

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Options for Primary Prevention: Modifiable Lifestyle Factors

Prevention

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- **Version 2011- 2017**
Dall / Diel / Gerber /Maass / Mundhenke Thomssen / von Minckwitz
- **Version 2018:**
Dall / Solbach

Non-modifiable Risk Factors for Breast Cancer

- **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, InvBC)
- **Breast density**
- **Chest irradiation**
- **Lifetime number of menstrual cycles**
Early menarche, late menopause, complications of pregnancy

Reproductive risk factors

- **Lower number of births or no pregnancy**
- **Advanced age at first full term delivery**

Modifiable

Risk Factors for Breast Cancer

- **Short duration or absence of breast feeding**
- **BMI < 18.5 and > 25 and especially > 40 (obesity)**
- **Diabetes mellitus Type II**
- **Food content**
- **Steroid hormone therapy**
 - Recent oral contraceptive use
 - Hormone therapy in postmenopausal women
- **Alcohol intake**
- **Smoking**
- **Light exposure at night (night shifts)**
- **Low physical activity**
- **Toxic agents in fetal and early childhood development (DES, polyfluoroalkyls)**
 - To date there is no evidence for a correlation between aluminium containing antiperspirants and breast cancer
 - To date there is no evidence for Glyphosate herbicide use and breast cancer

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

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

Secondary Prevention, Lifestyle and TNBC Subgroup

TNBC subgroup:

N = 518 pat., population-based prospective cohort study, FU 9.1 yrs.

factor:	risk of recurrence
phys. activity	HR 0.58 (0.39-0.86)
BMI	no differences

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Secondary Prevention, Lifestyle and ER-positive Subgroup

ER-positive subgroup:

n = 6295 pat., prospective pooling study, 5 yrs. after Dx

no weight gain	HR 1.00
≥ 10% weight gain	HR 1.24 (1.00-1.53)
BMI 30-34.99	HR 1.40 (1.05-1.86)
BMI >35	HR 1.41 (1.02-1.62)
no alcohol	HR 1.00
daily alcohol	HR 1.28 (1.091-1.62)
phys. activity	
none	HR 1.00
< 17.4 MET-h/wk	HR 0.81 (0.71-0.93)
≥ 17.4 MET-h/wk	HR 0.71 (0.61-0.82)

Nechuta et al., Int J Cancer, DOI 10.1002 (Epub ahead of print)

Prevention by Modifying Pregnancy Related Factors

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- 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)

Oxford		
LoE	GR	AGO
2b	B	
2b	B	
2b	B	
3a	B	

Prevention by Changing Lifestyle Factors: Body Mass Index / Diet

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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)

Oxford		
LoE	GR	AGO
2a	B	++
3a	B	++
2a	B	++
2b	B	++

BMI and epigenetics link between obesity and breast cancer?

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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?

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Methylation: Epigenetic "Software" that Programs the Genome

Histone modifications

DNA methylation

- 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

Prevention by Changing Lifestyle Factors: Diet

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- Preference of a balanced diet*
- Dietary components
 - Fat reduced food
 - Reduced consumption of red meat
 - Supplementation of vitamins, minerals, trace elements
 - Vitamin D substitution for prevention
 - Vegetables / fruits
 - Phytoestrogens / soy
 - Fiber containing food
 - Vegetarian diet (no risk reduction)
 - Vegan diet (no significant risk reduction)
 - nuts/peanuts (>10g/d)

	Oxford		
	LoE	GR	AGO
	2b	B	+
	2a	B	+
	2a	B	+
	2a	B	-
	3a	B	+/-
	2a	B	+/-**
	2a	B	+/-
	1b	A	+
	1b	B	+/-
	1b	B	+/-
	2B	B	+

* As recommended by German Society of Nutrition (DGE)

** Recommended as a part of healthy nutrition

Tree nut, peanut, and peanut butter intake and risk of postmenopausal breast cancer: The Netherlands Cohort Study

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n= 62573 women, aged 55-69

Follow up: 20.3 Years

2321 breast cancers and 1665 healthy subcohort members

Case cohort analysis

Tree nut or peanut intake >10g/day reduces HR-negative BC incidence

(HR 0.55 (CI 0.33-0.93), p=0.025)

No effect for peanut butter

Prevention by Modifying Lifestyle Risk Factors: Alcohol

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- Reduction of alcohol intake reduces risk of breast cancer

Particularly for

- ER+/PgR+ tumors
- Invasive lobular tumors

Oxford		
LoE	GR	AGO
2b	B	
2b	B	
2b	B	

Prevention by Modifying Lifestyle Risk Factors: Smoking

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- **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		
LoE	GR	AGO
2a	B	++

Prevention by Modifying Lifestyle Risk Factors: Physical Activity

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- **Physical exercise**

**(Metabolic equivalents to 3–5 hrs
moderate pace walking per week)**

Oxford		
LoE	GR	AGO
2a ⁽⁻⁾	B	++

Prevention by Modifying Lifestyle Risk Factors: Hormone Therapy in Postmenopausal Women

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- **Avoiding hormonal therapy in postmenopausal women**

- **Avoiding estrogen / progestin combinations**
- **Avoiding estrogens only**
(Estrogen alone 5 years after menopause does not show an increase in breast cancer risk)

Oxford		
LoE	GR	AGO
1b	A	+
1b	A	+/-

Prevention of Hormones in Postmenopausal Patients

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	N	MC-RR (95%CI)	Further information
WHI WHI: JAMA 2002, JAMA 2017	~ 27 000	1.3 (1,0-1,6)	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
HERS Hulley S: JAMA 2002	I 2763 RCT, med. 4.1 J II 2321 open-label, 2.7J	1.2 (0.95-1.5)	med. age 67 J no secondary prevention side effects as comp. to WHI + cholecystectomy ↗
Million Women Beral V: Lancet 2003	1.084 110 ~ 50% HRT 4.1 J. follow-up	1.66 (1.6-1.8)	EPC > E mode of applic. not relevant duration > 5 yrs. Tibolon RR 1.45 (1.2-1.7)
EPIC Int J Cancer 2010	1.153 747 person-years	1.4 (1.2-1.6) 1.8 (1.4-2.2)	E-Mono EPC > E
Metaanalyse Nelson HD: JAMA 2002	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, 13:917-24

Manson JE et al., JAMA 2017; 318: 927-938

Prevention of Hormones (EGC) in Postmenopausal Patients

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	N	MC-RR (95% CI)	Further statements
CLEAR-study (NSW)	1236 BC cases	2.09 (1,57-2.78)	current user
Case-Control-Study, retrospect. Australia		1.03 (0.82-1.28)	past user
		2.62 (1.56-4.38)	E/P combination
		1.80 (1.21-2.68)	E only

Prevention by Modifying Lifestyle Risk Factors: Oral Contraception (OC)

Oxford

LoE

- OC does not increase the risk of mortality from breast cancer
- Risk of breast cancer may be slightly increased, risk of ovarian, endometrial cancer is decreased

1a

1a⁽⁻⁾