


Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Options for Primary Prevention: Modifiable Lifestyle Factors



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Prevention

- **Versions 2011–2019:**
Dall / Diel / Gerber / Hanf / Maass / Mundhenke / Solbach / Solomayer / Thomssen / von Minckwitz
- **Version 2020:**
Dall / Mundhenke

Screened data bases

Pubmed 2005 – 2019, ASCO 2012 – 2019, SABCS 2012 – 2019, Cochrane data base 2019



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Risk Factors for Breast Cancer 1


- Older age
- Genetics
- Family history of cancer
- Personal history of breast lesions
 - Non-proliferative lesions
 - Proliferative lesions w/o atypia
 - High risk lesions (ADH, LIN)
 - Breast cancer (DCIS, Inv. BC)
- Breast density
- Chest irradiation
- Type II Diabetes mellitus

- Lifetime number of menstrual cycles
 - Early menarche, late menopause
- Maternal pregnancy factors (e.g. pre-eclampsia) (risk reduction), and low physical activity during pregnancy (risk increase)

Social risk factors

- Lower number of births or no pregnancy
- Advanced age at first full term delivery

1. 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.
2. 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.
3. 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



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Risk Factors for Breast Cancer 2

- **Short duration or absence of breast feeding**
- **BMI < 18.5 and > 25 and especially > 40 (obesity)**
- **Food content**
- **Steroid hormone therapy**
 - Recent oral contraceptive use
 - Hormone therapy (estrogen/gestagen combination) in postmenopausal women
- **Alcohol intake**
- **nicotine**


- **Light exposure at night (night shifts) *contradictory***
- **Low physical activity**
- **Endocrine disruptors in fetal and early childhood development (e.g. DES, bisphenol-A, DDT)**
- **Effect of carcinogenic substances / working materials**
- **Exposition to ionizing radiation**

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.
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3. 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.
4. Bao PP, Zhao GM, Shu XO et al..Modifiable Lifestyle Factors and Triple-negative Breast Cancer Survival: A Population-based Prospective Study. Epidemiology. 2015 Nov;26(6):909-16.
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8. American Cancer Society 2019 <https://www.cancer.org/cancer/breast-cancer/risk-and-prevention.html>

9. Rodgers KM, Udesky JO, Rudel RA et al. Environmental chemicals and breast cancer: An updated review of epidemiological literature informed by biological mechanisms. *Environ Res.* 2018 Jan;160:152-182. doi: 10.1016/j.envres.2017.08.045. Epub 2017 Oct 6.
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Deodorant-use and risk


Breast Cancer and Deodorants/Antiperspirants: a Systematic Review.

Allam MF¹: 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.

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High Proportion of Postmenopausal Breast Cancer Attributable to Lifestyle Factors

population attributable fractions (PAFs) of modifiable risk factors

Risk factors: obesity, physical inactivity, alcohol, low-fiber intake, smoking

Results: retrospective cohort study (Netherlands Cancer Registry)

<p>2000: subpopulations of obese women, inactive women, alcohol drinkers, smokers etc.</p> <p>2010: breast cancer incidence as compared to background incidence in these subgroups</p> <p>25.7% of postmenopausal breast cancer cases in the Netherlands in 2010 were attributable to lifestyle factors</p> <p>8.8% attributed to obesity</p> <p>6.6% attributed to alcohol</p> <p>5.5% attributed to physical inactivity</p> <p>3.2.% attributed to low fiber intake</p> <p>4.6% attributed to smoking</p>	<p>Update 2019: Tamimi et al, 2016 USA: more than a third of postmenopausal breast cancers are preventable through changes in modifiable risk factors</p>
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van Germert et al., Int J Cancer 2015; 152: 155-162

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Prevention by Pregnancy Related Factors			
	Oxford		
	LoE	GR	AGO
■ Any full term pregnancy	2b	B	
■ 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	
■ Assisted reproduction (no influence)	2b	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	
■ Polycystic Ovarian Syndrome PCO (no influence on BC)	3b	C	

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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.
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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.
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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]



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Prevention by Changing Lifestyle Factors: Body Mass Index / Diet

Oxford		
LoE	GR	AGO
2a	B	++
3a	B	++
2a	B	++
2b	B	++

- **Maintaining normal weight
(BMI at 18.5 – 25 kg/m²)***
 - Premenopausal
 - Postmenopausal
- **Prevention/screening and treatment of
diabetes mellitus type II
(reduction of breast cancer incidence and mortality)**

* Amount of body fat can be increased in people with normal BMI and correlates with breast cancer risk

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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.
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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.
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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.



