamimi et al, 2016
USA: more than a third of postmenopausal breast cancers are preventable through changes in modifiable risk factors

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

Guidelines Breast
Version 2024.1E



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^3 increase in PM2.5 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 et al. JNCI 2023; DOI: https://doi.org/10.1093/jnci/djad170

1. White et al.: Ambient fine particulate matter and breast cancer JNCI 2023; DOI: https://doi.org/10.1093/jnci/djad170

Pregnancy Related Factors

List of factors that are still being clarified

Prevention	Oxford LoE	Oxford GR
▪ Any full-term pregnancy	2b	B
▪ High number of pregnancies	2b	B
▪ Young age at first full-term pregnancy	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

Hohe Zahl voll ausgetragener Schwangerschaften, hohe Anzahl der Schwangerschaften, erste ausgetragene Schwangerschaft ≤ 30 Jahre

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.

Stillen (schützt, wenn Gesamtstilldauer 1,5–2 Jahre)

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.

Geringeres Geburtsgewicht des Erstgeborenen (3000–3500 g vs. > 4500 g, RR = 1,53), geringere Schwangerschaftsdauer

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.

Syndrom der Polyzystischen Ovarien (PCO-Syndrom)

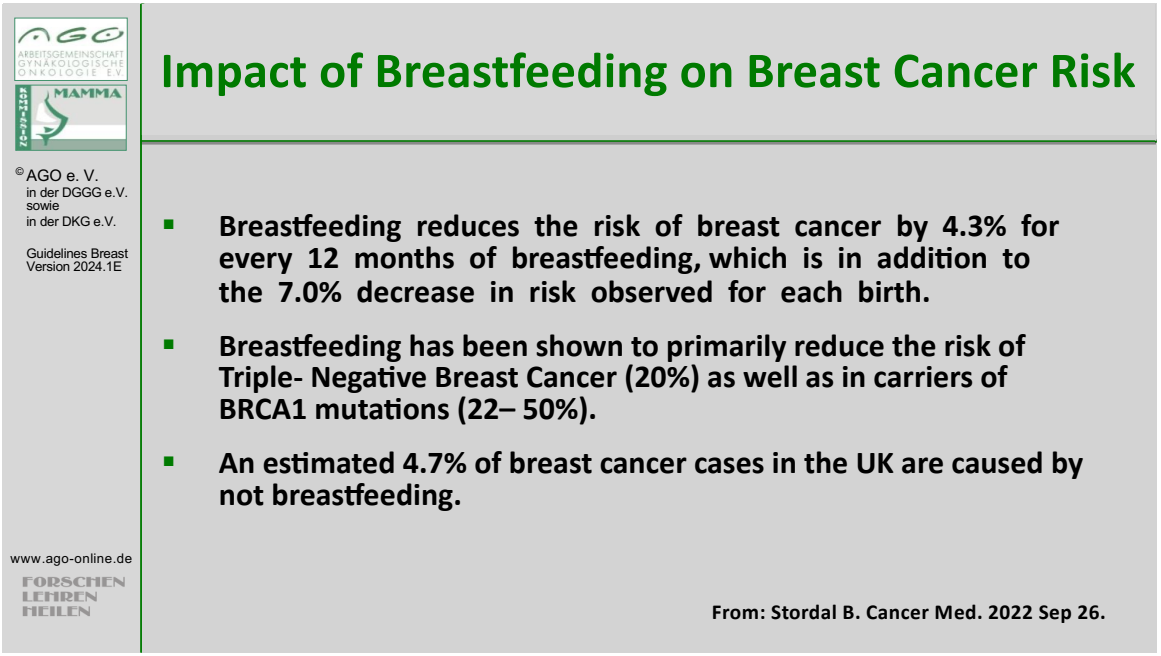
1. Li Z, Wang YH, Wang Llet al. Polycystic ovary syndrome and the risk of endometrial, ovarian and breast cancer: An updated meta-analysis. Scott Med J. 2022 Aug;67(3):109-120.
2. Ding DC, Chen W, Wang JH et al. Association between polycystic ovarian syndrome and endometrial, ovarian, and breast cancer: 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.

Assistierte Reproduktion

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.

Schwangerschaftsabbruch

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.



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.

Medical endocrine Prevention for Women at Increased Risk

Guidelines Breast
Version 2024.1E

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

	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 #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.

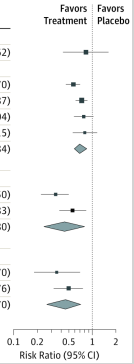
1. Cuzick J, Sestak I, Cawthorn S, et al. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. Lancet Oncol. 2015;16(1):67-75.
2. Cuzick J, Sestak I, Forbes JF, et al. Use of anastrozole for breast cancer prevention (IBIS-II): long-term 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.

