



ORIGINAL ARTICLE

BRCA1 and BRCA2 germ-line mutations and oral contraceptives: to use or not to use

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Received 5 September 2004; received in revised form 30 December 2004; accepted 27 January 2005

KEYWORDS

BRCA1 and BRCA2
germ-line mutations;
Oral contraception;
Ovarian cancer;
Breast cancer

Summary Approximately 10% of the cases of breast cancer and invasive ovarian cancer are hereditary, occurring predominantly in women with germ-line mutations in the BRCA1 or BRCA2 gene. In deciding whether women with germ-line mutations in the BRCA1 gene should use oral contraceptives a possible increase in the risk of breast cancer needs to be weighed against the convenience of this means of birth control and its potential to reduce the risk of ovarian cancer. In women with BRCA2 mutations, oral contraceptive use has not been associated with an increased risk of breast cancer and does have the potential to reduce the risk of ovarian cancer. Prophylactic surgical options and intensified surveillance should, of course, be discussed with these patients.

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Prevalence and risk of cancer in BRCA mutations

Breast cancer is the most common malignant condition among women with a lifetime risk of more than 10%. Ovarian cancer is rarer, with a lifetime risk of 1.8%, but is among the most lethal cancers.¹

Genetic, hormonal and environmental factors all have a role in the etiology of breast and ovarian

cancer. Approximately 10% of breast cancer and invasive ovarian cancer cases are hereditary, occurring predominantly in women with germ-line mutations in the BRCA1 or BRCA2 gene. In the Ashkenazi Jewish population, 29–41% of ovarian cancer cases are believed to be secondary to inheriting one of three founder mutations in the BRCA1 and BRCA2 genes, while only 10% of ovarian cancer cases are attributed to mutations of these genes in non-Ashkenazim.²

Several hundred mutations have been reported within the BRCA1 and BRCA2 genes.³ Nevertheless, BRCA mutations are rare, occurring in approximately 0.3% of the general population,^{4,5} and

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mutations in these genes account for less than one-fifth of the familial risk of breast cancer. These mutations are more common in women of Ashkenazi Jewish descent; about 2% of these women carry a deleterious BRCA1 or BRCA2 mutation and 12–30% of breast cancers in this group are thought to be attributable to mutations in the BRCA1 or BRCA2 gene.⁶ One estimate suggested that in a typical primary care practice with a patient population of 1000 women, one case of breast cancer would be diagnosed every one or two years; one case of breast cancer due to a BRCA1 or BRCA2 mutation would be diagnosed every 20 years.⁷

BRCA1 and BRCA2 gene abnormalities have a high penetrance. In women who have inherited BRCA1 or BRCA2 mutations, the lifetime risk of breast cancer is between 37% and 85% by the age of 70. The lifetime risk of ovarian cancer is 40–60% among women with BRCA1 mutations and 25% among those with BRCA2 mutations.⁸ In addition, individuals with BRCA1 mutations are more likely to develop colon cancer and men with BRCA1 mutations are at increased risk of developing prostate cancer.^{9,10}

The question of using hormonal therapy for the purposes of birth control and menopausal symptom management arises for most women, including those with BRCA1 or BRCA2 gene mutations. In deciding whether these women should use oral contraceptives a possible increase in the breast cancer risk needs to be weighed against the convenience of this means of birth control and its potential to reduce the risk of ovarian cancer.

In women who inherit BRCA1 and BRCA2 germ-line mutations, breast cancer usually occurs before 50 years of age.¹¹

Women with the BRCA1 mutation who develop breast cancer have estrogen receptor-negative tumors in approximately 80% of cases, whereas women with BRCA2 mutations who develop breast cancer have estrogen receptor-positive tumors in 80% of cases.^{12,13} Although the majority of BRCA1-associated cancers are estrogen-receptor negative, factors that influence endogenous hormone levels appear to modify the breast cancer risk. Among mutation carriers, the risk of breast cancer was decreased by bilateral oophorectomy¹⁴ and the risk of contralateral breast cancer was decreased by the use of tamoxifen.¹⁵

Kaduri et al. evaluated the correlation between hormonal factors and clinical presentation in 87 patients with BRCA1 or BRCA2 mutations. Oral contraceptive use was documented in 61% of patients with breast cancer compared with 11.8% of patients with ovarian cancer. There was no difference between the two groups with regard to other hormonal factors.¹⁶

