



® ADO e. V.  
in der DGGG e. V.  
in der DGBC e. V.  
Guidelines Breast  
Version 2021.1

STÄNDIGER  
LEBENS  
STIL

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

## Options for Primary Prevention: Modifiable Lifestyle Factors



## Prevention

- **Versions 2011–2020:**  
Dall / Diel / Gerber / Hanf / Maass / Mundhenke / Solbach / Solomayer / Thomssen / von Minckwitz
- **Version 2021:**  
Rhiem / Solomayer

### Screened data bases

Pubmed 2005 – 2020, ASCO 2012 – 2020, SABCS 2012 – 2020, Cochrane data base 2020



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.



Oct 6.

10. Gray JM, Rasanayagam S, Engel C et al. State of the evidence 2017: an update on the connection between breast cancer and the environment. *Environ Health*. 2017 Sep 2;16(1):94. doi: 10.1186/s12940-017-0287-4.
11. James P, Bertrand KA, Hart JE et al. Outdoor Light at Night and Breast Cancer Incidence in the Nurses' Health Study II. *Environ Health Perspect*. 2017 Aug 17;125(8):087010. doi: 10.1289/EHP935.
12. Lin X, Chen W, Wie F et al. Night-shift work increases morbidity of breast cancer and all-cause mortality: a meta-analysis of 16 prospective cohort studies. *Sleep Med*. 2015 Nov;16(11):1381-1387. doi: 10.1016/j.sleep.2015.02.543. Epub 2015 May 11.
13. Parida S, Sharma D. Microbial Alterations and Risk Factors of Breast Cancer: Connections and Mechanistic Insights. *Cells* 2020, 9, 1091; doi:10.3390/cells9051091
14. 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. PMID: 31474332; PMCID: PMC6891893.
15. 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.
16. 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.
17. 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.

© ADO e.V.  
 in der DGGG e.V.  
 sowie  
 in der DGG e.V.  
 Guidelines Breast  
 Version 2021.1

www.ago-online.de  
 8 750 000 000 000  
 8 750 000 000 000  
 8 750 000 000 000

## Deodorant-use and risk

Breast Cancer and Deodorants/Antiperspirants: a Systematic Review.

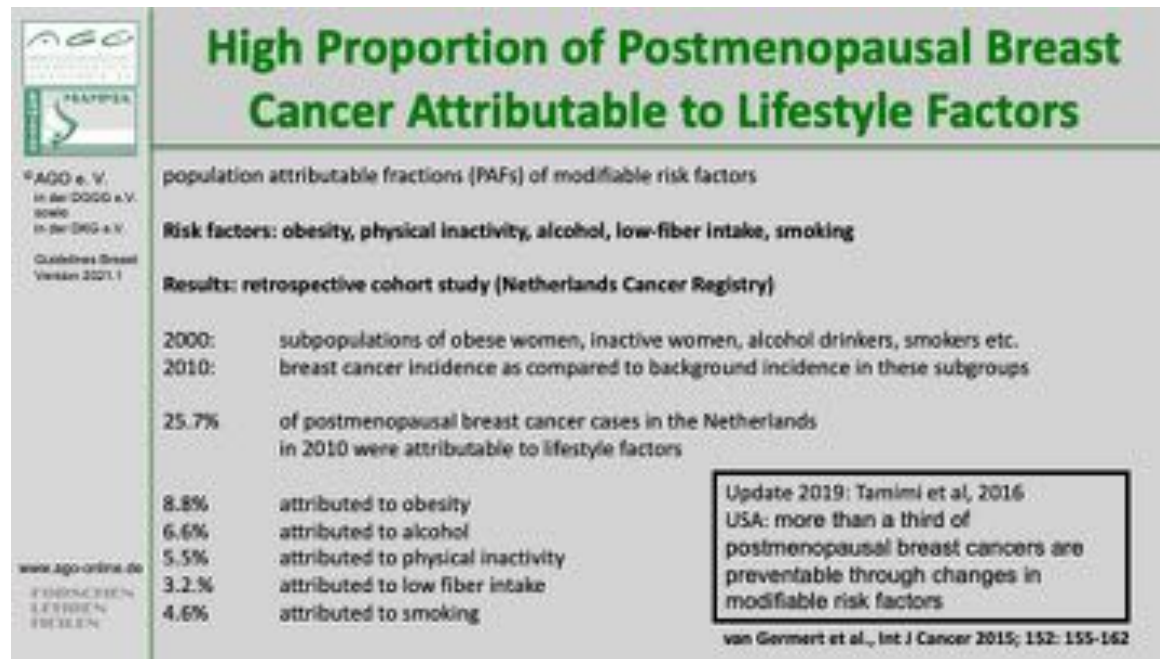
Allam MF<sup>1</sup>: Cent Eur J Public Health. 2016 Sep;24(3):245-247. doi: 10.21101/cejph.a4475.