Medical Endocrine Prevention

Guidelines Breast
Version 2024.1E

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

Source	Trial	Mean, y: Intended Treatment Duration	Mean, y: Total Follow-up	No. With Invasive Breast Cancer/Total Participants (%): Treatment	No. With Invasive Breast Cancer/Total Participants (%): Placebo	Rate per 1000 Women-Years: Treatment	Rate per 1000 Women-Years: Placebo	Risk Ratio (95% CI)
Tamoxifen, low dose								
DeCensi et al,[41] 2013	HOT	5	6.2	18/938 (1.9)	22/946 (2.3)	3.13	3.78	0.83 (0.42-1.62)
Tamoxifen								
Fisher et al,[82] 2005	NSABP-1	5	6.1	145/6681 (2.2)	250/6707 (3.7)	3.59	6.29	0.57 (0.46-0.70)
Cuzick et al,[74] 2015	IBIS-I	5	16.0	214/3579 (6.0)	289/3575 (8.1)	3.86	5.29	0.73 (0.61-0.87)
Powles et al,[83] 2007	Marsden	5	13.2	82/1238 (6.6)	104/1233 (8.4)	4.80	6.10	0.78 (0.58-1.04)
Veronesi et al,[84] 2007	Italian	4[a]	11.2	53/2700 (2.0)	66/2708 (2.4)	1.77	2.21	0.80 (0.56-1.15)
Combined								0.69 (0.59-0.84)
I^2 = 38.7%; Q = 4.9 for heterogeneity; P = .18								
Raloxifene								
Martino et al,[45] 2004	MORE/CORE	4 or 8[b]	5.4[b]	40/5129 (0.8)	58/2576 (2.3)	1.40	4.20	0.34 (0.22-0.50)
Barrett-Connor et al,[48] 2006	RUTH	5.1[a]	5.6	40/5044 (0.8)	70/5057 (1.4)	1.43	2.49	0.56 (0.38-0.83)
Combined								0.44 (0.24-0.80)
I^2 = 66.4%; Q = 3.0 for heterogeneity; P = .08								
Aromatase inhibitor								
Goss et al,[44] 2011	MAP.3	5[c]	2.9	11/2285 (0.5)	32/2275 (1.4)	1.66	4.85	0.35 (0.18-0.70)
Cuzick et al,[4] 2014	IBIS-II	5	5	32/1920 (1.7)	64/1944 (3.3)	3.29	6.62	0.50 (0.32-0.76)
Combined								0.45 (0.26-0.70)
I^2 = 0.0%; Q = 0.8 for heterogeneity; P = .39								



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

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*

	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

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.

Bisphosphanates

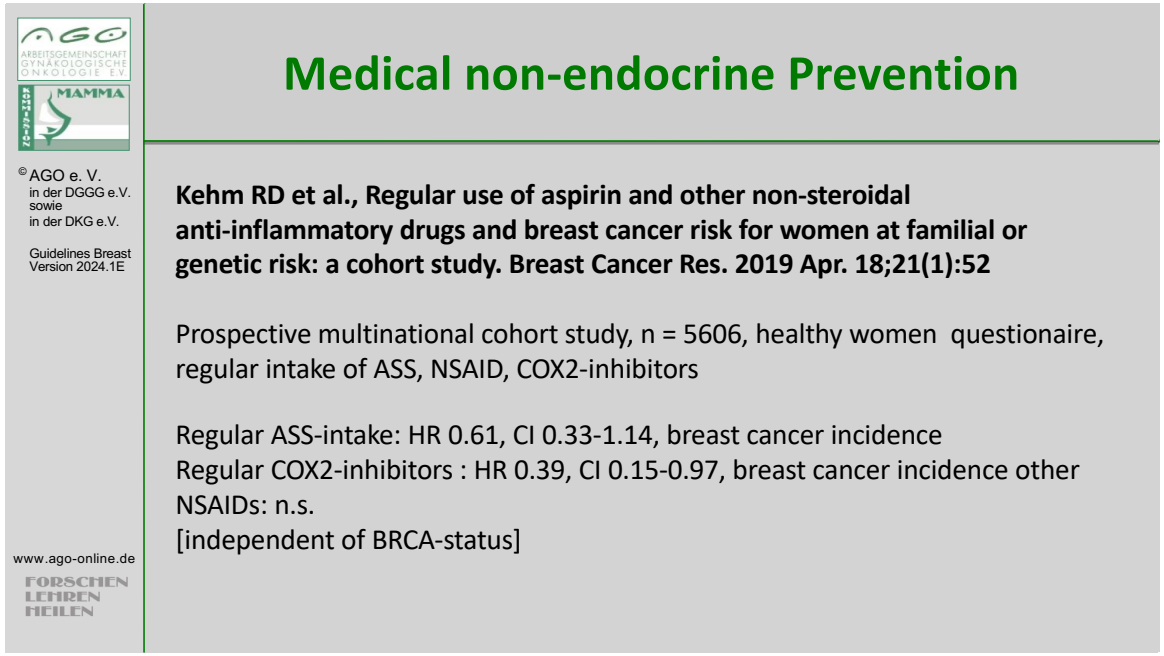
1. Peng R, Liang X, Zhang G et al. Association Use of Bisphosphonates with Risk of Breast Cancer: A Meta-Analysis. BioMed Research International Volume 2020, Article ID 5606573, 13 pages https://doi.org/10.1155/2020/5606573

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



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
▪ **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

