Options for Primary Prevention:
Modifiable Lifestyle Factors
Prevention

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

- **Version 2024:**
  Fasching / Solomayer
Risk Factors

- Female
- Family history of cancer
- Breast density
- Older age
- Genetics
- Lower number of births or no pregnancy
- Advanced age at first full term delivery
- Alcohol intake
- Nicotine
- Steroid hormone therapy
- Oral contraceptive use
- Hormone therapy (estrogen / gestagen combination) in postmenopausal women
- Adipositas in postmenopausal women
- Personal history of breast lesions
  - Non-proliferative lesions
  - Proliferative lesions w/o atypia
  - High risk lesions (ADH, LIN)
  - Breast cancer (DCIS, Inv. BC)
- Chest irradiation
- Air pollution (PM2,5)
Protective factors

- Full terminated pregnancies
- Early terminated pregnancies
- Regular physical movement
- Breastfeeding
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

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

A 10 ug/m³ 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
# Pregnancy Related Factors

## List of factors that are still being clarified

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Oxford</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Any full-term pregnancy</td>
<td>2b</td>
</tr>
<tr>
<td>- High number of pregnancies</td>
<td>2b</td>
</tr>
<tr>
<td>- Young age at first full-term pregnancy</td>
<td>2b</td>
</tr>
<tr>
<td>- Breast feeding (protective if total breast-feeding time exceeds 1.5-2 years)</td>
<td>3a</td>
</tr>
<tr>
<td>- Lower birth weight of the first born (3000-3500 vs. &gt; 4500g RR = 1.53)</td>
<td>2b</td>
</tr>
<tr>
<td>- Lower length of pregnancy first born</td>
<td>2b</td>
</tr>
<tr>
<td>(26-31. WOP vs. 40-41. WOP; HR = 2.38, p = 0.03)</td>
<td>2b</td>
</tr>
</tbody>
</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 endocrine Prevention for Women at Increased Risk

- **Tamoxifen for women > 35 years:**
  Risk reduction of invasive BC, DCIS and LN
  1a A +*

- **Raloxifen for postmenopausal women:**
  Risk reduction of invasive BC only
  1b A +*

- **AI for postmenopausal women
  1b A +**

* Risk situation as defined in NSABP P1-trial (1.66% in 5 years) or according to #Tyrer-Cuzick model (IBIS-II)

** Significant risk reduction was seen for anastrozole for ovarian and endometrial cancer, as well as skin, colorectal, hematologic, thyroid and urinary tract cancers. Chemopreventive regimes should only be offered after individual and comprehensive counseling. The net benefit strongly depends on risk status, age and pre-existing risk factors for side effects.
## Medical Endocrine Prevention

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

<table>
<thead>
<tr>
<th>Source</th>
<th>Trial</th>
<th>Intended Treatment Duration</th>
<th>Total Follow-up</th>
<th>Mean, y</th>
<th>No. With Invasive Breast Cancer/Total Participants (%)</th>
<th>Rate per 1000 Women-Years</th>
<th>Risk Ratio (95% CI)</th>
<th>Favors Treatment</th>
<th>Favors Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen, low dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DeCensi et al, 2013</td>
<td>HOT</td>
<td>5</td>
<td>6.2</td>
<td>18/938 (1.9)</td>
<td>22/946 (2.3)</td>
<td>3.13</td>
<td>3.78</td>
<td>0.83 (0.42-1.62)</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher et al, 2005</td>
<td>NSABP-1</td>
<td>5</td>
<td>6.1</td>
<td>145/6681 (2.2)</td>
<td>250/6707 (3.7)</td>
<td>3.59</td>
<td>6.29</td>
<td>0.57 (0.46-0.70)</td>
<td></td>
</tr>
<tr>
<td>Cuzick et al, 2015</td>
<td>IBIS-I</td>
<td>5</td>
<td>16.0</td>
<td>214/3579 (6.0)</td>
<td>289/3575 (8.1)</td>
<td>3.86</td>
<td>5.29</td>
<td>0.73 (0.61-0.87)</td>
<td></td>
</tr>
<tr>
<td>Powles et al, 2007</td>
<td>Marsden</td>
<td>5</td>
<td>13.2</td>
<td>82/1238 (6.6)</td>
<td>104/1233 (8.4)</td>
<td>4.80</td>
<td>6.10</td>
<td>0.78 (0.58-1.04)</td>
<td></td>
</tr>
<tr>
<td>Veronesi et al, 2007</td>
<td>Italian</td>
<td>4a</td>
<td>11.2</td>
<td>53/2700 (2.0)</td>
<td>66/2708 (2.4)</td>
<td>1.77</td>
<td>2.21</td>
<td>0.80 (0.56-1.15)</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.69 (0.59-0.84)</td>
<td></td>
</tr>
</tbody>
</table>