---

**So far there is no evidence of a correlation between aluminum containing deodorants and breast cancer risk**

- All observational studies that evaluated the association between breast cancer risk and deodorants/antiperspirants use were reviewed. We have only identified two case-control studies, carried out between 2002 and 2006.
- There was no risk of antiperspirants use in the pooled risk (odds ratio 0.40, 95% confidence interval 0.35-0.46).
- Our comprehensive search has identified an insufficient number of studies to conduct a quantitative review and obtain reliable results. Further prospective studies are strongly needed.

1. Allam MF. Breast Cancer and Deodorants/Antiperspirants: a Systematic Review.Cent Eur J Public Health. 2016 Sep;24(3):245-247. doi: 10.21101/cejph.a4475.



1. Van Germert, Lanting CI, Goldbohm RA et al.. The proportion of postmenopausal breast cancer cases in the Netherlands attributable to lifestyle-related risk factors. Breast Cancer Res Treat. 2015 Jul;152(1):155-162.
2. Tamini 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.



Pregnancy-Related Factors		
	Oxford	
	LoE	GR
<b>Prevention</b>		
• Any full term pregnancy	2b	B
• High number of pregnancies	2b	B
• First full term pregnancy before age of 30 years	2b	B
• Breast feeding (protective if total breast feeding time exceeds 1.5–2 years)	3a	B
• Lower birth weight of the first born (3000–3500 vs. > 4500g RR=1.53)	2b	B
• Lower duration of pregnancy first born (26–31. WGP vs. 40–41. WGP; HR=2.38, p=0.03)	2b	B
<b>No influence</b>		
• Polycystic Ovarian Syndrome PCO	3b	C
• Assisted reproduction	2b	B
• Abortion	2b	B

1. Li CI, Beaber EF, Tang MT et al.. Reproductive factors and risk of estrogen receptor positive, triple-negative, and HER2-neu overexpressing breast cancer among women 20–44 years of age. *Breast Cancer Res Treat.* 2013;137:579–87.
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. doi: 10.26355/eurrev\_201811\_16434.
3. 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. doi: 10.1186/s13058-018-1035-6.
4. 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. doi: 10.1097/MD.00000000000012608.
5. 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. doi: 10.1371/journal.pone.0201097. eCollection 2018.
6. 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.
7. 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.

## Medical Primary Prevention

	Oxford		
	LoE	GR	AGO
▪ ASS (especially for postmenopausal women with regard to DCIS and ER-positive invasive breast cancer)	4d	D	+/-
See slide 9			
▪ Bisphosphonates	2b	B	+/-
▪ Statins (no effect)	2b	B	-

1. Li CI, Beaber EF, Tang MT et al.: Reproductive factors and risk of estrogen receptor positive, triple-negative, and HER2-neu overexpressing breast cancer among women 20-44 years of age. *Breast Cancer Res Treat.* 2013;137:579-87.
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. doi: 10.26355/eurrev\_201811\_16434.
3. 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. doi: 10.1186/s13058-018-1035-6.
4. 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. doi: 10.1097/MD.00000000000012608.
5. 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. doi: 10.1371/journal.pone.0201097. eCollection 2018.
6. 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.
7. 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.



