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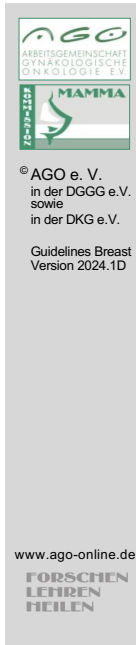
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# Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

## Optionen der primären Prävention: Veränderbare Lifestyle-Faktoren

# Prävention



- **Versionen 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



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## Risikofaktoren

- Weibliches Geschlecht
- Familiäre Krebsanamnese
- Hohe Mammografische Dichte
- Höheres Alter
- Genetische Prädisposition
- Geringe Geburtenzahl oder keine Schwangerschaft
- Höheres Alter bei erster Geburt
- Alkoholabusus
- Nikotinabusus
- Hormontherapie
- Orale Kontrazeptive
- Menopausale Hormontherapie (Östrogen / Gestagen-Kombination)
- Postmenopausales Übergewicht
- Persönliche Brustanamnese
  - Nicht-proliferative Läsionen
  - Proliferative Läsionen +/- Atypien
  - Hochrisikoläsionen (ADH, LIN)
  - Brustkrebs (DCIS, Inv. MaCa)
- Thoraxbestrahlung
- Luftverschmutzung (PM<sub>2,5</sub>)

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.

## Protektivfaktoren



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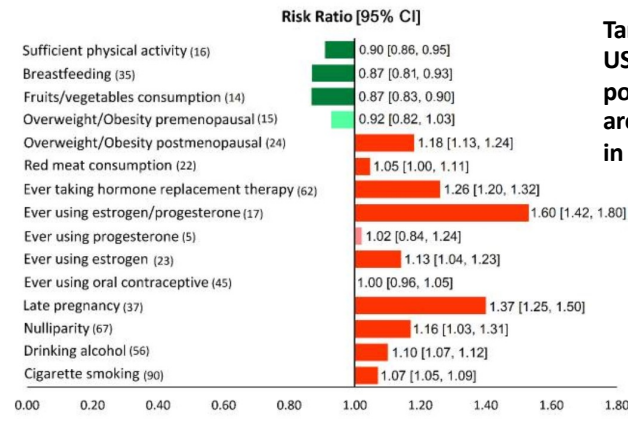
- **Abgeschlossene Schwangerschaften**
- **Frühe abgeschlossene Schwangerschaften**
- **Regelmäßige Körperliche Bewegung**
- **Stillen**

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.

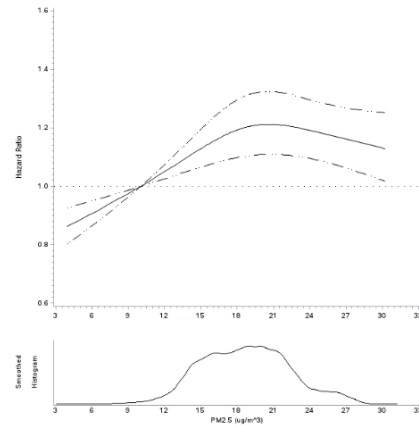
## Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies

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

A 10 µg/m<sup>3</sup> 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>



## Einfluss durch Reproduktionsfaktoren

### Auflistung von Faktoren, die sich noch in der Abklärung befinden

#### Präventiv

- Hohe Zahl voll ausgetragener Schwangerschaften
- Hohe Anzahl der Schwangerschaften
- Junges Alter bei erster ausgetragener Schwangerschaft
- Stillen (schützt, wenn Gesamtstilldauer 1,5–2 Jahre)
- Geringeres Geburtsgewicht des Erstgeborenen (3000–3500 g vs. > 4500 g, RR = 1,53)
- Geringere Schwangerschaftsdauer Erstgeborene (26-31. SSW vs. 40-41. SSW; RR = 2,38, p = 0,03)

#### Oxford

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



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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. 2022 Sep 26.

