Medical condition: Hormonal contraception and breast and ovarian cancer

Update February 2024 Gabriele Merki; Anne Gompel

Breast cancer risk – Epidemiology

% of the female population	BC Incidence New cases, All	BC Incidence New cases <50 Years	BC >50 years New cases	Death < 50 Years %	Death > 50 Years %
Northern Europe	3.4 %	2.2 %	4.3	1.1%	3.0
Western Europe	7.5 %	4.6%	8.7%	2.1%	7.4 %
India	7.9 %	11.4%	7.0%	7.0%	17.2 %
South Central Asia	11.3%	14.2%	10.0%	23.1	17.1

Approximately 1 in 8 women will develop breast cancer.
* Risk factors include lifestyle, genetics and reproductive factors (check notes).

Ref 1,2,3

Breast cancer risk in current CHC and HC users

Duration of use	Number of additional events /100.000 person-years CHC	Relative risk CHC	Relative risk any HC
1-<5 years	9 (3-14)	1.17 s	1.18 s
5-10 years	15 (8-21)	1.27 s	1.24 s
>10 years	21 (14-28)	1.46 s	1.38 s

- The risk is low, but increases with duration of use
- In some but not all studies this risk tends to decrease 5-10 years after stopping CHC use

s: significant $p<0.05$

Ref 1,2,3

Breast cancer risk in current Progestin-only contraceptive users

Newer data indicate an increase in BC risk for POC users *

Type of POC	Relative risk for current and recent use
POP	1.29 s
POC injection	1.18 s
POC implant	1.28 s
LNG-IUS	1.21 s

Last precription/Last use of a POP	RR
Recent 12 months	1.28 P<0.001
1-4 years ago	1.25 s P<0.001
> 5 years ago	1.19 s P<0.04

s: Significant

Ref 1-4

Breast cancer risk in current Progestin-only contraceptive users

Newer data indicate an increase in BC risk for POC users *

- The small increase in risk does not seem to differ from CHC
- Less than 5 years of discontinuation is not associated with a clear risk reduction
- The number of users of the drospirenone-only pill was very small, here no final conclusions are possible

Ref 1-4

Breast cancer risk in premenopausal LNG-20-IUS users

- Three high quality registry-based studies including women aged 18-49 years observing > 500000 wy of use found a minimal but significant risk increase for current users: RR 1.2-1.3 *(Ref 1,2.6)*.*
- Numbers *(Ref 1)*
  - Non-hormonal contraception 55 cases/100000 wy
  - LNG-IUS 70 cases/100000 wy

The LNG-IUS should not be used in women with breast cancer and as contraceptive after breast cancer !

An increased risk for older postmenopausal women was not found (*Ref 3,5*)

Ref 1-7

How to identify women at risk of hereditary breast cancer

Risk factors

- First- and second-degree relative (grandmother, mother, sister, aunt) on either the mother's or father's side of the family who had breast cancer diagnosed before age 50
- There is both breast and ovarian cancer on the same side of the family or in a single individual
- One relative(s) with triple-negative breast cancer*
- There are other cancers in the family in addition to breast, such as prostate, melanoma, pancreatic, stomach, uterine, thyroid, colon, and/or sarcoma
- Women in the family have had cancer in both breasts
- Ashkenazi Jewish (Eastern European) heritage
- African American and diagnosed with breast cancer at age 35 or younger
- A man in the family has had breast cancer
- There is a known abnormal breast cancer gene in the family

