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Current Opinion

Oral contraceptives, salpingo-oophorectomy and hormone replacement therapy in BRCA1–2 mutation carriers

Keywords: BRCA; Breast cancer; Ovarian cancer; Oral contraceptives; Hormone replacement therapy; Salpingo-oophorectomy

1. Introduction

Germline mutations in BRCA1 or BRCA2 genes predispose to hereditary breast and ovarian cancers. The estimated lifetime risk of breast cancer in BRCA1 mutation carriers ranges from 50% to 80%, while the estimated lifetime risk of ovarian cancer ranges from 20% to 65%. Although breast cancer risk is similar in women who inherit BRCA2 mutations, the lifetime risk of ovarian cancer is approximately 20% [1–3].

In the general population reproductive factors (such as parity, age at menopause, use of exogenous steroid hormones as contraceptives or after menopause) influence the risk of breast and ovarian cancer. In BRCA mutation carriers, these issues are much more complicated and not completely understood. Nonetheless, a growing number of data show that estrogens may modulate the risk of breast cancer in women with BRCA mutations. In these women estrogens may increase the probability of mutation due to enhanced proliferation and direct genotoxic effects of estrogen metabolites [4].

Women carrying BRCA1 and BRCA2 mutations face difficult decisions during the reproductive life. In the younger age period, they may be reluctant to using oral contraceptives (OCs) for the possible influence of these compounds on breast cancer incidence. After completion of childbearing, they may be offered the option of prophylactic oophorectomy, that is associated with a strong reduction of cancer risk, but also with the early onset of menopausal symptoms and the long-term consequences of estrogen deprivation.

2. OCs use and ovarian cancer risk in BRCA 1/2 mutation carriers

Several epidemiological studies have confirmed that OCs are protective against ovarian cancer in the general population. The risk reduction is related to the duration of use, ranging from 40% for the first year to more than 50% after 5 years or longer use. A lower incidence of ovarian cancer has been observed even 15 years or more after cessation of OCs use [5,6].

A recent metanalysis of data from 45 epidemiological studies substantiated that the reduction in ovarian cancer risk is proportional to the duration of OCs use. Nonetheless, the risk reduction per 5 years of OCs use seemed to be attenuated over years as it was 29% (95% CI 23–34%) for use that had been interrupted less than 10 years previously and only 15% (95% CI 9–21%) for use that had ceased 20–29 years previously. Ovarian cancer incidence and mortality were reduced from 1.2 to 0.8 and from 0.7 to 0.5 per 100 users, respectively. It was therefore estimated that for every 5000 woman—years of use, about two ovarian cancers and one death from the disease before age 75 are prevented. Though the risk reduction associated with OCs did not show significant changes according to the histotype,

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OCs use appeared to have only a little impact on the incidence of mucinous tumors [7].

Several studies seem to suggest that OCs may also reduce the risk of hereditary ovarian cancer (Table 1) The first study by Narod in 1998, enrolling 207 women with hereditary ovarian cancer and 161 of their sisters as controls, showed that the relative risk of ovarian cancer was 0.5 (95% CI 0.3–0.8) with any past use of OCs. The risk reductions did not vary when the authors separated the carriers by type of mutation (BRCA1 vs. BRCA2). The risk decreased as the duration of use increased, with a 60% reduction of risk for 6 or more years of use [8].