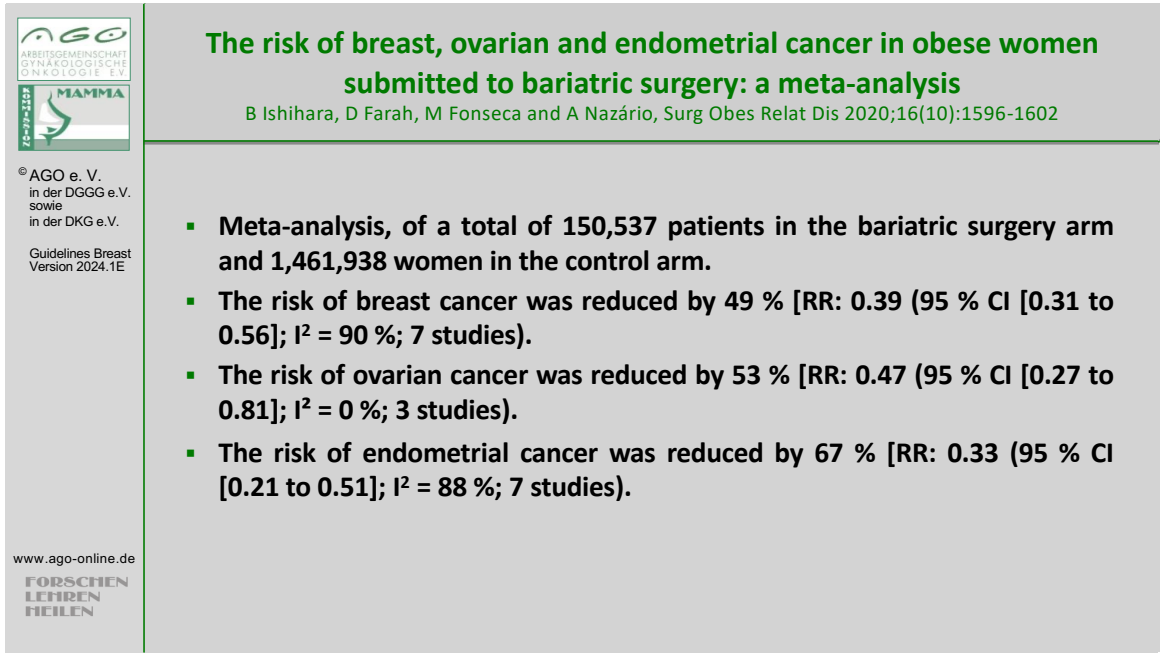
Maintaining normal weight

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

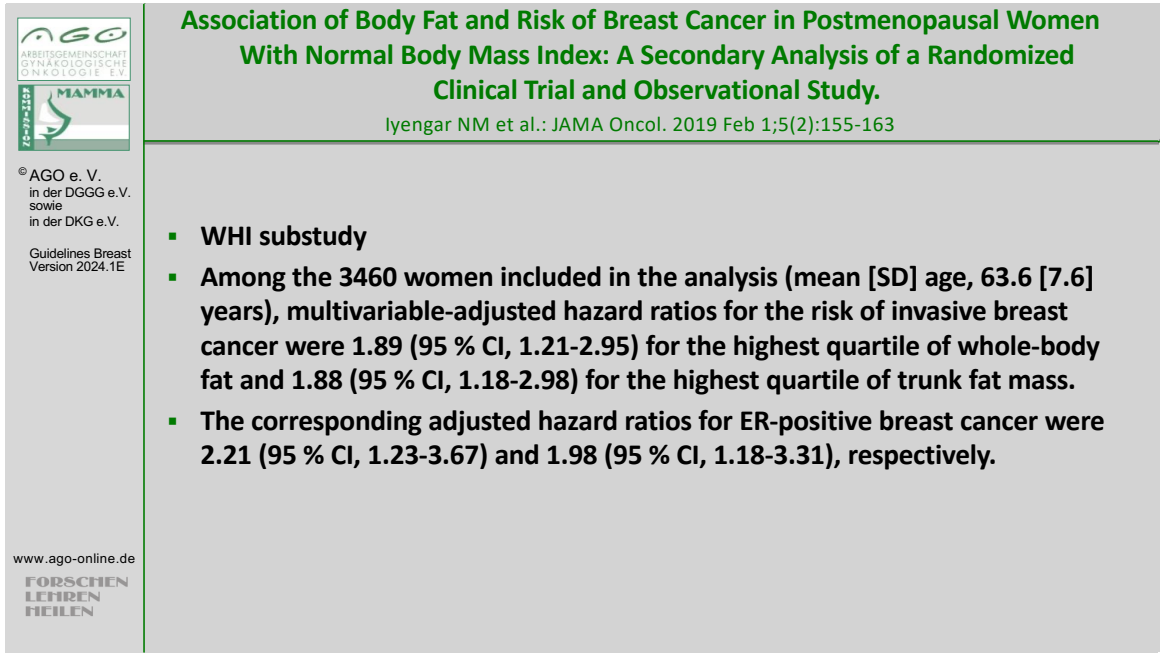
Typ II Diabetes

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



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.