Oral contraceptives and the risk of breast cancer in the general population

Long-term oral contraceptive use has been associated with a small increase in breast cancer in the general population. In a metaanalysis of 54 studies¹⁷ of women taking combined oral contraceptives, for a period of 10 years after stopping oral contraceptives, there is a small increase in the relative risk (RR) of having breast cancer diagnosed, with an RR in current users of 1.24, 1–4 years after stopping of 1.16, and 5–9 years after stopping of 1.07. There was no significant excess risk of having breast cancer diagnosed 10 or more years after stopping use (RR 1.01). Women who began oral contraceptive use before the age of 20 had a higher RR of having breast cancer diagnosed while they were using combined agents and in the 5 years after discontinuation compared with women who began use at an older age. However, the higher RRs apply at ages when breast cancer is rare and for a given duration of use. Earlier use did not result in more cancers being diagnosed than use beginning at an older age. Other features of hormonal contraceptive use such as duration of use, age at first use, and the dose and type of hormone within the contraceptives had little additional effect on breast cancer risk.

Because most oral contraceptive users are young, the RR of 1.24 represents a very small absolute risk. Only one additional breast cancer would be expected among 20 000 women who used oral contraceptives between the ages of 20 and 25 years.

Oral contraceptives and the risk of breast cancer in BRCA mutation carriers

The possibility that hormone exposure might influence breast cancer risk in high-risk women who carry a mutation in the BRCA1 or BRCA2 gene has recently been studied.

Narod et al. investigated whether the use of oral contraceptives influences the risk of breast cancer in women with the BRCA1 or BRCA2 mutations.¹¹ The study subjects were women who were known carriers of deleterious mutations of the BRCA1 or BRCA2 gene. There were 1311 matched case-control pairs, including 981 pairs with the BRCA1 mutation and 330 pairs with the BRCA2 mutation. Among the BRCA1 mutation carriers, the use of oral contraceptives was associated with a modestly increased risk of breast cancer (RR = 1.2). However, compared with BRCA1 mutation carriers who never used oral contraceptives, those who used

oral contraceptives for least 5 years were at increased risk of breast cancer (RR = 1.33), as were those who used oral contraceptives before the age of 30 (RR = 1.29), those who were diagnosed with breast cancer before the age of 40 (RR = 1.38; the possible cause is more sensitivity), and those who first used oral contraceptives before 1975 (OR = 1.42). Each additional year of oral contraceptive use before the age of 30 increased the risk of breast cancer by 3%. Compared with BRCA1 mutation carriers who never used oral contraceptives, those who began oral contraceptives after the age of 30 were not at increased risk of breast cancer.

For BRCA2 mutation carriers, the use of oral contraceptives had no association with an increased risk of breast cancer (RR 0.94)

Ovarian cancer and oral contraceptives in the general population

The risk of ovarian cancer is reduced by 50% or more in unselected women with long-term use of oral contraceptives. The risk was appreciably lower in those women who reported their first oral contraceptive use before 25 years of age (RR = 0.3 for first use before the age of 25, 0.8 for first use between the ages of 25 and 34, and 0.7 at the age of 35 or older). The risk decreased with increasing length of oral contraceptive use.^{18,19}

Several hypotheses have been proposed to explain the reduced risk of epithelial ovarian cancer associated with pregnancy and oral contraceptive use. The first states that some sequelae of ovulation increase the likelihood of malignancy, and that pregnancies and oral contraceptives protect by suppressing ovulation. The second hypothesis states that circulating levels of pituitary gonadotropins increase the risk of malignancy, and that pregnancies and oral contraceptives protect by suppressing secretion of these hormones. A third hypothesis is that the progestin in oral contraceptives induces apoptosis in the ovarian epithelium.²⁰

Oral contraceptives and the risk of ovarian cancer in BRCA mutation carriers

Narod et al. found that oral contraceptive use protected against ovarian cancer both for carriers of the BRCA1 mutation (RR 0.5) and for carriers of the BRCA2 mutation (RR 0.4).²¹ The risk decreased with increasing duration of use. The reduction in risk was 20% for up to 3 years of use, rising to 60% for 6 or more years of use. In this study, on average,

women stopped using oral contraceptives 17 years before the diagnosis of ovarian cancer and only 5.7% of women had taken an oral contraceptive agent during the 5-year period before diagnosis. Among the 63 patients who had had breast cancer in addition to ovarian cancer the average duration of oral contraceptive use was 5 years, compared with 4 years among those who had had no breast cancer.