### **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.

## Medikamentöse hormonelle Prävention für Frauen mit erhöhtem Risiko

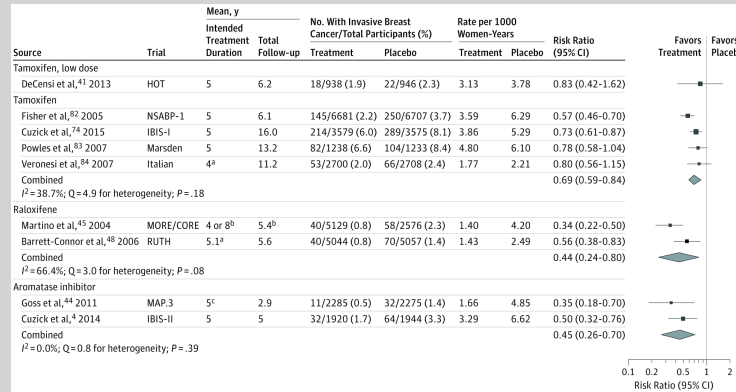
	Oxford		
	LoE	GR	AGO
▪ <b>Tamoxifen für Frauen &gt; 35 Jahre</b> <b>Risiko-Reduktion für invasives MaCa, DCIS und LN</b>	<b>1a</b>	<b>A</b>	<b>+*</b>
▪ <b>Raloxifen für postmenopausale Frauen</b> <b>Risiko-Reduktion für invasives MaCa</b>	<b>1b</b>	<b>A</b>	<b>+*</b>
▪ <b>Aromatasehemmer für postmenopausale Frauen</b>	<b>1b</b>	<b>A</b>	<b>+**</b>

\* Risiko definiert wie in der NSABP P1-Studie (1.66 % in 5 Jahren) oder nach #Tyrer-Cuzick-Modell (IBIS-II).

\*\* Signifikante Risikoreduktion unter Anastrozol für Ovarial- und Endometriumkarzinome, sowie Haut-, Kolorektal-, Schilddrüsen-, Harnwegskarzinome und hämatologische Tumoren  
Chemopräventive Therapien sollten nur nach individueller und umfassender Beratung angeboten werden. Der Nutzen hängt vom Risikostatus, Alter und vorbestehenden Risiken für Nebenwirkungen ab.

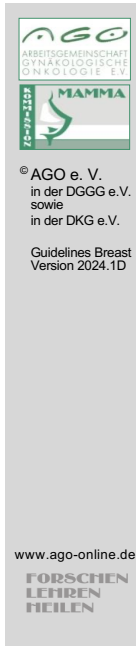
1. Cuzick J, Sestak I, Cawthorn S, et al. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. *Lancet Oncol.* 2015;16(1):67-75.
2. Cuzick J, Sestak I, Forbes JF, et al. Use of anastrozole for breast cancer prevention (IBIS-II): long-term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

## 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

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



## Medikamentöse nicht-hormonelle Primärprävention\*

- ASS
- COX2-Inhibitoren
- Bisphosphonate
- Vitamin D
- Statine

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

\* Keine Zulassung, Nebenwirkungsprofil muss berücksichtigt werden

### 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.

### Bisphosphonate

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

### **Statine**

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]

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



## Prävention durch Änderung von Lifestyle-Faktoren: Gewicht / Glucosestoffwechsel

	Oxford		
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▪ <b>Einhaltung Normalgewicht (BMI 18,5-25 kg/m<sup>2</sup>)*</b>	<b>2a</b>	<b>B</b>	<b>++</b>
▪ Prämenopausal	<b>3a</b>	<b>B</b>	<b>+/-</b>
▪ Postmenopausal	<b>2a</b>	<b>B</b>	<b>++</b>
▪ <b>Vermeidung bzw. Früherkennung und Einstellung eines Typ II Diabetes mellitus (Reduktion der Brustkrebsinzidenz und -mortalität)</b>	<b>2b</b>	<b>B</b>	<b>++</b>

\* die Menge an Körperfett kann auch bei normalem BMI erhöht sein und korreliert mit dem Brustkrebsrisiko

