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

**Screened data bases**


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


Any full-term pregnancy, high number of pregnancies, first full-term pregnancy before age of 30 years


Breast feeding Stillen (protective if total breast-feeding time exceeds 1.5–2 years)


Lower birth weight of the first born (3000–3500 g vs. > 4500 g, RR = 1.53), lower length of pregnancy first born (26-31. WOP vs. 40-41. WOP; HR = 2.38, p = 0.03)


<table>
<thead>
<tr>
<th>Prevention</th>
<th>Oxford LoE</th>
<th>GR</th>
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</thead>
<tbody>
<tr>
<td>Any full-term pregnancy</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>High number of pregnancies</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
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<td>B</td>
</tr>
<tr>
<td>Breast feeding (protective if total breast-feeding time exceeds 1.5–2 years)</td>
<td>3a</td>
<td>B</td>
</tr>
<tr>
<td>Lower birth weight of the first born (3000-3500 vs. &gt; 4500g RR = 1.53)</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Lower length of pregnancy first born</td>
<td>2b</td>
<td>B</td>
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Unfavourable influence possible

- Polycystic Ovarian Syndrome (PCOS)

No influence

- Assisted reproduction
- Abortion

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<th>Prevention</th>
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<tr>
<td>Polycystic Ovarian Syndrome (PCOS)</td>
<td>2b</td>
<td>C</td>
</tr>
<tr>
<td>Assisted reproduction</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Abortion</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

**Polycystic Ovarian Syndrom (PCOS)**


**Assisted reproduction**


**Abortion**


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.


Breastfeeding is protective

**Medical Primary Prevention**

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<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>ASS</td>
<td>2a B</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>COX2-Inhibitors</td>
<td>2a B</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>2b B</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td>2b B</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>2b B</td>
<td>-</td>
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</table>

* No approval, consider side effects

**ASS**

**Cox2**

**Bisphosphonates**

Vitamin D

Statins
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]

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
Prevention by Changing Lifestyle Factors:
Body Mass Index / Diet

<table>
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<tr>
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<td>2a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td></td>
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<td>++</td>
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<td></td>
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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

Maintaining normal weight

Typ II Diabetes
Prevention/ screening and treatment
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

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

### Preference of a balanced diet

### Mediterranean Diet

Olive oil

Fat reduced food

Reduced consumption of red meet

Nuts

Fiber containing food

**Vitamin D**


**Vegetables / fruits**


**Phytoestrogens/soy**


**Vegetarian/ vegan diet**


Coffee

Supplementation of vitamins, minerals, trace elements

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. 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.


Prevention by Modifying Lifestyle Risk Factors: Alcohol

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

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<td></td>
<td>2a</td>
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<td>+</td>
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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_{small effect bias} = 0.184, P_{excess significance bias} = 4 x 10^{-8})


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.

Physical activity


Physical activity in the interval between menarche and first pregnancy

All these effects are valid also for women with germline BRCA1/2 mutation and hereditary risk for breast cancer.


- 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)

Oxford

<table>
<thead>
<tr>
<th>LoE</th>
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<tbody>
<tr>
<td>1b</td>
<td>A</td>
<td>+</td>
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<tr>
<td>1b</td>
<td>A</td>
<td>+/-</td>
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**Epigenome-wide association study for lifetime estrogen exposure identifies an epigenetic signature associated with breast cancer risk.**


<table>
<thead>
<tr>
<th>Epidemiological data from EPIC-Italy (n = 31,864)</th>
</tr>
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<tbody>
<tr>
<td><strong>Study:</strong> estimated lifetime estrogen exposure</td>
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<tr>
<td><strong>Method:</strong> epigenome-wide association study, blood DNA samples, N = 216, and 440 healthy controls</td>
</tr>
<tr>
<td><strong>Results:</strong> 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 &lt; 0.05)</td>
</tr>
</tbody>
</table>

Johansson A et al. Epigenome-Wide Association Study for Lifetime Estrogen Exposure Identifies an Epigenetic Signature Associated with Breast Cancer Risk

Risk Reduction for Ipsi- and Contralateral Breast Cancer

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

<table>
<thead>
<tr>
<th>Additional preventive effect by</th>
<th>Oxford</th>
</tr>
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<tbody>
<tr>
<td>- Tamoxifen</td>
<td>1a</td>
</tr>
<tr>
<td>- Aromatase inhibitors</td>
<td>1a</td>
</tr>
<tr>
<td>- Suppression of ovarian function + Tamoxifen</td>
<td>1b</td>
</tr>
</tbody>
</table>

Tamoxifen (HR_{total}=0.71; HR_{ER^+}=0.62)

Aromatase inhibitors (HR=0.62 vs Tam)

GnRH-agonists + Tamoxifen (HR=0.56 vs Tam)
**Risk reduction for ipsi- and contralateral second breast cancers (“second primaries”)**

<table>
<thead>
<tr>
<th>Local-</th>
<th>HR / RR</th>
<th>95% CI</th>
<th>p-value</th>
<th>ref.</th>
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<tr>
<td><strong>Tamoxifen (vs nil)</strong></td>
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<tr>
<td>ipsilat.</td>
<td>0.47</td>
<td>SE 0.08</td>
<td>0.00001</td>
<td>EBCTCG 2005</td>
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<tr>
<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)</td>
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<tr>
<td>ER+ or unknown</td>
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<td>ipsilat.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>-</td>
<td>EBCTCG 2005</td>
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<tr>
<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>
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<tr>
<td>ipsilat.</td>
<td>0.74</td>
<td>0.58 - 0.95</td>
<td>0.020</td>
<td>EBCTCG 2015</td>
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<tr>
<td>contralat.</td>
<td>0.62</td>
<td>0.48 - 0.80</td>
<td>0.0003</td>
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<tr>
<td>GnRH-agonist + tamoxifen (vs Tam)</td>
<td></td>
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<tr>
<td>ipsilat.</td>
<td>11.8 vs 16.7%</td>
<td>-</td>
<td>-</td>
<td>Cochrane 2020</td>
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<tr>
<td>contralat.</td>
<td>0.56</td>
<td>0.29- 1.07</td>
<td>-</td>
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**Tamoxifen (HR_{total}=0.71; HR_{ER^+}=0.61)**


**Aromatase inhibitors (HR=0.62 vs Tam)**


**GnRHa + Tamoxifen (HR=0.56 vs Tam)**

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.