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The risk of breast, ovarian and endometrial cancer in obese women submitted to bariatric surgery: A meta-analysis

SABCS 2019, B Ishihara, D Farah, M Fonseca and A Nazário.

- Meta-analysis, of a total of 150,528 patients in the bariatric surgery arm and 1,461,938 women in the control arm.
- The risk of breast cancer was reduced by 61% [RR: 0.39 (95%CI [0.24 to 0.64]; I²= 90%; 6 studies).
- The risk of ovarian cancer was reduced by 53% [RR: 0.47 (95%CI [0.27 to 0.81]; I²= 0%; 3 studies).
- The risk of endometrial cancer was reduced by 67% [RR: 0.33 (95%CI [0.21 to 0.51]; I²= 88%; 7 studies).



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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.

BMI and epigenetics link between obesity and breast cancer?

Changing the ESR1-promoter activity by methylation of CpG-islands

n = 120 breast tissue samples of cancer free patients

ESR1-promoter methylation

BMI ≥ 30 > BMI 25–29 > BMI 25 kg/m² (p < 0.001 resp.)

postmenopausal > premenopausal (p = 0.046)


[multivariate analysis]

Daraei A., Genet Test Mol Biomarkers 2017, 21:464-470

BMI and epigenetics link between obesity and breast cancer?

- The epigenetic code (methyl marks) determines how the genome functions, dictating which genes are turned on and which genes are turned off
- Development is the critical period when this programming occurs, directing cell and organ development

Walker, CL, SABCS 2011

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	<p>* As recommended by German Society of Nutrition (DGE) ** Recommended as a part of healthy nutrition</p>		
■ Preference of a balanced diet*		Oxford	
		LoE	GR
		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
■ Supplementation of vitamins, minerals, trace elements		2a	B
■ Vitamin D substitution for prevention (MaCa HR1,02)		1b	B
■ Vegetables / fruits **		2a	B
■ Phytoestrogens / soy		2a	B
■ Fiber containing food		2a	B
■ Vegetarian/vegan diet (no significant risk reduction)		2b	C
■ Coffee reduces the BC risk (esp. receptor neg.)		2a	B
■ nuts/peanuts (> 10g/d) (peanut butter without effect)		2b	B

1. Zamora-Ros R, Ferrari P, González CA et al. Dietary flavonoid and lignan intake and breast cancer risk according to menopause and hormone receptor status in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study. Breast Cancer Res Treat. 2013 May;139(1):163-76.
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3. Chlebowski RT. Nutrition and physical activity influence on breast cancer incidence and outcome. Breast. 2013 Aug;22 Suppl 2:S30-7.
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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.
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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.
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outcomes. BMJ 2017 Nov 22;359:j5024. doi: 10.1136/bmj.j5024.

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Coffee Consumption and Risk of Breast Cancer: An Up- To-Date Meta-Analysis


Xiu Juan Li: PlosOne, January 2013 | Volume 8 | Issue 1 | e52681

49497 breast cancer cases


26 studies (16 cohort and 10 case–control studies)

The pooled RR showed a borderline significant influence of highest coffee consumption (RR = 0.96; 95% CI 0.93–1.00), low-to moderate coffee consumption (RR = 0.99; 95% CI 0.95–1.04), or an increment of 2 cups/ day of coffee consumption (RR = 0.98; 95% CI 0.97–1.00) on the risk of breast cancer.

In stratified analysis, a significant inverse association was observed in ER-negative subgroup. However, no significant association was noted in the others.