### Einhaltung Normalgewicht

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

#### Vermeidung, Früherkennung und Einstellung

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).**

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

- **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.**

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

## Prävention durch Änderung von Lifestyle-Faktoren: Ernährung

	Oxford		
	LoE	GR	AGO
* s. Empfehlungen der Dt. Gesellschaft f. Ernährung (DGE)			
** Empfohlen als Bestandteil einer gesunden Ernährung			
▪ <b>Bevorzugung einer ausgewogenen Ernährung*</b>	2b	B	+
▪ <b>mediterrane Kost</b>	2a	B	+
▪ <b>Nahrungszusammensetzung</b>			
▪ Olivenöl (natives O. extra) i. Rahmen mediterraner Diät	2b	B	+
▪ Fettreduzierte Nahrung	2a	B	+
▪ Verminderter Konsum an rotem Fleisch	2b	C	+
▪ Nüsse / Erdnüsse (> 10g/d) (Erdnussbutter ohne Effekt)	2b	B	+
▪ Ballaststoffreiche Ernährung	2a	B	+
▪ Vitamin-D-Substitution zur Prävention (MaCa RR1,02)	1b	B	+/-
▪ Gemüse / Obst **	2a	B	+/-
▪ Phytoöstrogene / Soja	2a	B	+/-
▪ Vegetarische / Vegane Diät (keine sign. Risikoreduktion)	2b	C	+/-
▪ Kaffee (keine signifikante Risikoreduktion)	2a	B	+/-
▪ Ergänzung von Vitaminen, Mineralien, Spurenelementen	2a	B	-

### Bevorzugung einer ausgewogenen Ernährung

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
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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
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### Mediterrane Kost

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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.
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### **Fettreduzierte Nahrung**

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

### **Weniger rotes Fleisch**

1. Poorolajal J, Heidari Moghis 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.

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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
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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**

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

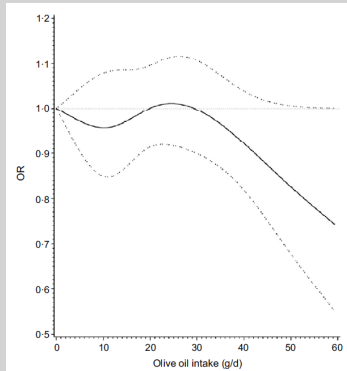


Fig. 5. Dose-response relationship between olive oil intake and breast cancer.

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

Group	Number of studies	OR	95% CI	I <sup>2</sup> (%)	P <sub>for heterogeneity</sub>
<b>Location</b>					
Italy, Spain, Greece	4	0.60	0.39, 0.95	85	<0.001
Other countries	4	1.06	0.72, 1.57	58	0.07
<b>Source of controls</b>					
Hospital based	5	0.94	0.69, 1.28	65	0.02
Population based	3	0.57	0.28, 1.19	90	<0.001
<b>Number of cases</b>					
<500 cases	5	0.71	0.37, 1.39	89	<0.001
≥500 cases	3	0.80	0.67, 0.95	0	0.47
<b>Exposure assessment</b>					
Assessed amount consumed	5	0.75	0.48, 1.15	88	<0.001
Assessed frequency consumed	3	0.77	0.39, 1.51	69	0.04
<b>Adjustment for total energy</b>					
Adjusts for total energy	5	0.67	0.46, 0.98	83	<0.001
No adjustment for total energy	3	0.98	0.50, 1.91	69	0.04

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

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.

## Prävention durch Änderung von Lifestyle-Faktoren: Alkohol

- **Reduktion des Alkoholkonsums vermindert Brustkrebsrisiko (ideal < 10g/d, class II evidence)**

Insbesondere für

- ER+ / PR+ Tumoren
- Invasiv lobuläre Tumoren

Oxford		
LoE	GR	AGO
2a	B	+
2a	B	
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 =  $5.2 \times 10^{-10}$ ,  $I^2 = 26\%$ ,**

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

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

## Prävention durch Änderung von Lifestyle-Faktoren: Rauchen

Oxford		
LoE	GR	AGO
2a	B	++

- **Frauen, die nie geraucht haben, haben ein verringertes Lebenszeitrisiko für einen Brustkrebs (~ 15-24 % Reduktion)**
- **Junge Frauen haben ein 60 % höheres Risiko für ein Mammakarzinom, wenn sie > 10 Jahre vor der Geburt des ersten Kindes geraucht haben (vs. Nichtraucherinnen)**

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;  $P = 0.22$ ).**

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.