These results have been subsequently confirmed by three studies [9–11]. In the case–control study by Whittemore on 451 BRCA1 or BRCA2 carriers, the relative risk of ovarian cancer associated with OCs use was 0.85 (95% CI 0.53–1.36), while the risk decreased to 0.62 (0.35–1.09) for more than 6 years of use with a risk reduction of 5% (1–9%) per year [9]. The study by McGuire compared 36 BRCA1 mutation carriers diagnosed with invasive epithelial ovarian cancer and 381 noncarriers cases with 568 random controls who were matched for age and race/ethnicity. In both carriers and noncarriers ever use of OCs was associated with a relative risk of ovarian cancer of 0.54 (95% CI 0.26–1.13) and 0.55 (95% CI 0.41–0.73), respectively. The protection was also associated with duration of use, reaching a risk reduction of 78% (95% CI 0.07–0.71) for more than 7 years of use [10]. Only in the study by Modan, a population-based study focused on Israeli Jewish women positive for the Ashkenazi founder mutations, OCs use did not influence the risk of ovarian cancer among BRCA mutations carriers, whereas a significant decrease of the risk was found among patients without mutations, particularly in long-term users [11]. Nonetheless, the null findings of this study may have occurred because the controls were older than the carrier cases. As a result, the controls had less opportunity for long-term exposure to OCs, which became widespread after 1960 [9].

A recent large case–control study on 3223 women from 10 countries, comparing 799 BRCA mutation carriers with a history of invasive ovarian cancer and 2424 carriers without ovarian cancer who did not undergo bilateral oophorectomy, confirmed the protective effect of OCs on the ovaries. The use of OCs significantly reduced the risk of ovarian cancer in both BRCA1 (OR = 0.56; 95% CI 0.45–0.71) and BRCA2 mutation carriers (OR = 0.39; 95% CI 0.23–0.66). A significant trend pointing towards higher protection with increasing duration of use was also observed, with a 53% decrease of ovarian cancer risk (95% CI 0.35–0.62) for more than 5 years of use [12].

Table 1
Oral contraceptives (OCs) use and risk of ovarian cancer in BRCA 1/2 mutation carriers

Author (year)	OCs use	OR (Odds ratio)	95% CI*
McLaughlin (2007)	Ever use	0.53	0.43–0.66
	0–1.0 years	0.67	0.50–0.89
	1.1–3.0 years	0.63	0.46–0.86
	3.1–5.0 years	0.36	0.25–0.53
	>5.0 years	0.47	0.35–0.62
Whittemore et al. (2004)	Ever use	0.85	0.53–1.4
	1–2 years	1.5	0.82–2.90
	3–5 years	0.69	033–1.40
	≥6 years	0.62	0.35–1.10
McGuire et al. (2004)	Ever use	0.54	0.26–1.13
	1–2 years	1.18	0.50–2.75
	3–6 years	0.46	0.16–1.28
	≥7 years	0.22	0.07–0.71
Modan et al. (2001)	0.1–1.9 years	1.14	0.67–1.94
	2.0–4.9 years	0.77	0.41–1.44
	≥5 years	1.07	0.63–1.83
Narod et al. (1998)	Ever use	0.5	0.3–0.8
	<3 years	0.8	0.4–1.4
	3–6 years	0.4	0.2–0.9
	≥6 years	0.4	0.2–0.7

* 95% CI: confidence interval.

3. OCs use and breast cancer risk in BRCA 1/2 mutation carriers

OCs have been consistently associated with a modest increase of breast cancer risk in general population [13].

In a comprehensive metanalysis of 54 studies, encompassing about 90% of the epidemiological data available at that time, the relative risk of diagnosing breast cancer in women currently assuming OCs was 1.24, while the risk was doubled for young women who used OCs within the past 5 years and who were under 20 years of age at first use. Conversely, breast cancer

risk was not increased in women who stopped taking OCs 10 or more years before enrolling in the study [14].

The association between OCs use and breast cancer risk in BRCA mutation carriers is still controversial. The estimated magnitude of the risk is crucial because breast cancer risk is particularly high in BRCA carriers at a young age, when OC are generally prescribed.

Only a few studies have assessed the effect of OCs among BRCA1/2 mutation carriers with inconsistent results. (Table 2) The definition of risk in this group of women appears particularly difficult because the design of studies suffer from testing, information and survival bias and results are confounded by prophylactic surgery. Furthermore, some studies are not enough informative due to the small sample size and because BRCA1/2 carriers were compared with controls who are likely to be noncarriers, but were not tested for mutations.