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

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

	Oxford LoE	Oxford 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	-

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. Llaha F, Gil-Lespinard 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, SharmaD. 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.
2. Toledo, E.; Salas-Salvado, J.; Donat-Vargas, C. et al. Mediterranean diet and invasive breast cancer risk among women at high cardiovascular risk in the PREDIMED trial: A randomized clinical trial. JAMA Intern. Med. 2015, 175, 1752–1760.

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-respond 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 meet

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.

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
2. Marc P. McRae. The Benefits of Dietary Fiber Intake on Reducing the Risk of Cancer: An Umbrella Review of Meta-analyses. Nutr J. 2018 Sep 21;17(1):87. doi: 10.1186/s12937-018-0394-2.

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
2. Jiang X, Dimou NL, Al-Dabhani K et al. Circulating vitamin D concentrations and risk of breast and prostate cancer: a Mendelian randomization study. N Engl J Med. 2019 Jan 3;380(1):33-44.
3. Manson JE, Cook NR, Lee IM et al; VITAL Research Group. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. Int J Epidemiol. 2018 Nov 8. doi: 10.1093/ije/dyy238. [Epub ahead of print]

Vegetables / fruits

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

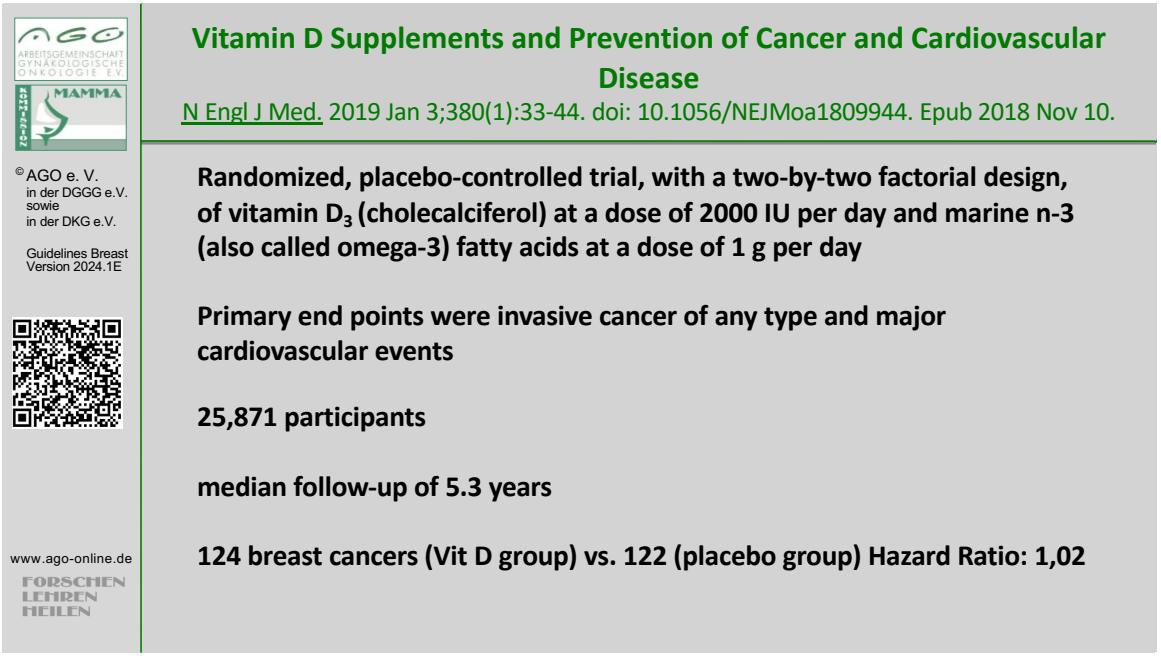
2. Chang-Claude J, Herman S, Eiber U, et al. Lifestyle Determinants and Mortality in German Vegetarians and Health-Conscious Persons: Results of a 21-Year Follow-up. Epidemiol Biomarker Prev 2005; 14(4)963-8

Coffee

1. Wang S, Li X, Yang Y, et al. Does Coffee, tea and caffein consumption reduce the risk of incident breast cancer risk? A systemativ 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.
3. Gapstur SM, Gaudet MM, Wang Y et al. Coffee Consumption and Invasive Breast Cancer Incidence among Postmenopausal Women in the Cancer Prevention Study-II Nutrition Cohort. Cancer Epidemiol Biomarkers Prev. 2020 Nov;29(11):2383-2386. doi: 10.1158/1055-9965.EPI-20-1051. Epub 2020 Aug 14. PMID: 32817071.
4. Poole R, Kennedy OJ, Roderick P et al. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. BMJ 2017 Nov 22;359:j5024. doi: 10.1136/bmj.j5024.
5. Grosso G, Godos J, Galvano F et al. Coffee, Caffeine, and Health Outcomes: An Umbrella Review. Annu Rev Nutr. 2017 Aug 21;37:131-156. doi: 10.1146/annurev-nutr-071816-064941.
6. Li XJ, Ren ZJ, Qin JW, et al. Coffee consumption and risk of breast cancer: an up-to-date meta-analysis. PLoS One2013;8:e52681 doi:10.1371/journal.pone.0052681

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.