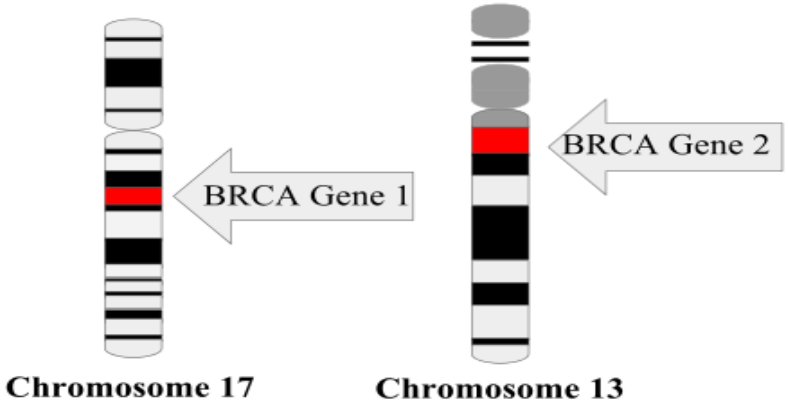
Ref 1

Hereditary breast cancer epidemiology

- Around 10% of breast cancers are hereditary
- The *BRCA1*/*BRCA2* mutations cause less than **20%** of all hereditary breast cancers
- The *BRCA1* mutation is associated with a 54–75% risk of developing breast cancer; *BRCA2* mutation with a 45% risk.
- Other genes are associated with the same or lower level of BC risk
- Over the whole population, *BRCA* mutations occur with a frequency of 0.3%
- In women with a family history suggesting a genetic factor the prevalence is 20%

Ref 1,2

What are *BRCA1*/*BRCA2* mutations?



- A *BRCA* mutation is a mutation in either of the *BRCA1* or *BRCA2* genes, which are tumour suppressor genes
- Harmful mutations in these genes produce a hereditary breast–ovarian cancer syndrome in affected individuals
- Each child of a genetic carrier, regardless of sex, has a 50% chance of inheriting the mutated gene from the parent who carries the mutation; therefore, history of both parents is important

Ref 1

BRCA1 and *BRCA2* mutations

- Associated risk of breast cancer
  BRCA1: 54–75% (mostly Triple negative)*
  BRCA2: 45%
- Associated risk of ovarian cancer**
  BRCA1: 18–60%
  BRCA2: 11–27%

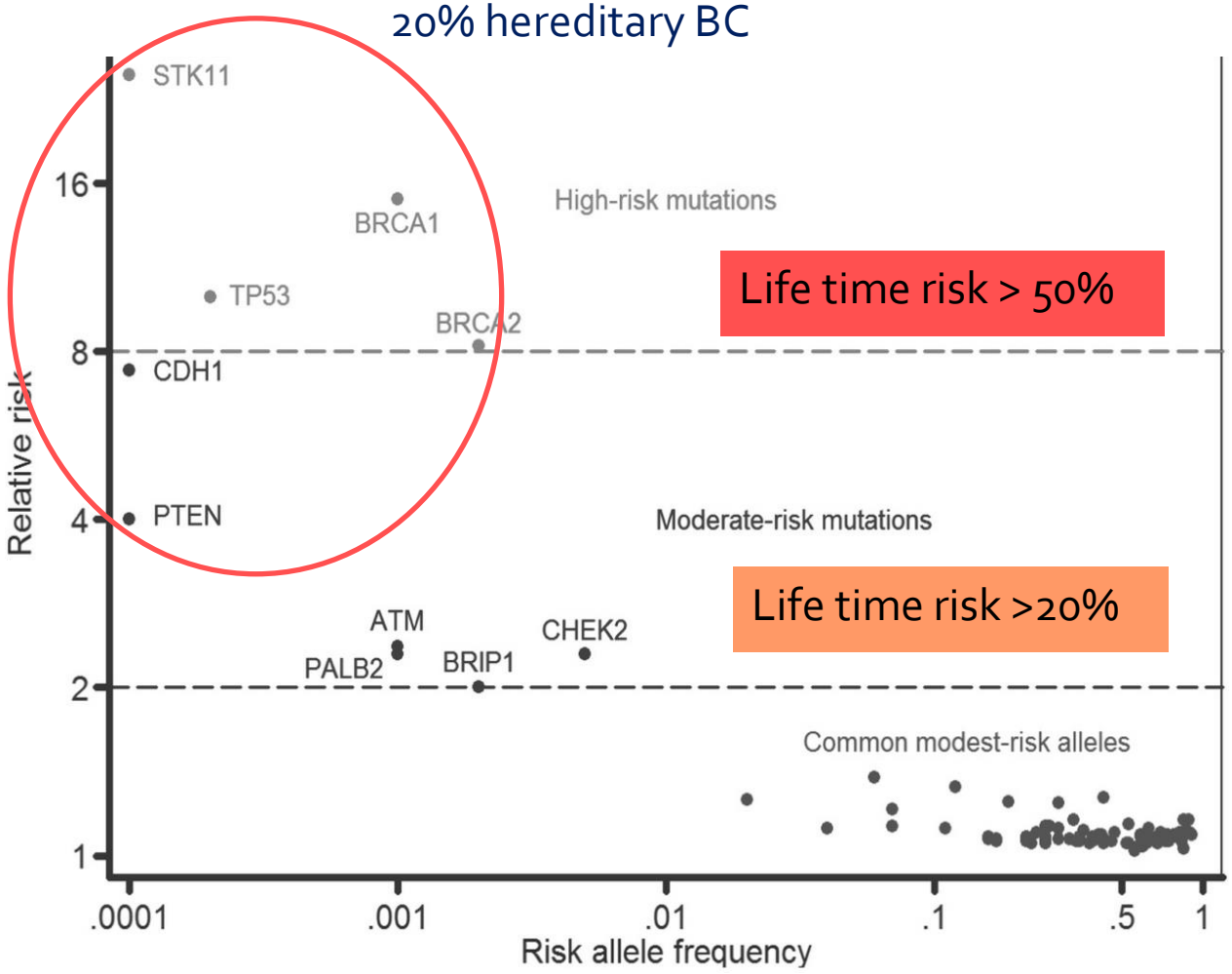
Breast cancer risk is very high in *BRCA1/BRCA2* mutation carriers