The study by Milne, for example, compared 1.156 incident cases of invasive breast cancer diagnosed before age 40 stratified for BRCA mutations (including 47 BRCA1 and 36 BRCA2 mutation carriers) and 815 unrelated population-based controls not tested for mutation [15]. The authors reported a protective effect of OCs use for BRCA1 (OR = 0.22; 95% CI 0.1–0.49) and essentially no effect in women carrying BRCA2 mutation (OR = 1.02; 95% CI 0.34–3.09). Interestingly, the protective effect of OC among BRCA1 mutation carriers was observed only for OC use after 1975; conversely, the older OCs use was associated with an increased breast cancer risk, although not significant, both in BRCA1 and BRCA2 mutation carriers [15]. The first important study addressing this issue was published by Narod in 2002 and found a modest, though significant, increase in breast cancer risk for ever use of OCs (OR = 1.20; 95% CI 1.02–1.40, $P = 0.003$). Compared with BRCA1 mutation carriers who never used OCs, those who used OCs for at least 5 years had an increased risk of breast cancer (OR = 1.33, 95% CI 1.11–1.60), as did those who used OCs before age 30 (OR = 1.29; 95% CI 1.09–1.52), and those who first used OCs before 1975 (OR = 1.42; 95% CI 1.17–1.75). Longer duration of use was associated with a higher risk only in BRCA1 carriers; indeed, the risk was found to be increased by about 30% after 5 or more years of use [16]. Opposite results were reported by Haile in a smaller case–control study on 497 BRCA1 and 307 BRCA2 mutation carriers. It was not found a significant association between breast cancer risk and OCs use in BRCA1 mutation carriers, independently from the duration of use. Conversely, breast cancer risk in BRCA2 mutation carriers showed a significant association with OC use for at least 5 years (OR = 2.06; 95% CI 1.08–3.94). The risk of women carrying BRCA2 mutations increased with ≥4 years of OC use before first full term pregnancy (OR = 3.46; 95% CI 2.10–5.70) and for

Table 2
Oral contraceptives (OCs) use and risk of breast cancer in BRCA 1/2 mutation carriers

Author (year)	OCs use	BRCA1 OR (95% CI)*	BRCA2 OR (95% CI)
Brohet et al. (2007)	Ever use	1.47 (1.13–1.91)	1.49 (0.8–2.70)
	1–3 years	1.36 (0.99–1.88)	1.23 (0.64–2.35)
	4–8 years	1.51 (1.10–2.08)	2.27 (1.10–4.65)
	>9 years	1.63 (1.17–2.29)	1.47 (0.66–3.28)
Haile et al. (2006)	Ever use	0.77 (0.53–1.12)	1.62 (0.90–2.92)
	<1 year	1.00	1.00
	1–4 years	0.68 (0.43–1.08)	1.16 (0.58–2.34)
	≥5 years	0.80 (0.54–1.18)	2.06 (1.08–3.94)
Milne et al. (2005)	Ever use	0.22 (0.1–0.49)	1.02 (0.34–3.09)
Narod et al. (2002)	Ever use	1.20 (1.02–1.40)	0.94 (0.72–1.24)
	0–4 years	1.10 (0.92–1.31)	0.90 (0.67–1.20)
	5–9 years	1.36 (1.11–1.67)	0.82 (0.56–1.91)
	10–14 years	1.27 (0.99–1.64)	1.16 (0.75–1.78)
	15–30 years	1.30 (0.91–1.87)	1.35 (0.71–2.56)

* OR (95% CI): odds ratio (95% confidence interval).

≥4 years of OC use before age 30 (OR = 2.2; 95% CI 1.26–3.85) [17].

There could be different explanations for the contrasting results obtained from the studies by Narod and Haile [16,17]. For instance, although both studies share a similar design, in the study by Narod the 52 centers distributed over 11 countries did not use the same standardized set of questions for recalling data. In addition, the interviews were conducted on average after 8 years from breast cancer diagnosis, while in the study by Haile most of women were interviewed after 3 years.