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

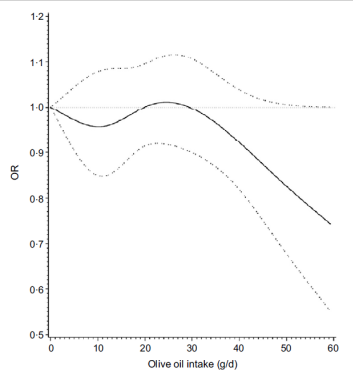


Fig. 5. Dose–response relationship between olive oil intake and breast cancer.

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.**

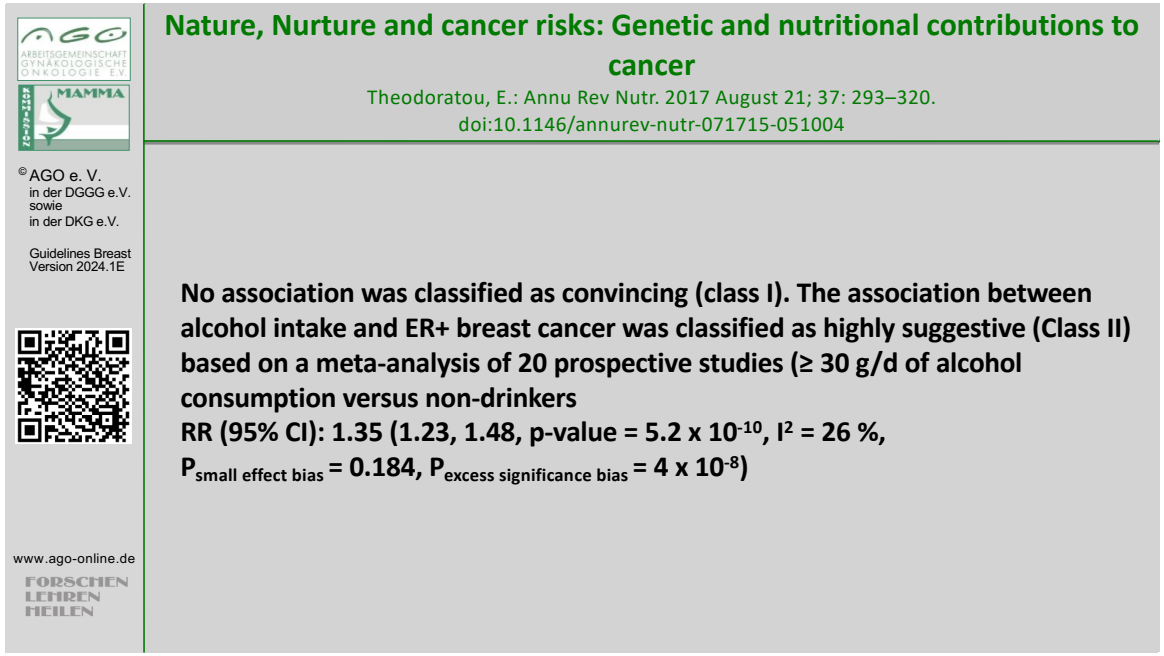
Sealy N et al. British Journal of Nutrition (2021), 125, 1148–1156

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
▪ **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	

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.



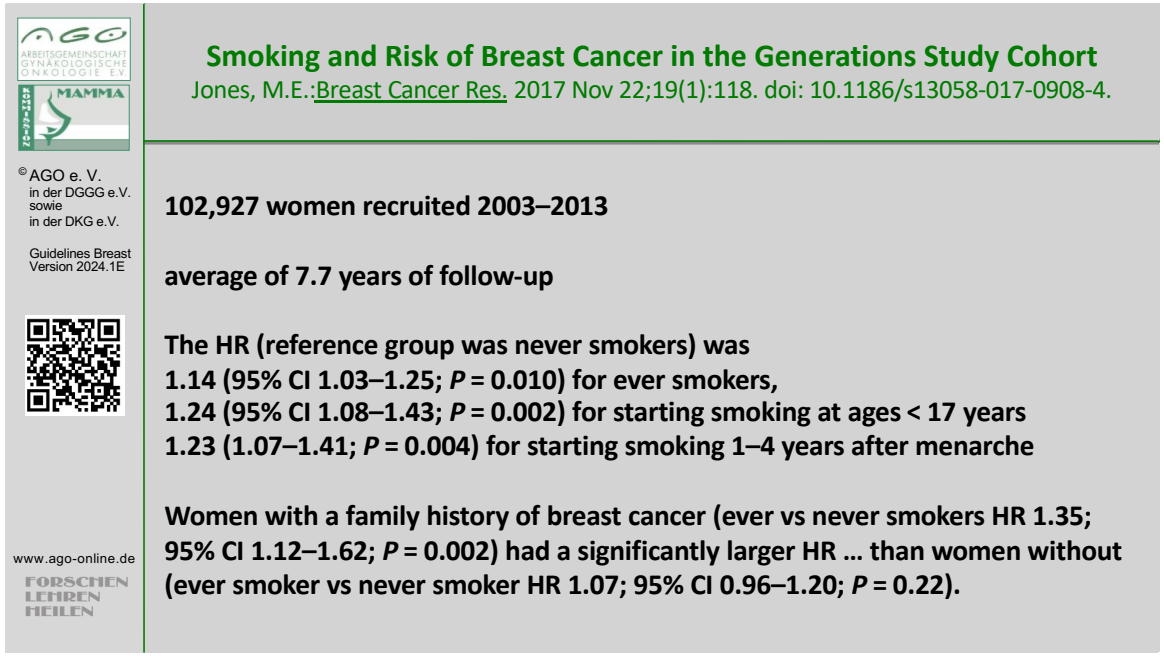
Theodoratou, E. Nature, Nurture and cancer risks: Genetic and nutritional contributions to cancer. Annu Rev Nutr. 2017 August 21; 37: 293–320. doi:10.1146/annurev-nutr-071715-051004