AGG e.V.  
in der DGGG e.V.  
in der DGO e.V.  
Guidelines Breast  
Version 2021.1

www.agg-online.de  
FACHGESAMTUNG  
STÄTTEN  
FACHLEITUNG

## Medical Prevention

**Kehm RD et al., Regular use of aspirin and other non-steroidal anti-inflammatory drugs and breast cancer risk for women at familial or Genetic risk: a cohort study, Breast Cancer Res. 2019 Apr. 18;21(1):52**

Prospective multinational cohort study, n=5606, healthy women questionnaire, regular intake of ASS, NSAID, COX2-inhibitors

Regular ASS-intake: HR 0.61, CI 0.33-1.14, breast cancer incidence

Regular COX2-inhibitors : HR 0.39, CI 0.15-0.97, breast cancer incidence other NSAIDs: n.s.

[independent of BRCA-status]

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

	Oxford
	LoE GR AGO
▪ Maintaining normal weight (BMI at 18.5 – 25 kg/m <sup>2</sup> )*	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

1. Cheraghi Z, Poorolajal J, Hashem T et al.. Effect of body mass index on breast cancer during premenopausal and postmenopausal periods: a meta-analysis. PLoS One. 2012;7(12):e51446.
2. Pierobon M, Frankenfeld CL. Obesity as a risk factor for triple-negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat. 2013 Jan;137(1):307-14.
3. Simpson ER, Brown KA. Obesity and breast cancer: role of inflammation and aromatase. J Mol Endocrinol. 2013 Nov 26;51(3):T51-9.
4. Brinton LA, Cook MB, McCormack V et al.. Anthropometric and hormonal risk factors for male breast cancer: male breast cancer pooling project results. J Natl Cancer Inst. 2014 Mar;106(3):djt46.
5. Chan DS, Vieira AR, Aune D et al. Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. Ann Oncol. 2014 Oct;25(10):1901-14.
6. Jiralerspong S, Goodwin PJ. Obesity and Breast Cancer Prognosis: Evidence, Challenges, and Opportunities JCO 2016, 34:4203-4216.
7. Penniecook-Sawyers JA, Jaceldo-Siegl K, Fan J et al. Vegetarian dietary patterns and the risk of breast cancer in a low-risk population, Br J Nutr. 2016; 115(10): 1790-1797.
8. Pizot C, Boniol M, Mullie P et al. Physical activity, hormone replacement therapy and breast cancer risk: A meta-analysis of prospective studies, Eur J Cancer. 2016; 52:138-54.
9. Daraei A, Izadi P, Khorasani G et al. Epigenetic changes of the ESR1 gene in breast tissue of healthy women: A missing link with

breast cancer risk factors? Genet Test Mol Biomarkers 2017; 21: 464-470.

10. Escala-Garcia M, Morra A, Canisius S et al. Breast cancer risk factors and their effects on survival: a Mendelian randomisation study. BMC Med. 2020 Nov 17;18(1):327. doi: 10.1186/s12916-020-01797-2. PMID: 33198768; PMCID: PMC7670589.
11. 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





AGO e. V.  
in der DGGG e. V.  
in der DGO e. V.  
Guidelines Breast  
Version 2021.1

[www.ago-online.de](http://www.ago-online.de)

STRENGTHEN  
SUPPORT  
SUPPORT

## Association of Body Fat and Risk of Breast Cancer in Postmenopausal Women With Normal Body Mass Index: A Secondary Analysis of a Randomized Clinical Trial and Observational Study.

Iyengar NM et al. JAMA Oncol. 2019 Feb 1;5(2):155-163.

- WHI substudy
- Among the 3460 women included in the analysis (mean [SD] age, 63.6 [7.6] years), multivariable-adjusted hazard ratios for the risk of invasive breast cancer were 1.89 (95% CI, 1.21-2.95) for the highest quartile of whole-body fat and 1.88 (95% CI, 1.18-2.98) for the highest quartile of trunk fat mass.
- The corresponding adjusted hazard ratios for ER-positive breast cancer were 2.21 (95% CI, 1.23-3.67) and 1.98 (95% CI, 1.18-3.31), respectively.







9. Limon-Miro AT, Lopez-Teros V, Astiazaran-Garcia H. Dietary Guidelines for Breast Cancer Patients: A Critical Review. *Adv Nutr*. 2017 Jul 14;8(4):613-623.
10. 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.
11. 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.
12. 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.
13. 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. doi: 10.1056/NEJMoa1809944. Epub 2018 Nov 10.
14. 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]
15. 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
16. 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.
17. 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.
18. 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.
19. Li XJ, Ren ZJ, Qin JW, et al. Coffee consumption and risk of breast cancer: an up-to-date meta-analysis. *PLoS One* 2013;8:e52681 doi:10.1371/journal.pone.0052681 pmid:23308117
20. 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.
21. 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.