More recently, a large retrospective study from the International BRCA1/2 Carrier Cohort Study (IBCCS) on 1.593 BRCA1/2 mutation carriers confirmed that OCs use is associated with an increased breast cancer risk. In this study, the risk was 1.47 (95% CI 1.16–1.87) for ever users and was found even higher in women who had used OCs before first full term pregnancy (HR = 1.85; 95% CI 1.17–2.93 for >9 years of use). Risk did not vary significantly according to BRCA mutation, time since stopping use, age at start, or calendar year at start, whereas it seemed to increase with duration of OCs use (HR = 1.61; 95% CI 1.18–2.20 for >9 years of use) [18].

In conclusion, available data suggest that OCs use may be associated with an increased risk of breast cancer in BRCA 1/2-mutation carriers. Nevertheless, it is still too early to give univocal advice to BRCA1/2 mutation carriers, since OCs use seems to reduce ovarian cancer risk as well as already demonstrated in the general population.

4. Risk-reducing oophorectomy in women with BRCA1 or BRCA2 germline mutations

Several studies have demonstrated the effectiveness of prophylactic oophorectomy to reduce the risk of both ovarian and breast cancer in BRCA1/2 mutation carriers [19–23].

A recent metanalysis confirmed the protective effect of prophylactic oophorectomy with a risk reduction ranging from 70% to 96% for gynaecologic cancers and from 47% to 68% for breast cancers [21]. Some authors suggested that the protection may differ between BRCA1 and BRCA2 mutation carriers. In fact, there are substantial differences in the phenotype of BRCA-associated breast cancer. Only 10–24% of BRCA1-associated breast cancers express estrogen receptors, compared with 65–80% of BRCA2-associated breast cancers [24–26]. Moreover, since the age-specific cancer risk of BRCA1 and BRCA2 mutation carriers is different, prophylactic surgery may exert a distinct age-related effect. In fact, about 39–46% of BRCA1 mutation carriers develop ovarian cancer by age 70 years compared with 10–27% of BRCA2 mutation carriers [2,21,24–26]. The effect on breast cancer risk associated with BRCA1 mutation decreases with age, from >30-fold in women <40 years old to about 10-fold in women >60 years old; in contrast, the increased risk for women with a BRCA2 mutation is on average 11-fold and there is not evidence that is higher at younger ages [2,15].

As a result, a case–control study reported that reduction in breast cancer risk was greater for BRCA1 mutation carriers who underwent oophorectomy before 40 years of age as compared with BRCA2 carriers. It is likely that the smaller overall effect in BRCA2 carriers was due to their later age at diagnosis, and consequently, a longer period of time elapsed between oophorectomy and breast cancer for BRCA2 than for BRCA1 mutation carriers [27].

As far as the surgical technique is concerned, given that both ovaries and fallopian tubes are at higher risk for malignant transformation, it is mandatory to remove as much tissue at risk as possible [28]. There is controversy as to whether this requires removal of the uterus, because a small portion of interstitial fallopian tube in the cornua of the uterus is left in situ if hysterectomy is not performed. However, in the largest clinical-pathologic study of fallopian tube cancer to date, 92% of cancers originated in the distal or mid-portion of the tube [29].

Several authors advocate the routinary removal of uterus at time of salpingo-oophorectomy also for other reasons. The Women's Health Initiative trial reported that estrogen alone replacement therapy (ERT) was not associated with increased breast cancer risk in hysterectomised postmenopausal women [30]. On the contrary, the association of estrogens plus a progestin, required to counterbalance the proliferative effect of estrogens on the endometrium, increased breast cancer risk by 26% [31]. These data have been confirmed by other trials and suggest that ERT therapy might be preferable when breast cancer risk is particularly high, as in BRCA carriers.