\[ \hat{\mu} = 38.7\%; Q = 4.9 for heterogeneity; P = .18 \]

**Raloxifene**

<table>
<thead>
<tr>
<th>Source</th>
<th>Trial</th>
<th>Intended Treatment Duration</th>
<th>Total Follow-up</th>
<th>Mean, y</th>
<th>No. With Invasive Breast Cancer/Total Participants (%)</th>
<th>Rate per 1000 Women-Years</th>
<th>Risk Ratio (95% CI)</th>
<th>Favors Treatment</th>
<th>Favors Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martino et al, 2004</td>
<td>MORE/CORE</td>
<td>4 or 8#</td>
<td>5.4#</td>
<td>40/5129 (0.8)</td>
<td>58/2576 (2.3)</td>
<td>1.40</td>
<td>4.20</td>
<td>0.34 (0.22-0.50)</td>
<td></td>
</tr>
<tr>
<td>Barrett-Connor et al, 2006</td>
<td>RUTH</td>
<td>5.1#</td>
<td>5.6</td>
<td>40/5044 (0.8)</td>
<td>70/5057 (1.4)</td>
<td>1.43</td>
<td>2.49</td>
<td>0.56 (0.38-0.83)</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.44 (0.24-0.80)</td>
<td></td>
</tr>
</tbody>
</table>

\[ \hat{\mu} = 66.4\%; Q = 3.0 for heterogeneity; P = .08 \]

**Aromatase inhibitor**

<table>
<thead>
<tr>
<th>Source</th>
<th>Trial</th>
<th>Intended Treatment Duration</th>
<th>Total Follow-up</th>
<th>Mean, y</th>
<th>No. With Invasive Breast Cancer/Total Participants (%)</th>
<th>Rate per 1000 Women-Years</th>
<th>Risk Ratio (95% CI)</th>
<th>Favors Treatment</th>
<th>Favors Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goss et al, 2011</td>
<td>MAP.3</td>
<td>5#</td>
<td>2.9</td>
<td>11/2285 (0.5)</td>
<td>32/2275 (1.4)</td>
<td>1.66</td>
<td>4.85</td>
<td>0.35 (0.18-0.70)</td>
<td></td>
</tr>
<tr>
<td>Cuzick et al, 2014</td>
<td>IBIS-II</td>
<td>5</td>
<td>5</td>
<td>32/1920 (1.7)</td>
<td>64/1944 (3.3)</td>
<td>3.29</td>
<td>6.62</td>
<td>0.50 (0.32-0.76)</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.45 (0.26-0.70)</td>
<td></td>
</tr>
</tbody>
</table>

\[ \hat{\mu} = 0.0\%; Q = 0.8 for heterogeneity; P = .39 \]

# Medical Primary non-hormonally Prevention*

<table>
<thead>
<tr>
<th>Category</th>
<th>Oxford</th>
<th>AGO</th>
</tr>
</thead>
<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>
</tr>
<tr>
<td>Statins</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

* No approval, consider side effects

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
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

