Options for Primary Prevention: Modifiable Lifestyle Factors
Prevention

- **Versions 2011–2022:**
  Dall / Diel / Gerber / Hanf / Maass / Mundhenke / Rhiem / Solbach / Solomayer / Thomssen / von Minckwitz

- **Version 2023:**
  Albert / Thomssen
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
- Hyperthyreoidism

- 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
Risk Factors for Breast Cancer 2

- Short duration or absence of breast feeding
- Postmenopausal 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
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

Pregnancy Related Factors

Prevention
- Any full-term pregnancy
- High number of pregnancies
- First full-term pregnancy before age of 30 years
- Breast feeding (protective if total breast-feeding time exceeds 1.5-2 years)
- Lower birth weight of the first born (3000-3500 vs. > 4500g RR = 1.53)
- Lower length of pregnancy first born (26-31. WOP vs. 40-41. WOP; HR = 2.38, p = 0.03)

Unfavourable influence possible
- Polycystic Ovarian Syndrome (PCOS)

No influence
- Assisted reproduction
- Abortion

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
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<tbody>
<tr>
<td>Prevention</td>
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<tr>
<td>Any full-term pregnancy</td>
<td>2b</td>
<td>B</td>
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<tr>
<td>High number of pregnancies</td>
<td>2b</td>
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<tr>
<td>First full-term pregnancy before age of 30 years</td>
<td>2b</td>
<td>B</td>
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<tr>
<td>Breast feeding (protective if total breast-feeding time exceeds 1.5-2 years)</td>
<td>3a</td>
<td>B</td>
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<td>Lower birth weight of the first born (3000-3500 vs. &gt; 4500g RR = 1.53)</td>
<td>2b</td>
<td>B</td>
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<td>2b</td>
<td>B</td>
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<tr>
<td>Polycystic Ovarian Syndrome (PCOS)</td>
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<td>C</td>
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<tr>
<td>Assisted reproduction</td>
<td>2b</td>
<td>B</td>
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<tr>
<td>Abortion</td>
<td>2b</td>
<td>B</td>
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</table>
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.

### Medical Primary Prevention*

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<thead>
<tr>
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<tbody>
<tr>
<td>ASS</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>COX2-Inhibitors</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>2b</td>
<td>B</td>
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<tr>
<td>Statins</td>
<td>2b</td>
<td>B</td>
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* No approval, consider side effects
Medical Prevention


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

- 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
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]; I² = 90 %; 7 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).
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.
Prevention by Changing Lifestyle Factors: Diet

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

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<tbody>
<tr>
<td></td>
<td>2b</td>
<td>B</td>
<td>+</td>
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<tr>
<td>Preference of a balanced diet*</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mediterranean Diet</td>
<td>2a</td>
<td>B</td>
<td>+</td>
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<tr>
<td>Dietary components</td>
<td></td>
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<tr>
<td>Olive oil (extra virgin olive oil), as part of mediterranean diet</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Fat reduced food</td>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Reduced consumption of red meat</td>
<td>2b</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Nuts / peanuts (&gt; 10g/d) (peanut butter without effect)</td>
<td>2b</td>
<td>B</td>
<td>+</td>
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<tr>
<td>Fiber containing food</td>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Vitamin D substitution for prevention (MaCa HR1,02)</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Vegetables / fruits **</td>
<td>2a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Phytoestrogens / soy</td>
<td>2a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Vegetarian / vegan diet (no significant risk reduction)</td>
<td>2b</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>Coffee (no significant reduction)</td>
<td>2a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Supplementation of vitamins, minerals, trace elements</td>
<td>2a</td>
<td>B</td>
<td>-</td>
</tr>
</tbody>
</table>

* As recommended by German Society of Nutrition (DGE)
** Recommended as a part of healthy nutrition
Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease


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
Olive oil consumption and breast cancer risk

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
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

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</table>
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 (≥ 30 g/d of alcohol consumption versus non-drinkers)

RR (95% CI): 1.35 (1.23, 1.48, p-value = 5.2 x 10^{-10}, I^2 = 26 %, P_{small effect bias} = 0.184, P_{excess significance bias} = 4 x 10^{-8})
Prevention by Modifying Lifestyle Risk Factors: Smoking

- Never smoking reduces risk of breast cancer (~ 15-24 % reduction of lifetime risk)

- Young women smoking have a 60 % increased risk of BC, when smoking > 10 years before the first childbirth (vs. never smokers)

LoE   GR    AGO
2a    B     ++
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; \( P = 0.22 \)).
Prevention by Modifying Lifestyle Risk Factors: Physical Activity

- Physical exercise
  
  (Metabolic equivalents to 3–5 hrs moderate pace walking per week)

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


- Prospective cohort study
- N = 15 550, women with fam. Hx of breast cancer
- Multiplicative interactions of physical activity with predicted absolute breast cancer familial risk based on pedigree data and with BRCA1 and BRCA2 mutation status
- Higher physical activity → 20% reduction of breast cancer incidence
- (HR0.80, CI 0.68-0.93), independent of BRCA-status or pedigree risk
Prevention by Modifying Lifestyle Risk Factors: Hormone Therapy in Postmenopausal Women

- Avoiding hormonal therapy in postmenopausal women
  - Avoiding estrogen / progestin combinations
  - Avoiding estrogens only
    (no increased, possibly reduced breast cancer risk, but increased risk for endometrial cancer, if not hysterectomized)
Epigenome-wide association study for lifetime estrogen exposure identifies an epigenetic signature associated with breast cancer risk.