* Please check notes for further information

Ref 1-6

Other genes

20% hereditary BC



Life time risk > 50%

Life time risk >20%

Ref 1

Lifetime risk of breast, ovarian and other cancers in gene mutation carriers

	Breast cancer[a]	Tubo-ovarian cancers[b]	Pancreatic cancer[c]	Colon cancer[d]	Other cancers
ATM	Yes 25%-30%	Yes ≤5%	Yes <5%	No	Prostate 30%
BARD1	Yes ~20%	No	No	No	No
BRCA1	Yes >60%	Yes 40%-60%	Yes <5%	No	
BRCA2	Yes >60%	Yes 15%-30%	Yes <5%	No	Prostate 33%
BRIP1	No	Yes 5%-10%	No	No	No
CDH1	Yes (LBC) 40%	No	No	No	Diffuse gastric cancer 35%-45%
CHEK2	Yes 25%-30%	No	No	Yes 15%	
PALB2	Yes 40%-60%	Yes 3%-5%	Yes 2%-3%	No	No
PTEN	Yes 40%	No	No	Yes 10%	Thyroid 20%; endometrial 20%
RAD51C	Yes 20%	Yes 10%	No	No	No
RAD51D	Yes 10%	Yes 10%	No	No	No
STK11	Yes 40%	No	Yes 10%-30%	Yes 30%	Gastric 30%; Sertoli-Leydig 10%-20%
TP53	Yes 40%	No	Possibly	Possibly	Sarcoma, brain, leukaemia, adrenocortical carcinoma

HBOC, hereditary breast and ovarian cancer syndrome; LBC, lobular breast cancer; PV, pathogenic variant.
Lifetime risk in general 'average-risk' population:
[a]breast cancer 11%.
[b]ovarian cancer 1.3%.
[c]pancreatic cancer 1.6%.
[d]colon cancer 4%.