Others claimed that the surgical morbidity associated with hysterectomy procedure was significantly outweighed by the risk reduction of endometrial cancer associated with tamoxifen used for preventive purposes [32]. Furthermore, it has been reported that BRCA mutation carriers are at higher risk of endometrial serous cancer, although the lifetime risk is as low as 1–2 cases per 1000 carriers [33]. Hysterectomy eliminates the risk of serous carcinoma of the uterus, but it remains unclear whether this relatively low lifetime risk may warrant concomitant hysterectomy at time of prophylactic salpingo-oophorectomy.

At present, all guidelines agree that hysterectomy may be reasonably performed at time of salpingo-oophorectomy, though it is not a required component of the procedure [21]. Women with BRCA mutations undergoing prophylactic salpingo-oophorectomy should be informed of the relative risks and benefits also deriving from concomitant hysterectomy and should make an informed decision in concert with their surgeon.

5. Hormone replacement therapy (HRT) in BRCA1/2 mutation carriers

The immediate consequence of prophylactic bilateral oophorectomy in premenopausal women with BRCA 1/2 mutations is the induction of a premature surgical menopause. Beyond the loss of fertility, iatrogenic menopause is characterised by typical early symptoms, such as hot flushes, night sweats, vaginal dryness, mood disturbances and by long-term consequences, such as an increased risk of heart disease, osteoporosis and a relevant decline in sexual interest and activity.

HRT should be the ideal therapy for all these problems, but there is a strong reluctance to the use of estrogens in women at high risk of breast cancer. Non-hormonal therapies may be useful for the relief of specific symptoms in some women as well. For instance, treatment with selective serotonin reuptake inhibitors can reduce the frequency and severity of vasomotor symptoms in approximately two thirds of women with breast cancer; however, there remains a substantial group of symptomatic women refractory to this approach [34].

Similarly, non-hormonal topic therapy for the management of vaginal symptoms may be ineffective in a variable number of menopausal women who will continue to experience a bothersome vaginal atrophy [35].

The analysis of a prospective cohort of women with BRCA 1/2 mutations who underwent prophylactic oophorectomy showed that HRT is highly effective in relieving vasomotor symptoms and urogenital atrophy [36]. Nonetheless, there is no consensus about whether HRT use may revert the reduction of breast cancer risk obtained with bilateral prophylactic oophorectomy in BRCA1/2 mutation carriers. So far, only one study addressed this problem by comparing 155 women who underwent bilateral prophylactic oophorectomy (60% of them using HRT after surgery for a mean period of 3.2 years) and 307 women with intact ovaries. The authors reported that the reduction in breast cancer risk associated with oophorectomy was not modified by the use of HRT [37].

A major concern is the optimal duration of HRT in BRCA mutation carriers who underwent prophylactic oophorectomy. The study by Rebbeck supports the hypothesis that short-term use of HRT to manage immediate menopausal symptoms may not influence the risk of breast cancer [37].

Further information may be drawn from a Markov decision analytic model developed to assess the impact of bilateral prophylactic oophorectomy, bilateral prophylactic mastectomy and HRT use on life expectancy of BRCA 1/2 mutation carriers for hypothetical cohorts of 30, 35 and 40 years of age [38]. In this model women with BRCA1/2 mutations who underwent bilateral prophylactic oophorectomy alone or bilateral prophylactic oophorectomy plus mastectomy between the age of 30 and 40 years experienced a significant gain in life expectancy as compared to those women who did not undergo any prophylactic surgery, irrespective of their decision about HRT use after oophorectomy, if hormonal therapy was suspended at the age of natural menopause. The gain of life expectancy obtained with prophylactic oophorectomy decreased as age at the time of oophorectomy increased; the addition of prophylactic mastectomy was associated with a greater increase of life expectancy. The overall effect of HRT use on life expectancy ranged from a gain of 0.79 years for women who underwent prophylactic oophorectomy plus mastectomy at the age of 40 and used HRT until

50 years of age, to a loss of 1.09 years for women who had prophylactic oophorectomy alone at the age of 30 and assumed HRT for the entire life [38].

