

BRCA 1 and BRCA 2 Mutations

Recommendations for Contraception

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Topics

- Breast Cancer risk
- Breast Cancer risk and hormonal Contraception
- BRCA 1/2 mutations and changes in risk for breast and ovarian cancer caused by use of hormonal contraception

Breast cancer

- Breast cancer is the most frequent cancer diagnosis in women with a 10% risk for this condition during lifetime
- Ovarian cancer is more rare with an a lifetime risk to develop this cancer of 1.8%, however the mortality is higher

BRCA 1 and BRCA 2 Mutation

- Associated risk for breast cancer
BRCA 1: 54-75%
BRCA 2: 45%
- Associated risk for ovarian cancer
BRCA 1: 18-60%
BRCA 2: 11-27%
- BRCA 1: elevated risk for colon cancer

Tal Genader, The Breast 2005 14,264, Ganducci,A..Gynecol Endocrinol 2010

BRCA1 / BRCA 2

- Around 10% of breast cancers are of hereditary origin and mainly affect women with BRCA1 or BRCA2 mutation
- Today several hundred mutations of these genes have been identified.
- Over the whole population the BRCA mutations occur with a frequency of 0.3%
- The mutations cause less than 20 % of all hereditary breast cancers

BRCA 1 und BRCA 2 Mutations ...and hormonal therapy



If hormonal contraception or HRT are needed in carriers of these mutations the potential benefits have to be weighted against potential risk including variations in the incidence of breast or ovarian cancer.

BRCA 1 und BRCA 2 Mutationen Question

Are Combined hormonal contraceptives allowed ?



The exact mechanisms how estrogens might modify the breast cancer risk in BRCA – mutation carriers are still not known

Some epidemiologic studies have been published

Estrogen exert their effects on breast cancer cells via certain receptors

The breast cancer tissue in mutation carriers is usually :

BRCA 1	80% ER – negativ
BRCA 2	80% ER - positiv

Estrogen exert their effects on breast cancer cells via certain receptors

However

today we know that estrogens also can exert direct non-receptor mediated effects on tumor cells

Example

Bilateral removal of tubes and the ovary in BRCA1 carriers reduces the breast cancer risk in these patients.
Use of tamoxifen can reduce the risk for contralateral breast cancer

CHC and breast cancer in women without predisposition

CHC : Pill, Vaginal ring, Patch

CHC and breast cancer

Normal population

- Current use RR 1.24
- 10 years after use RR 1.07
- Young starters (<20y) RR 1.59

Norwegian and swedish studies 2002/2005 found higher risk in current und recent users: OR 1.5-1.6

Lancet 1996: includes 54 epidemiologic studies
Collaborative reanalysis: Collaborative group on Hormonal Factors in Breast cancer

Hereditary breast cancer and CHC

- Risk is not elevated by use of CHC *
- Risk increases 3fold in sisters and daughters of women with BC if these relatives used CHCs (mainly higher dosed formulations)
- In both those studies the BRCA – situation of the population involved, is not known

*Collaborative reanalysis: Collaborative group on Hormonal Factors in Breast cancer Lancet 1996; includes 54 epidemiologic studies
 **Grabrick, DM; JAMA 2000; 284: 1791

BRCA 1/2 - Carriers

CHC and Ovarian Cancer in BRCA Mutation carriers

Protective Effect !!

BRCA 1 : OR 0.5
 BRCA 2 : OR 0.4

The reduction in risk increases with duration of use. This is demonstrated in several studies.

Ganducci A, Gynecol Endocrinol 2010; Mc Laughlin, Lancet Oncol 2007; Perri T, Fert Ster 2015

CHC and Ovarian cancer in BRCA mutation carriers

TABLE 4

Multivariate model for impact of hormone and reproductive factors on ovarian cancer risk in BRCA-mutation carriers, adjusted for age.

Factor	BRCA1		BRCA2		BRCA1 and BRCA2	
	95% CI	OR	95% CI	OR	95% CI	OR
Parity	0.81-3.33	1.64	-	-	0.95-3.61	1.85
OCP	0.14-0.33	0.21*	0.09-0.61	0.24*	0.14-0.31	0.21*
HT	0.89-3.08	1.66*	1.19-7.6	3.04*	1.21-3.25	1.98*
Fertility treatment						
No						Reference
Any	0.43-1.53	0.81	0.31-3.30	1.01	0.46	0.80
IVF	0.23-2.93	0.82	0.20-16.48	1.81	0.31	0.53
Gonadotropins	0.06-4.26	0.50	-	-	0.03	0.26
CC	-	-	0.57-17.14	3.14	0.08	0.34
Mixed	0.70-4.15	1.8	0.09-6.95	0.77	0.68	1.45

Note: BRCA = breast cancer resistance protein; CC = dopamine cycle; CI = confidence interval; HT = hormone replacement therapy; IVF = in vitro fertilization; OCP = oral contraceptive use; OR = odds ratio.
 *P < .001.
 From: BRCA mutation and fertility drugs. *Fert Ster* 2015.