## Prävention durch Änderung von Lifestyle-Faktoren: Körperliche Aktivität

Oxford		
LoE	GR	AGO
2a	B	++

- **Körperliche Aktivität**  
**Metabolisches Equivalent zu 3–5 Std. Spaziergänge pro Woche mit moderater Schrittgeschwindigkeit**

Diese Effekte gelten auch für *BRCA1/2*-Mutationsträgerinnen und für Frauen mit erhöhtem familiärem Risiko.

### Körperliche Aktivität

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.

### Körperliche Aktivität im Intervall zwischen Menarche und erster Schwangerschaft

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.

Diese Effekte gelten auch für *BRCA1/2*-Mutationsträgerinnen und für Frauen mit erhöhtem familiärem Risiko.



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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 = 15550, women with fam. history of breast cancer**
- **Multiplicative interactions of physical activity with predicted absolute breast cancer familial risk based on pedigree data and with BRCA1 and BRCA2 mutation status**
- **Higher physical activity → 20% reduction of breast cancer incidence**
- **(HR 0.80, CI 0.68-0.93), independent of BRCA-status or pedigree risk**

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.



## Prävention durch Lifestyle-Faktoren: Hormontherapie in der Postmenopause

### Vermeidung von Hormontherapie in der Postmenopause

- Vermeidung von Östrogen- / Gestagen-Kombination
- Vermeidung von alleiniger Östrogentherapie  
(kein erhöhtes, evtl. sogar verringertes Brustkrebsrisiko bei  
alleiniger Östrogentherapie, aber erhöhtes EM Ca Risiko)

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.



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## 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)**

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. Tibolon RR 1.45 (1.2-1.7)
<b>EPIC</b> Int J Cancer 2010	<b>1.153 747</b> person-years	<b>1.4</b> (1.2-1.6) <b>1.8</b> (1.4-2.2)	E-Mono EPC > E
<b>Metaanalyse</b> Nelson HD: JAMA 2002	<b>16 Studies</b>	<b>1.21-1.40</b>	side effects as compared to WHI +

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

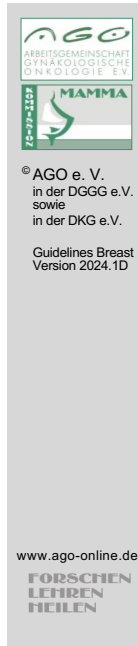
Salagame et al., Int J Cancer. 2016;138(8):1905-14

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.

## Prävention durch Änderung von Lifestyle-Faktoren: Orale Kontrazeption (OC)

	Oxford
	LoE
<ul style="list-style-type: none"> <li>■ Insgesamt erhöht die OC <u>nicht</u> das Risiko an Brustkrebs zu versterben.</li> </ul>	1a
<ul style="list-style-type: none"> <li>■ <u>Risiko</u> für Mammakarzinom leicht erhöht, Risiko für Ovarial- und Endometriumkarzinom wird erniedrigt.</li> </ul>	1a <sup>(-)</sup>

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.



## Risikoreduktion für ipsi- und kontralaterale Zweitkarzinome

Frauen nach Brustkrebs haben ein erhöhtes Risiko für ein ipsi- oder kontralaterales Zweitkarzinom.

Präventiver Zusatznutzen durch

- Tamoxifen
- Aromatasehemmer
- GnRH-Agonist + Tamoxifen

Oxford

LoE	GR	AGO
1a	A	+
1a	A	+
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.

### Aromatasehemmer ( $HR=0.62$ 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.

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



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### 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.

### Aromatasehemmer (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.
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