Options for Primary Prevention: Modifiable Lifestyle Factors
Prevention

- **Versions 2011–2019:**
  Dall / Diel / Gerber / Hanf / Maass / Mundhenke / Solbach / Solomayer / Thomssen / von Minckwitz

- **Version 2020:**
  Dall / Mundhenke
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
- 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
- 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
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
Prevention by Pregnancy Related Factors

- Any full term pregnancy
- 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)
- Assisted reproduction (no influence)
- 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)
- Polycystic Ovarian Syndrome PCO (no influence on BC)
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
The risk of breast, ovarian and endometrial cancer in obese women submitted to bariatric surgery: A meta-analysis
SABCS 2019, B Ishihara, D Farah, M Fonseca and A Nazário.

- Meta-analysis, of a total of 150,528 patients in the bariatric surgery arm and 1,461,938 women in the control arm.
- The risk of breast cancer was reduced by 61% [RR: 0.39 (95%CI [0.24 to 0.64]; I²= 90%; 6 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.
BMI and epigenetics link between obesity and breast cancer?

Changing the ESR1-promoter activity by methylation of CpG-islands

n = 120 breast tissue samples of cancer free patients

ESR1-promoter methylation

BMI $>30$ > BMI 25–29 > BMI 25 kg/m² (p < 0.001 resp.)

postmenopausal > premenopausal (p = 0.046)

[multivariate analysis]

BMI and epigenetics link between obesity and breast cancer?

- The epigenetic code (methyl marks) determines how the genome functions, dictating which genes are turned on and which genes are turned off.

- Development is the critical period when this programming occurs, directing cell and organ development.

Walker, CL, SABCS 2011
**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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<td>2b</td>
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<td>2a</td>
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- Preference of a balanced diet*
- Mediterranean Diet
- Dietary components
  - 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 +
  - Supplementation of vitamins, minerals, trace elements 2a B -
  - Vitamin D substitution for prevention (MaCa HR1,02) 1b B +
  - Vegetables / fruits ** 2a B +/-
  - Phytoestrogens / soy 2a B +/-
  - Fiber containing food 2a B +
  - Vegetarian/vegan diet (no significant risk reduction) 2b C +/-
  - Coffee reduces the BC risk (esp. receptor neg.) 2a B +/-
  - nuts/peanuts (> 10g/d) (peanut butter without effect) 2b B +
Coffee Consumption and Risk of Breast Cancer: An Up-To-Date Meta-Analysis
Xiu Juan Li: PlosOne, January 2013 | Volume 8 | Issue 1 | e52681

49497 breast cancer cases
26 studies (16 cohort and 10 case–control studies)

The pooled RR showed a borderline significant influence of highest coffee consumption (RR = 0.96; 95% CI 0.93–1.00), low-to moderate coffee consumption (RR = 0.99; 95% CI 0.95–1.04), or an increment of 2 cups/day of coffee consumption (RR = 0.98; 95% CI 0.97–1.00) on the risk of breast cancer.

In stratified analysis, a significant inverse association was observed in ER-negative subgroup. However, no significant association was noted in the others.
randomized, placebo-controlled trial, with a two-by-two factorial design, of vitamin D$_3$ (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
Conclusions and further perspectives

...probably the most apparent relationship prevails for consumption of isoflavones, whereas beneficial effects seem to be expressed only at high intake levels typical to Asian women ... compared to Western countries where the intake of soy products is remarkably low.

Protective activities of isoflavones might appear only in females consuming soy foods since their early age as childhood and adolescence can be crucial periods of exposure.

At present: “Recommendations for consumption of high-dose isoflavones ... to reduce the individual susceptibility towards breast carcinogenesis are still premature and can also be not completely without .. risks.”
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+/PgR+ tumors
  - Invasive lobular tumors

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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%, Psmall 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)

Oxford

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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 for 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
Avoiding hormonal therapy in postmenopausal women

- Avoiding estrogen/progestin combinations
  - Oxford LoE 1b, GR A, AGO +
- Avoiding estrogens only
  - (no increased, possibly reduced breast cancer risk, but increased risk for endometrial cancer, if not hysterectomized)
  - Oxford LoE 1b, GR A, AGO +/-
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 = 3 × 10^-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>
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<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>Hulley S: JAMA 2002</td>
<td>1 2763</td>
<td>1.2 (0.95-1.5)</td>
<td>1.4 (1.1-1.9) insults</td>
</tr>
<tr>
<td><strong>HERS</strong></td>
<td>1.2321 open-label, 2.7J</td>
<td>1.2 (0.95-1.5)</td>
<td>2.1 (1.4-3.3) pulmonary embolism</td>
</tr>
<tr>
<td><strong>Million Women</strong></td>
<td>1.084 110</td>
<td>1.66 (1.6-1.8)</td>
<td>2.1 (1.5-2.9) deep vein thrombosis</td>
</tr>
<tr>
<td>Beral V: Lancet 2003</td>
<td>4.1 J follow-up</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>EPC &gt; E mode of applic. not relevant duration &gt; 5 yrs.</td>
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<tr>
<td>Int J Cancer 2010</td>
<td>1.8 (1.4-2.2)</td>
<td></td>
<td>Tibolone RR 1.45 (1.2-1.7)</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>
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<tr>
<td>Nelson HD: JAMA 2002</td>
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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

**Further information**:
- 1.3 (1.1-1.6) coronary events
- 1.4 (1.1-1.9) insults
- 2.1 (1.4-3.3) pulmonary embolism
- 2.1 (1.5-2.9) deep vein thrombosis
- Med. age 67 J
- No secondary prevention
- Side effects as compared to WHI + cholecystectomy
- EPC > E mode of applic. not relevant duration > 5 yrs.
- Tibolone RR 1.45 (1.2-1.7)
- Side effects as compared to WHI +
## Prevention of Hormones (EGC) in Postmenopausal Patients

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<th>N</th>
<th>MC-RR (95% CI)</th>
<th>Further statements</th>
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<tbody>
<tr>
<td>CLEAR-study (NSW)</td>
<td>1236 BC cases</td>
<td>2.09 (1.57-2.78)</td>
<td>current user</td>
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<td></td>
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<td>1.03 (0.82-1.28)</td>
<td>past user</td>
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<td>2.62 (1.56-4.38)</td>
<td>E/P combination</td>
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<td>1.80 (1.21-2.68)</td>
<td>E only</td>
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Salagame et al., Int J Cancer. 2016;138(8):1905-14

**CLEAR**-

study (NSW) Case-Control-Study, retrospect. Australia
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(-)