Overall, these data suggest that all women carrying BRCA1/2 mutations should be strongly encouraged to undergo bilateral prophylactic oophorectomy after completion of childbearing, should decide about the use of short term HRT after surgery on the basis of quality of life, and should plan to discontinue its use at or before the expected age of natural menopause.

6. Conclusions and future directions

Over the last few years, different preventive strategies have been developed to reduce gynaecologic cancer risk in BRCA 1/2-mutation carriers. OCs use reduces the risk of ovarian cancer in the general population and probably also in BRCA mutations carriers. Unfortunately OCs seem to be associated with an increase of breast cancer risk in mutation carriers. As consequences, it is still too early to recommend OCs use as a chemoprevention strategy against ovarian cancer in high-risk women.

Though intensive screening programs and chemoprevention with tamoxifen play a role in the management of women with BRCA mutations, prophylactic surgery is clearly the most effective strategy to reduce the incidence of breast and ovarian cancer. On the other hand, prophylactic bilateral oophorectomy is associated with the abrupt onset of menopausal symptoms in premenopausal women at the time of surgery. HRT is effective in relieving vasomotor and urogenital dystrophic symptoms, but it is still controversial whether it may or may not decrease the protective effect of oophorectomy on breast cancer risk. The few data available do not demonstrate any adverse modification of breast cancer risk by short-term use of HRT after oophorectomy, though further studies are needed to confirm the efficacy and safety of different preparations.

The body of knowledge on cancer hereditary syndromes is growing at rapid pace and we are now able to provide women with more detailed information on their cancer risk. Nevertheless, all efforts should be directed towards a better understanding of the biology of cancers associated with BRCA1 and BRCA2 germline mutations. This may allow to improve prevention and surveillance strategies and hopefully avoid that these women will have to face the drastic choice of prophylactic surgery.

References

[1] Ford D, Easton DF, Bishop DT, et al. Risks of cancer in BRCA1-mutation carriers. Lancet 1994;343:692–5.
[2] Antoniou A, Pharoah PDP, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003;72:1117–30.
[3] Easton DF, Ford D, Bishop DT. Breast and ovarian cancer incidence in BRCA1-mutation carriers breast cancer linkage consortium. Am J Hum Genet 1995;56:265–71.
[4] Nourizinia M, Coupier I, Pujol P. Is BRCA1/BRCA2-related breast carcinogenesis estrogen dependent? Cancer 2005;104:1567–74.
[5] Ness RB, Grisso JA, Klapper J, et al. Oral contraceptives, other methods of contraception, and reduced risk for ovarian cancer. Epidemiology 2001;12:307–12.
[6] Bosetti C, Negri E, Trichopoulos D, et al. Long-term effects of oral contraceptives on ovarian cancer risk. Int J Cancer 2002;102:262–5.
[7] Collaborative Group on Epidemiological Studies of Ovarian Cancer. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23.257 women with ovarian cancer and 87.303 controls. Lancet 2008;371:303–14.
[8] Narod SA, et al., Hereditary Ovarian Cancer Clinical Study Group. Oral contraceptives and the risk of hereditary ovarian cancer. N Engl J Med 1998;339:424–8.
[9] Whittemore AS, Balise RR, Pharoah PDP, et al. Oral contraceptive use and ovarian cancer risk among carriers of BRCA1 or BRCA2 mutations. Br J Cancer 2004;91:1911–5.
[10] McGuire V, Felberg A, Mills M, et al. Relation of contraceptive and reproductive history to ovarian cancer risk in carriers and noncarriers of BRCA1 gene mutations. Am J Epidemiol 2004;160:613–8.
[11] Modan B, Hartge P, Hirsh-Yechezel G, et al. Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. N Engl J Med 2001;345:235–45.
[12] McLaughlin JR, Risch HA, Lubinski J, et al. Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case–control study. Lancet Oncol 2007;8:26–34.
[13] Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. Epidemiol Rev 1993;15:36–47.
[14] Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer form 54 epidemiological studies. Lancet 1996;346:1713–27.