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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 D₃(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



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Epidemiological Evidences on Dietary Flavonoids and Breast Cancer Risk: A Narrative Review

Sak, K.: [Asian Pac J Cancer Prev. 2017 Sep 27;18\(9\):2309-2328.](#)


Conclusions and further perspectives

...probably the most apparent relationship prevails for consumption of isoflavones, whereas beneficial effects seem to be expressed only at high intake levels typical to Asian womencompared to Western countries where the intake of soy products is remarkably low.



protective activities of isoflavones might appear only in females consuming soy foods since their early age as childhood and adolescence can be crucial periods of exposure

At present: “recommendations for consumption of high-dose isoflavones ... to reduce the individual susceptibility towards breast carcinogenesis are still premature and can also be not completely without .. risks.”

1. 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.


 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	Prevention by Modifying Lifestyle Risk Factors: Alcohol		
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Reduction of alcohol intake reduces risk of breast cancer (ideal <10g/d, class II evidence) <p>Particularly for</p> <ul style="list-style-type: none"> ER+/PgR+ tumors Invasive lobular tumors 	2a	B	+
	2a	B	
	2a	B	

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2. 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.
3. 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]
4. 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.
5. 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.

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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** ($\geq 30\text{g/d}$ 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

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Smoking and risk of breast cancer in the Generations Study cohort

Jones, M.E.:[Breast Cancer Res.](#) 2017 Nov 22;19(1):118. doi: 10.1186/s13058-017-0908-4.


102,927 women recruited 2003–2013

average of 7.7 years of follow-up

The HR (reference group was never smokers) was
1.14 (95% CI 1.03–1.25; $P = 0.010$) for ever smokers,
1.24 (95% CI 1.08–1.43; $P = 0.002$) for starting smoking at ages < 17 years
1.23 (1.07–1.41; $P = 0.004$) for starting smoking 1–4 years after menarche

Women with a family history of breast cancer (ever vs never smokers HR 1.35; 95% CI 1.12–1.62; $P = 0.002$) had a significantly larger HR ... than women without (ever smoker vs never smoker HR 1.07; 95% CI 0.96–1.20; $P = 0.22$).

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Prevention by Modifying Lifestyle Risk Factors: Physical Activity

	Oxford		
	LoE	GR	AGO
<p>■ Physical exercise</p> <p>(Metabolic equivalents to 3–5 hrs moderate pace walking per week)</p> <p>These effects also apply to BRCA1/2 mutation carriers and for women with an increased family risk.</p>	2a(-)	B	++

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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. 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**

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.

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				Oxford		
				LoE	GR	AGO
<p>■ Avoiding hormonal therapy in postmenopausal women</p>						
<p>■ Avoiding estrogen / progestin combinations</p>				1b	A	+
<p>■ Avoiding estrogens only (no increased, possibly reduced breast cancer risk, but increased risk for endometrial cancer, if not hysterectomized)</p>				1b	A	+/-

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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: 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 = 3×10^{-12}) in EPIC-Italy.
694 CpG sites were associated with ELEE (FDR Q < 0.05)

Prevention of Hormones in Postmenopausal Patients



	N	MC-RR (95%CI)	Further information
WHI WHI: JAMA 2002, JAMA 2017	~ 27 000	1.3 (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
HERS Hulley S: JAMA 2002	I 2763 RCT, med. 4.1 J II 2321 open-label, 2.7J	1.2 (0,95-1,5)	med. age 67 J no secondary prevention side effects as comp. to WHI + cholecystectomy?
Million Women Beral V: Lancet 2003	1.084 110 ~ 50% HRT 4.1 J. follow-up	1.66 (1,6-1,8)	EPC > E mode of applic. not relevant duration > 5 yrs. Tibolon RR 1.45 (1,2-1,7)
EPIC Int J Cancer 2010	1.153 747 person-years	1.4 (1,2-1,6) 1.8 (1,4-2,2)	E-Mono EPC > E
Metaanalyse Nelson HD: JAMA 2002	16 Studies	1.21-1.40	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

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

 	<h2 style="text-align: center;">Prevention by Modifying Lifestyle Risk Factors: Oral Contraception (OC)</h2>	
<p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1</p>	<p style="text-align: center;">Oxford <u>LoE</u></p>	<ul style="list-style-type: none"> ■ OC does <u>not</u> increase the risk of mortality from breast cancer ■ <u>Risk</u> of breast cancer slightly increased, risk of ovarian, endometrial cancer is decreased
<p>www.ago-online.de</p> <p style="text-align: center;">FORSCHEN LEHREN HEILEN</p>		

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