22. 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
23. 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
24. Parida S, Sharma D. Microbial Alterations and Risk Factors of Breast Cancer: Connections and Mechanistic Insights. *Cells* 2020, 9, 1091; doi:10.3390/cells9051091. Breast Cancer Primary Prevention and Diet: An Umbrella Review
25. 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
26. 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.

\*AGO e. V.  
 in der DGGG e. V.  
 in der DGMG e. V.  
 Guidelines Street  
 Version 2021.1

[www.ago-online.de](http://www.ago-online.de)  
 0 7 55 00 42 10 10  
 0 7 55 00 42 10  
 0 7 55 00 42 10

## 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

## Prevention by Modifying Lifestyle Risk Factors: Alcohol

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

### Particularly for

- ER+/PR+ tumors
- Invasive lobular tumors

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

- McDonald JA, Goyal A, Terry MB. Alcohol Intake and Breast Cancer Risk: Weighing the Overall Evidence. Curr Breast Cancer Rep. 2013 Sep;5(3). doi: 10.1007/s12609-013-0114-z.
- Bagnardi V, Rota M, Botteri E et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer. 2015 Feb 3;112(3):580-93.
- 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. doi: 10.1093/ije/dyy238. [Epub ahead of print]
- 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.
- Bagnardi V, Rota M, Botteri E et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer. 2015;112:580–93.
- 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)

© ADO e. V.  
 in der DGGG e. V.  
 in der DGG e. V.  
 Guidelines Breast  
 Version 2021.1

[www.ago-online.de](http://www.ago-online.de)  
 07.08.2021 14:00:00  
 07.08.2021 14:00:00

## Nature, Nurture and cancer risks: Genetic and nutritional contributions to cancer

Theodoratou, E.: Annu Rev Nutr. 2017 August 21; 37: 293–320.  
 doi:10.1146/annurev-nutr-071715-051004

No association was classified as convincing (class I). The association between alcohol intake and ER+ breast cancer was classified as highly suggestive (Class II) based on a **meta-analysis of 20 prospective studies** ( $\geq 30\text{g/d}$  of alcohol consumption versus non-drinkers)  
 RR (95% CI): 1.35 (1.23, 1.48,  $p\text{-value}=5.2 \times 10^{-10}$ ,  $I^2 = 26\%$ ,  
 $P_{\text{small effect bias}} = 0.184$ ,  $P_{\text{excess significance bias}} = 4 \times 10^{-8}$ )

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

## 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,**  
if smoking > 10 years before first childbirth  
(vs. never smokers)

1. Gaudet MM, Gapstur SM, Sun J et al. Active smoking and breast cancer risk: original cohort data and meta-analysis. J Natl Cancer Inst. 2013 Apr 17;105(8):515-25.
2. Bjerkaas E, Parajuli R, Weiderpass E et al. Smoking duration before first childbirth: an emerging risk factor for breast cancer? Results from 302,865 Norwegian women. Cancer Causes Control. 2013 Jul;24(7):1347-56.
3. Dossus L, Boutron-Ruault MC, Kaaks R et al. Active and passive cigarette smoking and breast cancer risk: results from the EPIC cohort. Int J Cancer. 2014 Apr 15;134(8):1871-88.
4. Jones ME, Schoemaker MJ, Wright LB, Ashworth A, Swerdlow AJ. 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.
5. 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.