[15] Milne RL, Knight JA, John EM, et al. Oral contraceptive use and risk of early onset breast cancer in carriers and noncarriers of BRCA1 and BRCA2 mutations. Cancer Epidemiol Biomarkers Prev 2005;14:350–6.
[16] Narod SA, Dubé MP, Klijn J, et al. Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 2002;94:1773–9.
[17] Haile RW, Thomas DC, McGuire V, et al. BRCA1 and BRCA2 mutation carriers, oral contraceptive use, and breast cancer before age 50. Cancer Epidemiol Biomarkers Prev 2006;15:1863–70.
[18] Brohet RM, Goldgar DE, Easton DF, et al. Oral contraceptives and breast cancer risk in the international BRCA1/2 carrier cohort study: a report from EMBRACE, GENEPSO, GEO-HEBON, and the IBCCS Collaborating Group. J Clin Oncol 2007;25:3831–6.
[19] Anderson K, Jacobson JS, Heitjan DF, et al. Cost-effectiveness of preventive strategies for women with a BRCA1 or a BRCA2 mutation. Ann Intern Med 2006;144:397–406.
[20] Bermejo-Pérez MJ, Márquez-Calderón S, Llanos-Méndez A. Effectiveness of preventive interventions in BRCA1/2 gene mutation carriers: a systematic review. Int J Cancer 2007;121:225–31.
[21] Kauff ND, Barakat RR. Risk-reducing salpingo-oophorectomy in patients with germline mutations in BRCA1 or BRCA2. J Clin Oncol 2007;25:2921–7.
[22] Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 2004;22:2328–35.
[23] Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med 2002;346:1616–22.
[24] King MC, Marks JH, Mandell JB, New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 2003;302:643–6.
[25] Anglian Breast Cancer Study Group. Prevalence of penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Br J Cancer 2000;83:1301–8.
[26] Satagopan JM, Boyd J, Kauff ND, et al. Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. Clin Cancer Res 2002;8:3776–81.
[27] Eisen A, Lubinski J, Klijn J, et al. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case–control study. J Clin Oncol 2005;20(23):7491–6.
[28] Levine DA, Argenta PA, Yee CJ, et al. Fallopian tube and primary peritoneal carcinomas associated with BRCA mutations. J Clin Oncol 2003;21:4222–7.
[29] Alvarado-Cabrero I, Young RH, Vamvakas EC, et al. Carcinoma of the fallopian tube: a clinicopathological study of 105 cases with observations on staging and prognostic factors. Gynecol Oncol 1999;72:367–79.
[30] Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the women's health initiative randomized controlled trial. JAMA 2004;291:1701–12.
[31] Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. JAMA 2002;288:321–33.
[32] Beiner ME, Finch A, Rosen B, et al. The risk of endometrial cancer in women with BRCA1 and BRCA2 mutations A prospective study. Gynecol Oncol 2007;104:7–10.
[33] Lavie O, Ben-Arie A, Pilip A, et al. BRCA2 germline mutation in a woman with uterine serous papillary carcinoma—case report. Gynecol Oncol 2005;99:486–8.
[34] Nelson HD, Vesco KK, Haney E, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. JAMA 2006;295:2057–71.
[35] Loprinzi CL, Abu-Ghazaleh S, Sloan JA, et al. Phase III randomized double-blind study to evaluate the efficacy of a polycarbophil-based vaginal moisturizer in women with breast cancer. J Clin Oncol 1997;15:969–73.
[36] Madalinska JB, van Beurden M, Bleiker EM, et al. The impact of hormone replacement therapy on menopausal symptoms in younger high-risk women after prophylactic salpingo-oophorectomy. J Clin Oncol 2006;24:3576–82.
[37] Rebbeck TR, Friebel T, Wagner T, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol 2005;23:7804–10.
[38] Armstrong K, Schwartz JS, Randall T, et al. Hormone replacement therapy and life expectancy after prophylactic oophorectomy in women with BRCA1/2 mutations: a decision analysis. J Clin Oncol 2004;22:1045–54.

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