Prevention by Modifying Lifestyle Risk Factors: Smoking

	Oxford		
	LoE	GR	AGO
▪ **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)**

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.



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
▪ **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.

Physical activity

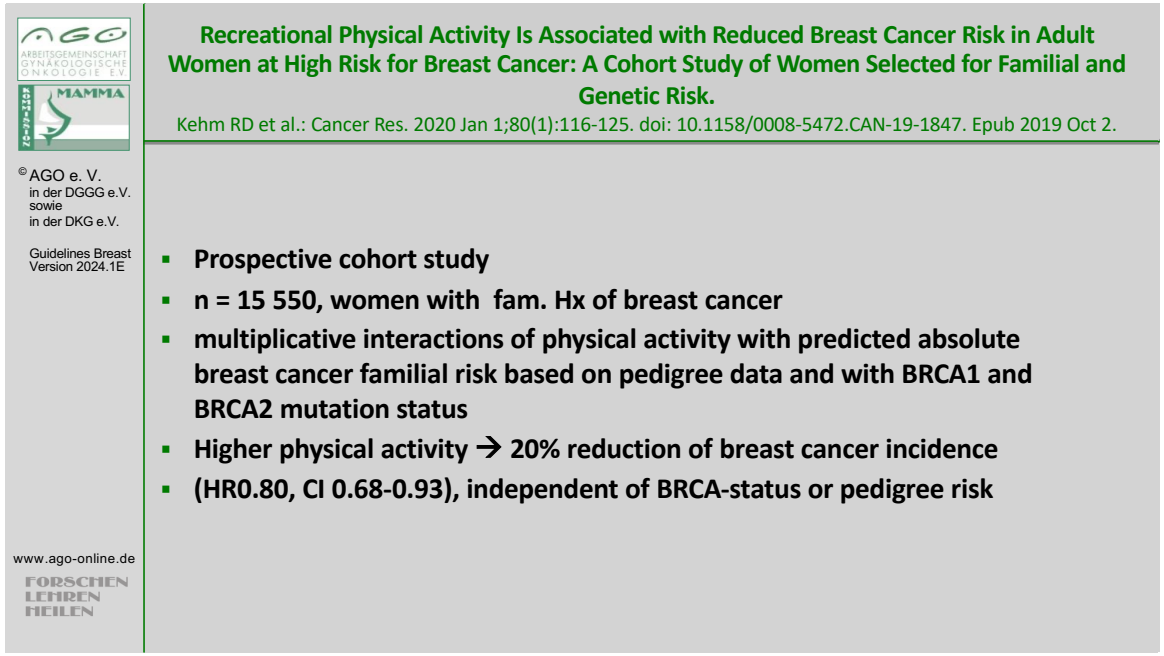
1. Poorolajal J, Heidarimoghis F, Karami M, et al. Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies. J Res Health Sci. 2021 Jul 20;21(3):e00520.
2. Orange ST, Hicks KM, Saxton JM.: Effectiveness of diet and physical activity interventions amongst adults 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.

Physiscal 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
Körperliche Aktivität



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.