\*AGO e. V.  
 in der DGGG e. V.  
 in der DGO e. V.  
 Guidelines Breast  
 Version 2021.1

[www.ago-online.de](http://www.ago-online.de)  
 0 30 33 33 33 33  
 0 30 33 33 33 33  
 0 30 33 33 33 33

## 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.

AGO e. V.  
in der DGGG e. V.  
in der DGGG e. V.  
Guidelines Breast  
Version 2021.1

www.ago-online.de

## Prevention by Modifying Lifestyle Risk Factors: Physical Activity

---

• **Physical exercise**

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

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

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

1. Wu Y, Zhang D, Kang S. Physical activity and risk of breast cancer: a meta-analysis of prospective studies. *Breast Cancer Res Treat.* 2013 Feb;137(3):869-82.
2. Chlebowski RT. Nutrition and physical activity influence on breast cancer incidence and outcome. *Breast.* 2013 Aug;22 Suppl 2:S30-7.
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. doi: 10.1158/1055-9965.EPI-18-0175. Epub 2018 Jul 10.
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. doi: 10.1097/GME.0000000000000745
6. Megan S. Rice, ScD, A. Heather Eliassen, ScD, Susan E. Hankinson et al. Breast Cancer Research in the Nurses' Health Studies: Exposures Across the Life Course *Am J Public Health.* 2016 September; 106(9): 1592–1598. Published online 2016 September. doi: 10.2105/AJPH.2016.303325 PMCID: PMC4981804 PMID: 27459456



7. de Boer MC, Wörner EA, Verlaan D et al. The Mechanisms and Effects of Physical Activity on Breast Cancer. *Clin Breast Cancer*. 2017 Jul;17(4):272-278. doi: 10.1016/j.clbc.2017.01.006. Epub 2017 Jan 24.
8. Pizot C, Boniol M, Mullie P et al. Physical activity, hormone replacement therapy and breast cancer risk: A meta-analysis of prospective studies. *Eur J Cancer*. 2016 Jan;52:138-54. doi: 10.1016/j.ejca.2015.10.063. Epub 2015 Dec 11.

**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.**  
 Kehrer RD et al. | Cancer Res. 2020 Jan 1;80(1):116-125. doi: 10.1158/0008-5472.CAN-19-1847. Epub 2019 Oct 2.

\*AGO e. V.  
 in der DGBC e. V.  
 50460  
 in der DGBC e. V.  
 Guidelines Breast  
 Version 2021.1

- **Prospective cohort study**
- **N=15550, 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**

[www.ago-online.de](http://www.ago-online.de)  
 01.10.2020 11:11:14  
 01.10.2020 11:11:14  
 01.10.2020 11:11:14

We examined associations of adult and adolescent recreational physical activity (quintiles of age-adjusted total metabolic equivalents per week) with breast cancer risk using multivariable Cox proportional hazards regression, adjusted for demographics, lifestyle factors, and body mass index. We tested for multiplicative interactions of physical activity with predicted absolute breast cancer familial risk based on pedigree data and with BRCA1 and BRCA2 mutation status. Baseline recreational physical activity level in the highest four quintiles compared with the lowest quintile was associated with a 20% lower breast cancer risk (HR, 0.80; 95% confidence interval, 0.68-0.93). The association was not modified by familial risk or BRCA mutation status (P interactions >0.05). No overall association was found for adolescent recreational physical activity. Recreational physical activity in adulthood may lower breast cancer risk for women across the spectrum of familial risk.

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

	Oxford		
	LoE	GR	AGO
▪ <b>Avoiding hormonal therapy in postmenopausal women</b>			
▪ Avoiding estrogen / progestin combinations	1b	A	+
▪ Avoiding estrogens only (no increased, possibly even reduced breast cancer risk, but increased risk for endometrial cancer, unless after hysterectomy)	1b	A	+/-

1. Beral V; Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003; 362: 419 – 27.
2. Chlebowski RT, Hendrix SL, Langer RD et al.. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA* 2003; 289: 3243–3253.
3. Reeves GK, Beral V, Green J et al. Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. *Lancet Oncol* 2006; 7: 910–918.
4. De P, Neutel CI, Olivotto I et al. Breast cancer incidence and hormone replacement therapy in Canada. *J Natl Cancer Inst* 2010; 102: 1489 – 95.
5. Chlebowski RT, Anderson GL, Gass M et al. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. *JAMA* 2010;304: 1684–1692.
6. Sæther S, Bakken K, Lund E. The risk of breast cancer linked to menopausal hormone therapy. *Tidsskr Nor Lægeforen* 2012;132: 1330–1334.
7. Marjoribanks J, Farquhar C, Roberts H et al. Long term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database Syst Rev*. 2012 Jul 11;7:CD004143.
8. Manson JE, Chlebowski RT, Stefanick ML et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA*. 2013 Oct 2;310(13):1353-68.
9. Chlebowski RT, Anderson GL, Prentice RL et al. Reliable evidence from placebo-controlled, randomized, clinical trials for menopausal hormone therapy's influence on incidence and deaths from breast cancer. *Climacteric*. 2015 Jun;18(3):336-8.