Modan et al., however, showed minimal or no reduction in the odds of ovarian cancer in Israeli Jewish women carrying BRCA1 and BRCA2 mutations (0.2% reduction per year of oral contraceptive use).²² Multiparity was shown to reduce ovarian cancer risk in mutation carriers and noncarriers. In this study only 1.7% of controls were BRCA mutation carriers and controls were matched to all patients with invasive ovarian cancer. Thus, the controls were older than women with BRCA mutations and fewer controls had had long-term exposure to oral contraceptives. Only 8.5% of the Israeli controls had used oral contraceptives for 5 or more years, compared with 23% in the study by Narod et al.²³

In addition, Narod et al.²³ reported a case control study of 186 women with ovarian cancer and 186 individually matched controls, all of whom were Ashkenazi Jews with BRCA mutations. The odds ratio for ovarian cancer in the group that had used oral contraceptives for 5 or more years was 0.45 among North American women and 0.13 among Israeli women. The risk reduction of invasive epithelial ovarian cancer was 4.4% for each year of oral contraceptive use.

Calculated lifetime benefit/risk in women with BRCA1 and BRCA2 mutations who take oral contraceptives

The following calculations are at best approximations and are based on data presented above. In patients with BRCA1 the increased risk of breast cancer over a lifetime averaged 61% (range 37–85%).⁸ Taking oral contraceptives increases this by 20% for a net increase of 12% over a lifetime.¹¹ Thus, if there were 1000 women with BRCA1 taking oral contraceptives a net increase of 120 women with breast cancer over their lifetime would be predicted. For ovarian cancer in women with BRCA1 there is a 50% chance (range 40–60%) of developing this cancer, which is diminished by 50% in women taking oral contraceptives.²³ Thus, in 1000 women with BRCA1 taking oral contraceptives over their lifetime, there should be a decrease of 250 cases of ovarian cancer.

In patients with BRCA2 the lifetime risk of breast cancer averages 61% (range 37–85%).⁸ Since oral contraceptives do not alter this risk there should be no change in the incidence of this cancer over their lifetime.¹¹ In women with BRCA2 there is a lifetime risk of ovarian cancer of 25%. This risk is reduced by 60% by taking oral contraceptives.²³ Thus, in 1000 women with BRCA2 taking oral contraceptives there should be 150 fewer cases of ovarian cancer over their lifetime. It should be acknowledged that these calculations are only rough approximations and may well change as additional data are gathered.

Other options for the prevention of breast and ovarian cancer in high-risk women

In addition to prophylactic surgical options, intensified surveillance should be discussed with patients, with the understanding that patient decisions in this regard are highly individual and should be respected. The risk of breast cancer may be reduced by both prophylactic mastectomy and oophorectomy, while risk reduction for ovarian cancer is limited to bilateral oophorectomy.^{24,25}

According to the Cancer Genetics Studies Consortium Consensus Statement from 1999,²⁶ surveillance for female BRCA mutation carriers should include:

- beginning by the age of 18: monthly breast self-examination;
- beginning at the age of 25 or 10 years earlier than the age at which cancer was first diagnosed in the family: annual or semiannual clinical breast examinations, annual mammography, and annual or semiannual transvaginal ultrasounds and serum CA-125 level measurements.

Several small studies have suggested that MRI is significantly more sensitive for detecting breast cancers in high-risk women than mammography or ultrasound.^{27,28}

Recently published results of the New York Breast Cancer Study showed that physical activity and lack of obesity in adolescence were associated with significantly delayed breast cancer onset in BRCA mutation carriers.²⁹

Conclusions

Approximately 10% of cases of breast cancer and invasive ovarian cancer are hereditary, occurring predominantly in women with germ-line mutations

in the BRCA1 or BRCA2 gene. Hormonal factors also play a role in the etiology of breast and ovarian cancer. Long-term oral contraceptive use has been associated with a small increase in breast cancer and a 50% decrease in ovarian cancer in the general population. Among BRCA1 mutation carriers, the use of oral contraceptives at any time was associated with a modest increase in the risk of breast cancer. Women who use oral contraceptives before the age of 30 or take oral contraceptives for more than 5 years have an increased risk of breast cancer. For BRCA2 mutation carriers, the use of oral contraceptives at any time was not associated with an increased risk of breast cancer. Oral contraceptive use protects against ovarian cancer for carriers of the BRCA1 and BRCA2 mutations and for women without these mutations.

In deciding whether women with germ-line mutations of the BRCA1 gene should use oral contraceptives a possible increase in the risk of breast cancer needs to be weighed against the convenience of this means of birth control and its potential to reduce the risk of ovarian cancer. At this time, women with BRCA1 mutations should be advised of the potential for a slightly greater risk of breast cancer with the use of oral contraceptives, but their use is not contraindicated. In women with BRCA2 mutations, oral contraceptive use has not been associated with an increased risk of breast cancer and does have the potential to reduce the risk of ovarian cancer. It should be acknowledged that once ovarian cancer develops it has a poor prognosis. Prophylactic surgical options and intensified surveillance should, of course, be discussed with these patients.

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