Ref: 1

Hereditary breast cancer risk and CHCs

- Risk is not elevated with use of combined hormonal contraceptives (CHCs) (Ref 1)
- In the reports listed, the presence of the *BRCA* gene was unknown in the study populations
- Risk is significantly increased in women with hereditary risk of breast cancer if COCs are used for >7 years (Ref 3)

According to present knowledge, hereditary breast cancer risk alone is no reason not to prescribe CHCs

Ref 1–4

Does CHC use increase breast cancer (BC) risk in women with *BRCA1*?

BRCA1	Odds Ratio
Kotsopoulos 2014	
• Ever-use	1.18*
• Use >5 years	1.22*
• Start <20 years	1.45*
• Breast cancer diagnosis < age 40	1.38*
Brohet 2007	1.47*

*Significant $p<0.05$

Metaanalyses 2018 BRCA 1*	Hazard ratio
Prospective data 2276 women 12 % with BC	1,08
• This could be n.s. due to survival bias or the underrepresentation of young women in the cohort	
Retrospective data 1 3828 women 28% with BC	1.26*
• Increase with longer duration of use >10y	1.37*
Retrospective data 2 5705 women 44% with BC	1.39*
Younger age of use trend to increased risk p<0.001	

Yes, under certain circumstances check notes

Ref 1-6

Does CHC use increase breast cancer risk in women with *BRCA2* mutations ?

BRCA2	OR
Haile 2006	
• Use >5 years	2.0*
• Duration of use/year *BRCA2*	1.08*
Brohet 2007	
• Use of 4–8 years	2.3

*Significant $p<0.05$

Metaanalyses 2018 BRCA 2	Hazard ratio
Prospective data 1610 women 10 % with BC	1.75*
• No change with duration of use, age at first use	
Retrospective data 1 2512 women 30% with BC	1.06
Retrospective data 2 3521 women 44% with BC	1.52*
Younger age 18-22 years	1.66*
Longer duration of use >10 years	1.70*

Ref 1-6

Yes, and this is higher under certain circumstances

CHCs and ovarian cancer in *BRCA* mutation carriers

BRCA1: OR 0.5*

BRCA2: OR 0.4*

CHCs are protective

The reduction in risk increases with duration of use

This has to be balanced against the 30% increase in breast cancer risk !

*Significant

Ref 1–4

Recommendations for CHC use in *BRCA1* mutation carriers

- *BRCA1* + CHC → 20-30% increased risk in breast cancer
- Consider that this adds to the very high baseline risk of developing the disease of 54–75%

1. Short-term use of CHCs is possible
2. Longer term use, especially in teenagers, cannot be recommended
3. The copper IUD is the best option, as the effect of progestin-only contraception on breast cancer risk of these women is unknown

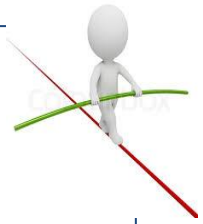
(These recommendations differ from the WHO guidelines and comment below and are based on data in the references in the notes)

Ref 1–5

Recommendation for CHC use in *BRCA2* mutation carriers

- *BRCA2* + CHC > 50% increased risk in breast cancer if use is longer than 5 years
- However, data are not consistent: **one study demonstrated no increase in risk**
- Consider that this adds to the very high baseline risk of developing the disease of 45%

1. CHC use is possible; however, benefits should be weighed against individual risk
2. Try to limit duration of use
3. Discuss use of copper IUD



(These recommendations differ from WHO guidelines and are based on data in the references)

Ref 1–5

CHC use in BRCA1/2 carriers

- Use of CHC to reduce the risk of ovarian cancer in these women is not justified, as …
- **Risk-reducing salpingo-oophorectomy** (around the age of 40 is currently recommended to BRCA1/2 mutation carriers. This procedure decreases the elevated ovarian cancer risk by 80–96 % but it initiates premature menopause as well.

Contraceptive options for women after breast cancer treatment

- Estrogens and progestins exert their effects via receptors
- We now know that estrogens and progestins can also exert direct non-receptor-mediated effects on tumour cells*
- Insofar they could have also have some impact on estrogen- and progesterone-receptor-negative breast cancer **Copper IUD or permanent methods can be used without concern**