## Preference of a balanced diet*

- Olive oil (extra virgin olive oil), as part of mediterranean diet (2b B +)
- Fat reduced food (2a B +)
- Reduced consumption of red meat (2b C +)
- Nuts / peanuts (> 10g/d) (peanut butter without effect) (2b B +)
- Fiber containing food (2a B +)
- Vitamin D substitution for prevention (MaCa HR1,02) (1b B +/-)

## Mediterranean Diet

- Vegetables / fruits ** (2a B +/-)
- Phytoestrogens / soy (2a B +/-)
- Vegetarian / vegan diet (no significant risk reduction) (2b C +/-)
- Coffee (no significant reduction) (2a B +/-)
- Supplementation of vitamins, minerals, trace elements (2a B -)

---

* 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)**

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

  Particularly for
  - **ER+ / PR+ tumors**
    - 2a B
  - **Invasive lobular tumors**
    - 2a B
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_{\text{small effect bias}} = 0.184, P_{\text{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)
Smoking and Risk of Breast Cancer in the Generations Study Cohort

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
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)

<table>
<thead>
<tr>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b A</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>1b A</td>
<td>+/-</td>
<td></td>
</tr>
</tbody>
</table>
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&lt;br&gt;1.4 (1.1-1.9) insults&lt;br&gt;2.1 (1.4-3.3) pulmonary embolism&lt;br&gt;2.1 (1.5-2.9) deep vein thrombosis</td>
</tr>
<tr>
<td>WHI: JAMA 2002, JAMA 2017</td>
<td></td>
<td></td>
<td></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.&lt;br&gt;no secondary prevention&lt;br&gt;side effects as comp. to WHI + cholcystectomy</td>
</tr>
<tr>
<td>Hulley S: JAMA 2002</td>
<td></td>
<td></td>
<td></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&lt;br&gt;mode of appl. not relevant&lt;br&gt;duration &gt; 5 yrs.&lt;br&gt;Tibolon RR 1.45 (1.2-1.7)</td>
</tr>
<tr>
<td>Beral V: Lancet 2003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EPIC</strong></td>
<td>1.153 747</td>
<td>1.4 (1.2-1.6)</td>
<td>E-Mono&lt;br&gt;EPC &gt; E</td>
</tr>
<tr>
<td>Int J Cancer 2010</td>
<td></td>
<td></td>
<td></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>
<tr>
<td>Nelson HD: JAMA 2002</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chlebowski et al., Climacteric 2015, 18:336-8<br>Chlebowski et al., J Natl Compr Canc Netw 2015, 13:917-24<br>Manson JE et al., JAMA 2017; 318: 927-938
Prevention of Hormones (EGC) in Postmenopausal Patients

<table>
<thead>
<tr>
<th>Study Details</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>
</tr>
<tr>
<td></td>
<td></td>
<td>2.62 (1.56-4.38)</td>
<td>E/P combination</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.80 (1.21-2.68)</td>
<td>E only</td>
</tr>
</tbody>
</table>

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

Oxford LoE

1a

1a(−)
**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

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Suppression of ovarian function + Tamoxifen</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>
## 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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tamoxifen (vs nil)</strong></td>
<td>ipsilat.</td>
<td>0.47</td>
<td>SE 0.08</td>
<td>0.000001</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>
<td></td>
</tr>
<tr>
<td><strong>Tamoxifen (vs nil)</strong></td>
<td>ipsilat.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>-</td>
<td>EBCTCG 2005</td>
</tr>
<tr>
<td><strong>ER+ or unknown</strong></td>
<td>contralat.</td>
<td>0.61</td>
<td>0.50–0.73</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Aromatase inhibitor (vs Tam)</strong></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>
</tr>
<tr>
<td><strong>GnRH-agonist + tamoxifen (vs Tam)</strong></td>
<td>ipsilat.</td>
<td>11.8 vs 16.7%</td>
<td>-</td>
<td>Cochrane 2020</td>
<td></td>
</tr>
<tr>
<td></td>
<td>contralat.</td>
<td>0.56</td>
<td>0.29-1.07</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>