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
Risk Factors for Breast Cancer 1 → background

- 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

Legend: *explicitly also for DCIS
Risk Factors for Breast Cancer 2 Æ background

- 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

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.
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)

2000: subpopulations of obese women, inactive women, alcohol drinkers, smokers etc.
2010: breast cancer incidence as compared to background incidence in these subgroups

25.7% of postmenopausal breast cancer cases in the Netherlands in 2010 were attributable to lifestyle factors

- 8.8% attributed to obesity
- 6.6% attributed to alcohol
- 5.5% attributed to physical inactivity
- 3.2% attributed to low fiber intake
- 4.6% attributed to smoking

Update 2019: Tamimi et al, 2016
USA: more than a third of postmenopausal breast cancers are preventable through changes in modifiable risk factors

van Germert et al., Int J Cancer 2015; 152: 155-162

Options for Primary Prevention: Modifiable Lifestyle Factors
## Pregnancy-Related Factors

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Oxford</th>
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<tbody>
<tr>
<td>Any full term pregnancy</td>
<td>2b B</td>
</tr>
<tr>
<td>High number of pregnancies</td>
<td>2b B</td>
</tr>
<tr>
<td>First full term pregnancy before age of 30 years</td>
<td>2b B</td>
</tr>
<tr>
<td>Breast feeding (protective if total breast feeding time exceeds 1.5–2 years)</td>
<td>3a B</td>
</tr>
<tr>
<td>Lower birth weight of the first born (3000-3500 vs. &gt; 4500g RR=1.53)</td>
<td>2b B</td>
</tr>
<tr>
<td>Lower duration of pregnancy first born (26-31. WOP vs. 40-41. WOP; HR=2.38, p=0.03)</td>
<td>2b B</td>
</tr>
</tbody>
</table>

No influence

- Polycystic Ovarian Syndrome PCO                                          | 3b C   |
- Assisted reproduction                                                    | 2b B   |
- Abortion                                                                 | 2b B   |

Options for Primary Prevention: Modifiable Lifestyle Factors
## Medical Primary Prevention

<table>
<thead>
<tr>
<th>Options for Primary Prevention: Modifiable Lifestyle Factors</th>
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</thead>
<tbody>
<tr>
<td><strong>ASS (especially for postmenopausal women with regard to DCIS and ER-positive invasive breast cancer)</strong></td>
</tr>
<tr>
<td>See slide 9</td>
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<tr>
<td><strong>Bisphosphonates</strong></td>
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<tr>
<td><strong>Statins (no effect)</strong></td>
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<tr>
<td>ASS</td>
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<tr>
<td>Bisphosphonates</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Statins (no effect)</td>
<td>2b</td>
<td>B</td>
<td>-</td>
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</table>
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]
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

Options for Primary Prevention: Modifiable Lifestyle Factors

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<tbody>
<tr>
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<td>2a</td>
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<td>3a</td>
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<td>++</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
</tbody>
</table>
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).
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.
## Prevention by Changing Lifestyle Factors: Diet

### Options for Primary Prevention: Modifiable Lifestyle Factors

#### Preference of a balanced diet*

* As recommended by German Society of Nutrition (DGE)

<table>
<thead>
<tr>
<th>Dietary components</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
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<tbody>
<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>Supplementation of vitamins, minerals, trace elements</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>Fiber containing food</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>Nuts/peanuts (&gt; 10g/d) (peanut butter without effect)</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

** Recommended as a part of healthy nutrition
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
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

Oxford

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

2a B

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

RR (95% CI): 1.35 (1.23, 1.48, p-value=5.2 x 10^{-10}, I² = 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, if smoking > 10 years before first childbirth (vs. never smokers)*

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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 to women with an increased family risk.


- 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
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 even reduced breast cancer risk, but increased risk for endometrial cancer, unless after hysterectomy)

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</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>WHI</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>HERS</td>
<td>I 2763</td>
<td>1.2 (0.95-1.5)</td>
<td>med. age 67 J</td>
</tr>
<tr>
<td>Hulley S: JAMA 2002</td>
<td></td>
<td></td>
<td>no secondary prevention</td>
</tr>
<tr>
<td></td>
<td>II 2321</td>
<td></td>
<td>side effects as comp. to WHI + cholcystectomy</td>
</tr>
<tr>
<td>Million Women</td>
<td>1.084 110</td>
<td>1.66 (1.6-1.8)</td>
<td>EPC &gt; E</td>
</tr>
<tr>
<td>Beral V: Lancet 2003</td>
<td></td>
<td></td>
<td>mode of applic. not relevant duration &gt; 5 yrs.</td>
</tr>
<tr>
<td>EPIC</td>
<td>1.153 747</td>
<td>1.4 (1.2-1.6)</td>
<td>E-Mono</td>
</tr>
<tr>
<td>Int J Cancer 2010</td>
<td></td>
<td>1.8 (1.4-2.2)</td>
<td>EPC &gt; E</td>
</tr>
<tr>
<td>Metaanalyse</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>
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</tr>
</tbody>
</table>

**Further Information:***

- **WHI:** JAMA 2002, JAMA 2017
- **HERS:** Hulley S: JAMA 2002
- **Million Women:** Beral V: Lancet 2003
- **EPIC:** Int J Cancer 2010
- **Metaanalyse:** Nelson HD: JAMA 2002

**Additional References:**

- 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

**Options for Primary Prevention: Modifiable Lifestyle Factors**
### Prevention of Hormones (EGC) in Postmenopausal Patients

<table>
<thead>
<tr>
<th>CLEAR-study (NSW)</th>
<th>N</th>
<th>MC-RR (95% CI)</th>
<th>Further statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-Control-Study, retrospect. Australia</td>
<td>1236 BC cases</td>
<td>2.09 (1.57-2.78)</td>
<td>current user</td>
</tr>
<tr>
<td></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 or endometrial cancer is decreased

Oxford

LoE

1a

1a(-)