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 = 3x10^{-12}) in EPIC-Italy. 694 CpG sites were associated with ELEE (FDR Q < 0.05)
## Prevention of Hormones in Postmenopausal Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>MC-RR (95%CI)</th>
<th>Further information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WHI</strong></td>
<td>~ 27 000</td>
<td>1.3 (1.0-1.6)</td>
<td>1.3 (1.1-1.6) coronary events</td>
</tr>
<tr>
<td><strong>HERS</strong></td>
<td>1 2763</td>
<td>1.2 (0.95-1.5)</td>
<td>Med. age 67 yrs. no secondary prevention</td>
</tr>
<tr>
<td><strong>Million Women</strong></td>
<td>1.084 110</td>
<td>1.66 (1.6-1.8)</td>
<td>EPC &gt; E mode of applic. not relevant duration &gt; 5 yrs. Tibolon RR 1.45 (1.2-1.7)</td>
</tr>
<tr>
<td><strong>EPIC</strong></td>
<td>1.153 747</td>
<td>1.4 (1.2-1.6)</td>
<td>E-Mono EPC &gt; E</td>
</tr>
<tr>
<td><strong>Metaanalyse</strong></td>
<td>16 Studies</td>
<td>1.21-1.40</td>
<td>Side effects as compared to WHI +</td>
</tr>
</tbody>
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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

<table>
<thead>
<tr>
<th>Study Description</th>
<th>N</th>
<th>MC-RR (95% CI)</th>
<th>Further statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLEAR-study (NSW)</td>
<td>1236 BC cases</td>
<td>2.09 (1.57-2.78)</td>
<td>current user</td>
</tr>
<tr>
<td>Case-Control-Study, retrospect. Australia</td>
<td></td>
<td>1.03 (0.82-1.28)</td>
<td>past user</td>
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<tr>
<td></td>
<td></td>
<td>2.62 (1.56-4.38)</td>
<td>E/P combination</td>
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<tr>
<td></td>
<td></td>
<td>1.80 (1.21-2.68)</td>
<td>E only</td>
</tr>
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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, endometrial cancer is decreased
Risk Reduction for Ipsi- and Contralateral Breast Cancer

Rationale: Women with breast cancer have an increased risk for a second primary

Additional preventive effect by

- Tamoxifen
- Aromatase inhibitors
- Suppression of ovarian function + Tamoxifen

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<td>A</td>
<td>+</td>
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<td></td>
<td>1b</td>
<td>B</td>
<td>+</td>
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## Risk reduction for ipsi- and contralateral second breast cancers ("second primaries")

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Localization</th>
<th>HR / RR</th>
<th>95% CI</th>
<th>p-value</th>
<th>ref.</th>
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<tbody>
<tr>
<td>Tamoxifen (vs nil)</td>
<td>ipsilat.</td>
<td>0.47</td>
<td>SE 0.08</td>
<td>0.00001</td>
<td>EBCTCG 2005</td>
</tr>
<tr>
<td></td>
<td>contralat.</td>
<td>0.71</td>
<td>SE 0.06</td>
<td>&lt; 0.00001</td>
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<tr>
<td>Tamoxifen (vs nil) ER+ or unknown</td>
<td>ipsilat.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>-</td>
<td>EBCTCG 2005</td>
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<tr>
<td></td>
<td>contralat.</td>
<td>0.61</td>
<td>0.50–0.73</td>
<td>-</td>
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<tr>
<td>Aromatase inhibitor (vs Tam)</td>
<td>ipsilat.</td>
<td>0.74</td>
<td>0.58 – 0.95</td>
<td>0.020</td>
<td>EBCTCG 2015</td>
</tr>
<tr>
<td></td>
<td>contralat.</td>
<td>0.62</td>
<td>0.48 – 0.80</td>
<td>0.0003</td>
<td></td>
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<tr>
<td>GnRH-agonist + tamoxifen (vs Tam)</td>
<td>ipsilat.</td>
<td>11.8 vs 16.7%</td>
<td>-</td>
<td>Cochrane 2020</td>
<td></td>
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<tr>
<td></td>
<td>contralat.</td>
<td>0.56</td>
<td>0.29–1.07</td>
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Deodorant-use and risk

Breast Cancer and Deodorants/Antiperspirants: a Systematic Review.

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.