10. 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.
11. 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.
12. 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.
13. Beckermann MJ, Inwald E, Strowitzki T et al. For the guideline group Peri- and postmenopause—diagnosis and interventions interdisciplinary S3 guideline of the association of the scientific medical societies in Germany (AWMF 015/062): short version. *Archives of Gynecology and Obstetrics* (2020) 302:763–777



AGE e. V.  
in der DGGG e. V.  
in der DGG e. V.  
Guidelines Breast  
Version 2021.1

www.age-online.de  
FUNKTIONEN  
LEBENSZEIT  
FUNKTIONEN

## Epigenome-wide association study for lifetime estrogen exposure identifies an epigenetic signature associated with breast cancer risk.

Johansson A et al.: Clin Epigenetics. 2019 Apr 30;11(1):66.

epidemiological data from EPIC-Italy (n = 31,864)

Study: estimated lifetime estrogen exposure

Method: epigenome-wide association study, blood DNA samples, N=216 ,  
and 440 healthy controls

Results: an estimated 5% increase in breast cancer risk per 1-year longer ELEE  
(OR = 1.05, 95% CI 1.04-1.07, P =  $3 \times 10^{-12}$ ) in EPIC-Italy.  
694 CpG sites were associated with ELEE (FDR Q < 0.05)



© ADO e. V.  
in der DGGG e. V.  
in der DGO e. V.  
Guidelines Breast  
Version 2021.1

www.ago-online.de  
FACHLEITUNG  
LEITUNG  
REDAKTION

## 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)	1.1 (1.1-1.2) coronary events 1.4 (1.1-1.8) stroke 2.1 (1.4-3.2) pulmonary embolism 2.1 (1.3-3.5) deep vein thrombosis
<b>HERS</b> Hulley Sr: JAMA 2002	I 2763 RCT, med. 4.1 J II 2321 open-label, 2.71	<b>1.2</b> (0.95-1.5)	med. age 67 J no secondary prevention side effects as comp. to WHI + cholesteroleum, R
<b>Million Women</b> Beral V: Lancet 2005	1.084 110 ~ 50% WHI 4.1 J, follow-up	<b>1.66</b> (1.6-1.8)	EPC > I mode of applic. not relevant duration > 5 yrs. Tibolon RR 1.45 (1.2-1.7)
<b>EPIC</b> Int J Cancer 2003	1.153 747 person-years	<b>1.4</b> (1.2-1.6) <b>1.8</b> (1.4-2.2)	E-Memo EPC > I
<b>Metaanalyse</b> Nelson HD: JAMA 2002	16 Studies	<b>1.21-1.40</b>	side effects as compared to WHI =

Chlebowski et al., Climacteric 2005, 18:334-8  
Chlebowski et al., J Natl Compr Canc Netw 2015, 13:917-24  
Manson JE et al., JAMA 2017, 318: 927-938



© ADO e. V.  
in der DGGG e. V.  
in der DGO e. V.  
Guidelines Breast  
Version 2021.1

www.ago-online.de

PROFESSORIN  
FÜR GYNEKOLOGIE  
UND GEBURTSHILFE  
AN DER UNIVERSITÄT  
DUISBURG-ESSEN

## Prevention of Hormones (EGC) in Postmenopausal Patients

	N	MC-RR (95% CI)	Further statements
CLEAR-study (NSW)  Case-Control-Study, retrospect. Australia	1236 BC cases	2.09 (1.57-2.79)	current user
		1.03 (0.82-1.28)	past user
		2.62 (1.94-4.88)	E/P combination
		1.80 (1.31-2.48)	E only

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

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

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

Oxford

LoE

1a

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

1. 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.
2. 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.
3. Mørch LS, Skovlund CW, Hannaford PC et al. Contemporary hormonal contraception and the risk of breast cancer. *N Engl J Med.* 2017 Dec 7;377(23):2228-2239.
4. 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