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2024.1E

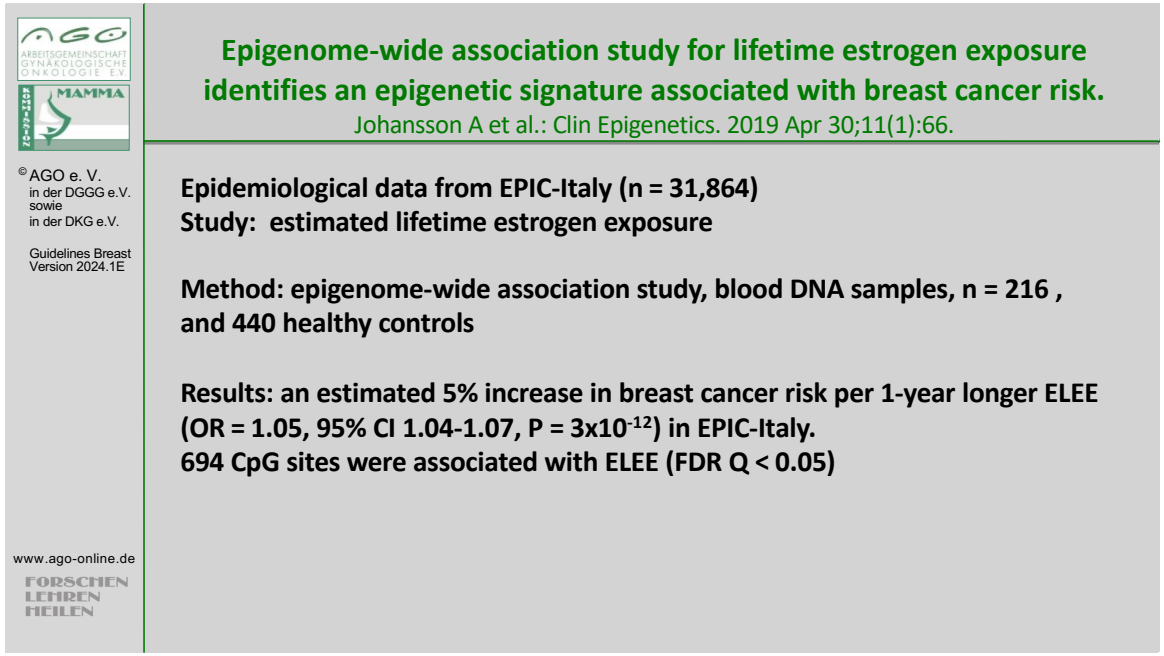
www.ago-online.de

FORSCHEN
LEHREN
HEILEN

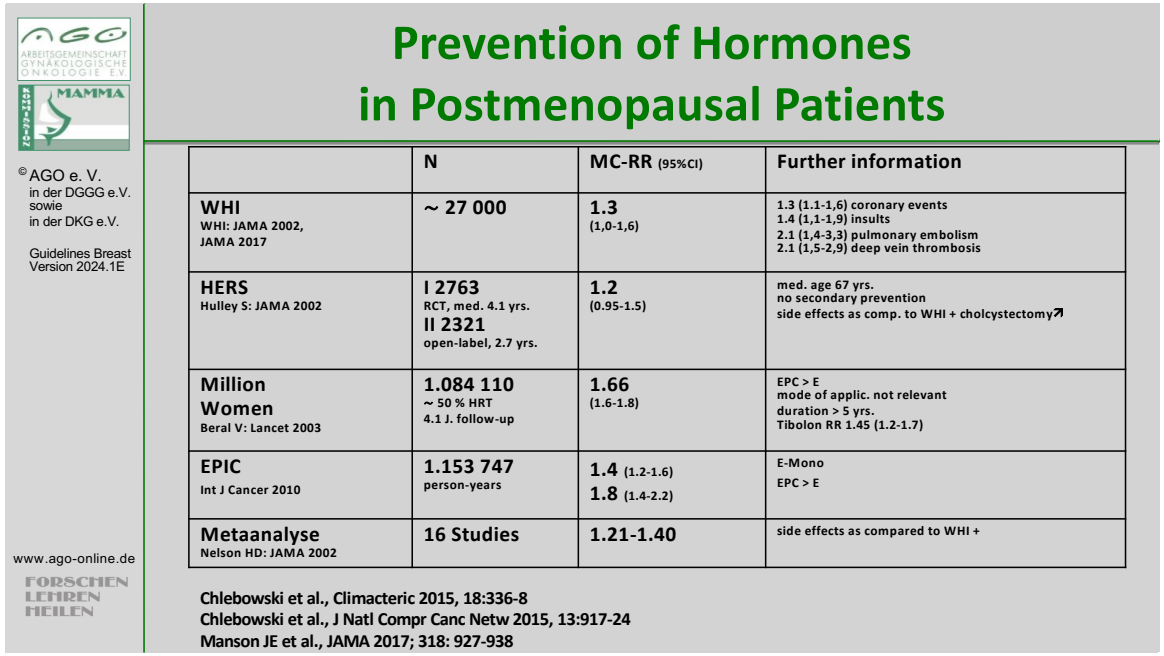
Prevention by Modifying Lifestyle Risk Factors: Hormone Therapy in Postmenopausal Women