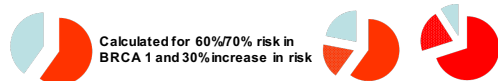
T.Perri et al.: Fert Ster 2015

CHC and breast cancer in BRCA mutation carriers

Breast Cancer risk

BRCA 1: 54-75%
 BRCA 2: 45%

A small (10 %) increase in risk is relevant as the baseline risk is so high.



CHC and breast cancer in BRCA mutation carriers

Study	Design und N	BRCA1 OR vs. Never-user	BRCA2 OR vs. Never-user	Remarks
Vessey 2006	Cohorte/case-control 981 BRCA 1 330 BRCA2	1.2 *	0.9	Nächste Folie
Brohet 2007	Retrospektiv 1181 BRCA1 412 BRCA2	1.47*	1.49 n.s.	BRCA1: 4-8J. OR 1.5* BRCA2: 4-8J. OR 2.3*
Pasanini 2009	Case-control 3123 Breast cancer <45j.;	1.3* Probable genetic cases N=382		COC 18-20J OR 1.6

Additional analyses in those studies

Vessey 2006 BRCA 1

- | | |
|------------------------------|-------|
| • Use > 5 years | 1.33* |
| • Start < 20 years | 1.36* |
| • BC diagnosis < age 40 | 1.38* |

Haile 2006 BRCA1/2 n=497/307

- | | OR |
|--------------------------------|-------|
| • BRCA 1 | 0.77 |
| • BRCA 2 Use > 5 years | 2.0* |
| • Duration of use / year BRCA2 | 1.08* |

CHC and breast cancer in BRCA mutation carriers

Studies from 2011

CHC und breast cancer

Retrospective Study

405 women with a history of breast cancer and CHC use

Analyses according to duration of use:

CHC < oder > 7 Jahre

Result: significant increase in risk for

- BRCA mutation carriers
- Women with hereditary risk for breast, ovarian-, colon cancer, if COC > 7 Jahre

Iatrakis, G. Clin Exp Obstet Gynecol 2011

CHC and breast cancer in BRCA mutation carriers

- CHC – use significantly reduces the risk for ovarian cancer (0.57). Reduction increases further with duration of use .
- Case-Control studies do not demonstrate a significant increase in breast cancer risk in BRCA1/BRCA2 carriers
- **In 1 Cohort study the increase in risk for BRCA 1 was OR1.5**

Cibula, D, Expert Rev Anticancer Ther ; Review 2011

Smoking and risk of breast cancer in carriers of mutations in BRCA1 or BRCA2 aged less than 50 years

Compared to non-smokers, the OR for risk of breast cancer for women with **five or more pack-years** of smoking was **2.3 (95% confidence interval 1.6-3.5) for BRCA1 carriers and 2.6 (1.8-3.9) for BRCA2 carriers**. Risk increased 7% per pack-year ($p < 0.001$) in both groups

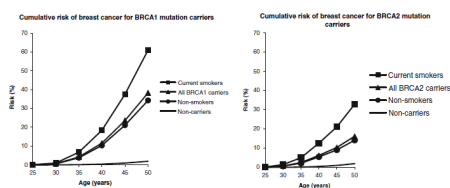


Fig. 1 Estimated cumulative incidence of breast cancer to age 50 in carriers of a BRCA1 or BRCA2 mutation. Cumulative incidence estimated by combining age-specific incidence data among BRCA1 and BRCA2 mutation carriers (5) with the smoking prevalence among controls of Table 2, and the odds-ratio estimates of Table 3

Conclusion BRCA 1

1. CHC increase the risk for breast cancer in BRCA1 carriers. (RR1.2-1.47)
2. The risk is especially high, if CHC are started in women aged <20 years. (OR 1.36-1.6)
3. The risk increases with duration of use (> 5 Jahre OR 1.36-1.5)
4. The effect of POC in these women is not known.
5. CHC reduce the risk for ovarian ancer by more than 50%

BRCA 1 Recommendations

- Longterm use of CHC **might** not be the best contraceptive option for BRCA1 mutation carriers, especially teenagers
- Copper-releasing –IUD are a safe and efficient option.
- CHC reduce the risk for ovarian cancer (RR 50%) however ovariectomy at age > 35 years might be the safer option.
- Good and specialised counselling is needed for the individual patient

Conclusion BRCA 2

- Data with regard to CHC use and breast cancer risk are inconsistent.
- Explanation:
 - In most studies number of cases is small, what potentially explains the lacking significance. In addition BRCA2 mutation carriers are at lower risk to develop breast cancer.
- 2 studies with higher numbers of cases indicate an increase in risk, if CHC are used for > 5 years.

BRCA 2 Recommendation?

- CHC use is possible, however benefits have to be weighted against risk for the individual woman.
- Indication for use must be need for contraception.
- Try to limit duration of use.
- Discuss Copper-releasing –IUD.
- CHC reduce the risk for ovarian cancer (RR 50%) however ovariectomy at age > 35 years might be the safer option