Options for Primary Prevention:
Modifiable Lifestyle Factors
Prevention

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

- **Version 2021:**
  Rhiem / Solomayer

**Screened data bases**
**Risk Factors for Breast Cancer**

<table>
<thead>
<tr>
<th>Risk Factors for Breast Cancer 1</th>
<th>background</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Older age</td>
<td>- Lifetime number of menstrual cycles</td>
</tr>
<tr>
<td>- Genetics</td>
<td>- Early menarche, late menopause</td>
</tr>
<tr>
<td>- Family history of cancer</td>
<td>- Maternal pregnancy factors (e.g. pre-eclampsia) (risk reduction), and low physical activity during pregnancy (risk increase)</td>
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<tr>
<td>- Personal history of breast lesions</td>
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<tr>
<td>Non-proliferative lesions</td>
<td></td>
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<tr>
<td>Proliferative lesions w/o atypia</td>
<td></td>
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<tr>
<td>High risk lesions (ADH, LIN)</td>
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<tr>
<td>Breast cancer (DCIS, Inv. BC)</td>
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<tr>
<td>- Breast density</td>
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<tr>
<td>- Chest irradiation</td>
<td></td>
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<tr>
<td>- Type II Diabetes mellitus</td>
<td></td>
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<tr>
<td>Hyperthyroidism</td>
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</tbody>
</table>

**Legend:** *explicitly also for DCIS


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.


### Medical Primary Prevention

<table>
<thead>
<tr>
<th>Options for Primary Prevention: Modifiable Lifestyle Factors</th>
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<tbody>
<tr>
<td>ASS (especially for postmenopausal women with regard to DCIS and ER-positive invasive breast cancer)</td>
</tr>
<tr>
<td>Bisphosphonates</td>
</tr>
<tr>
<td>Statins (no effect)</td>
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<tr>
<td>Oxford LoE GR AGO</td>
</tr>
<tr>
<td>4d</td>
</tr>
<tr>
<td>2b</td>
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<tr>
<td>2b</td>
</tr>
</tbody>
</table>

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See slide 9
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;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]
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)

Oxford

<table>
<thead>
<tr>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
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<tbody>
<tr>
<td>2a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>3a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>2a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
</tbody>
</table>

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

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...


- 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.


- 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


Options for Primary Prevention: Modifiable Lifestyle Factors

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

\[ \text{RR (95\% CI): } 1.35 \ (1.23, \ 1.48, \ p\text{-value}=5.2 \times 10^{-10}, \ I^2 = 26\%, \ P_{\text{small effect bias}} = 0.184, \ P_{\text{excess significance bias}} = 4 \times 10^{-8}) \]

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, 
  if smoking > 10 years before first childbirth 
  (vs. never smokers)

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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 to women with an increased family 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.
Options for Primary Prevention: Modifiable Lifestyle Factors


Epidiome-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: epimenome-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>Options</th>
<th>N</th>
<th>MC-RR (95%CI)</th>
<th>Further information</th>
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</thead>
</table>
| WHI     | ~ 27 000 | 1.3 (1.0-1.6) | 1.3 (1.1-1.6) coronary events  
1.4 (1.1-1.8) strokes  
2.1 (1.3-3.3) pulmonary embolism  
2.1 (1.3-3.9) deep vein thrombosis |
| HERS    | 1 2763   | 1.2 (0.9-1.6) | ~/no secondary prevention  
side effects as comp. to WHI + cholecystectomy  
mod. age 67 |
| Million Women | 1.084 110  | 1.66 (1.3-2.0) | ~EUROCARE  
mod. of aspirin, not relevant  
duration ≥ 5 yrs.  
Triptolit IV 1.45 (1.2-1.7) |
| EPIC    | 1.153 747 | 1.4 (1.3-1.6) | ≥-Men  
EPE > E |
| Metaanalysis | 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, 13:017-24  
Manson JE et al., JAMA 2017, 318: 937-948
## Prevention of Hormones (EGC) in Postmenopausal Patients

<table>
<thead>
<tr>
<th>Study</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 (1.57-2.76)</td>
<td>current user</td>
</tr>
<tr>
<td>Case-Control-Study, retrospect. Australia</td>
<td></td>
<td>1.03 (0.82-1.38)</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>

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