	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	+/-

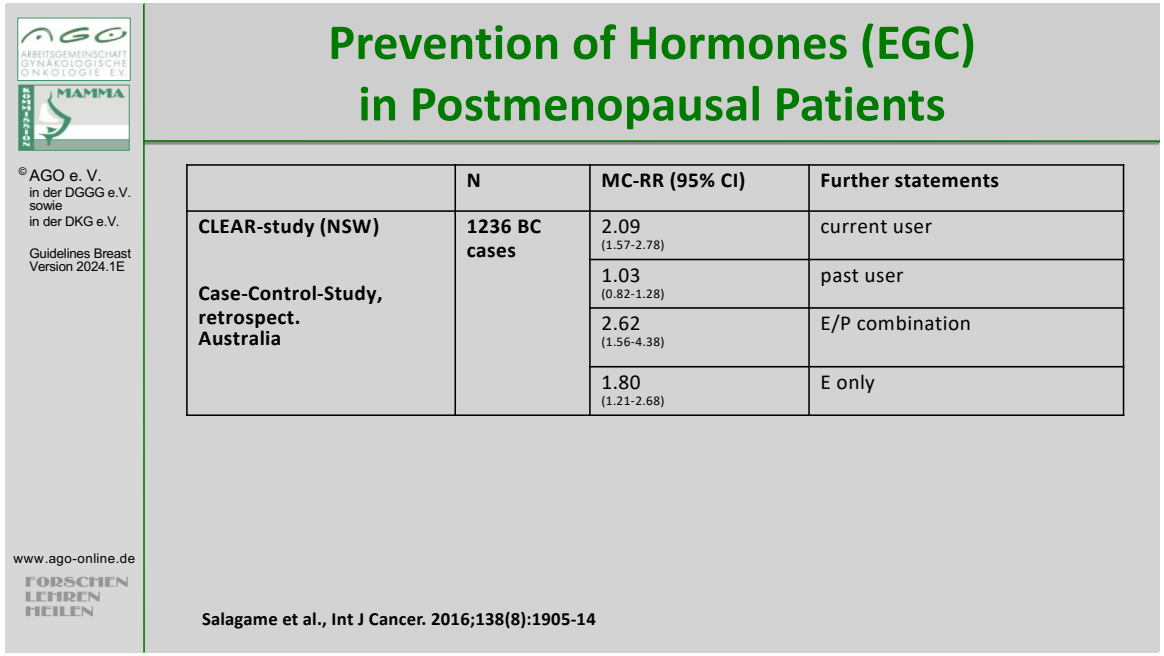
1. Poorolajal J, Heidarimoghis F, Karami M: Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies. J Res Health Sci. 2021 Jul 20;21(3):e00520. doi: 10.34172/jrhs.2021.57.
2. Saeaib N, Peeyananjarassri K, Liabsuetrakul T, er al. Hormone replacement therapy 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.



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.



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.



Prevention of Hormones (EGC) in Postmenopausal Patients

	N	MC-RR (95% CI)	Further statements
CLEAR-study (NSW)	**1236 BC cases**	2.09 (1.57-2.78)	current user
Case-Control-Study, retrospect. Australia		1.03 (0.82-1.28)	past user
		2.62 (1.56-4.38)	E/P combination
		1.80 (1.21-2.68)	E only

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

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 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(-)**

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

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

Tamoxifen (HR_{total}=0.71; HR_{ER+}=0.62)

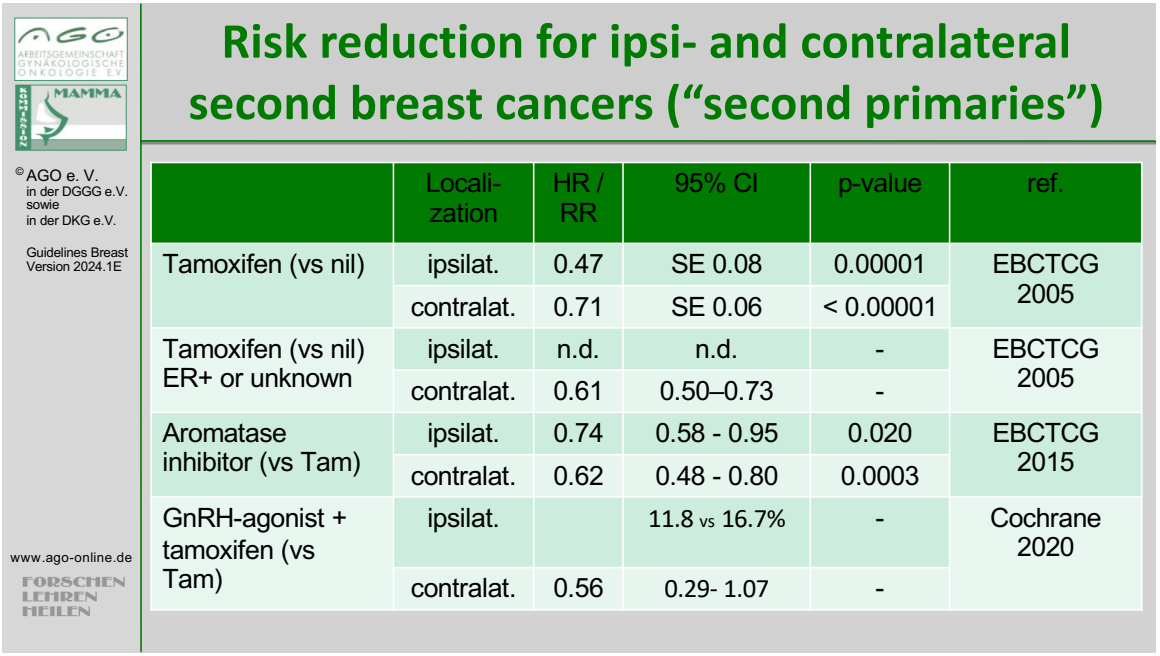
1. Early Breast Cancer Trialists' Collaborative G. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365(9472):1687-717.

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.



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

	Localization	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_{total}=0.71; HR_{ER+}=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.