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REVIEW

# Gynaecologic challenging issues in the management of BRCA mutation carriers: oral contraceptives, prophylactic salpingo-oophorectomy and hormone replacement therapy

ANGIOLO GADDUCCI[1], NICOLETTA BIGLIA[2], STEFANIA COSIO[1],
PIERO SISMONDI[2], & ANDREA RICCARDO GENAZZANI[1]

[1]*Department of Procreative Medicine, Division of Gynecology and Obstetrics, University of Pisa, Italy and* [2]*Academic Department of Gynecological Oncology, Institute for Cancer Research and Treatment, University of Turin, Candiolo, Italy*

**Abstract**
BRCA1 and BRCA2 mutation carriers have a 54–85% and 45% lifetime risk of developing breast cancer, respectively, and a 18–60% and 11–27% lifetime risk of developing ovarian cancer, respectively. Oral contraceptives (OCs) significantly reduce the risk of ovarian cancer also in BRCA1/BRCA2 mutation carriers. The association between OC use and breast cancer risk in these women is controversial. Some studies showed a modestly increased risk especially among BRCA1 mutation carriers. The risk appears to be greater for women who took OCs for at least 5 years and who took OCs before the age of 30 years. Other studies reported that duration of use before first full-term pregnancy has a positive association with breast cancer risk. Salpingo-oophorectomy reduces the risk of coelomic epithelial cancer of 80–95% and the risk of breast cancer of approximately 50%. BRCA1 and BRCA2 mutation carriers should be encouraged to undergo prophylactic bilateral salpingo-oophorectomy at the age of 35–40 years or when childbearing is complete. Short-term use of hormone replacement therapy may relieve menopausal symptoms and does not appear to affect the breast cancer risk reduction obtained with salpingo-oophorectomy.

**Keywords:** *Ovarian cancer, tubal cancer, primary peritoneal cancer, breast cancer*

## Introduction

Breast and ovarian cancers are the second and fifth leading causes of cancer death, respectively, among women in Western countries [1]. The large majority of these malignancies are sporadic, and only 7–10% are hereditary. BRCA1 and BRCA2 are the two major susceptibility genes involved in hereditary breast and ovarian cancer. BRCA1 and BRCA2 mutation carriers have a 54–85% and 45% lifetime risk of developing breast cancer, respectively, and a 18–60% and 11–27% lifetime risk of developing ovarian cancer, respectively [2–6]. BRCA1 mutation carriers have also a not negligible risk for fallopian tube carcinoma [7–10] and primary peritoneal carcinoma [10–13]. The risk for this latter malignancy for BRCA2 mutation carriers is lower than for BRCA1 carriers. Also, uterine serous papillary carcinoma appears to be a BRCA1-related disease, but it can

occur in only 1–2 cases per 1000 BRCA mutation carriers [14–16].

Several epidemiological, experimental and clinical data have detected that oestrogens play a major role in the development and progression of breast cancer in general population [17]. These hormones can enhance breast carcinogenesis by stimulating cell proliferation rate and thereby increasing the number of errors occurring during DNA replication, as well as by causing DNA damage via their genotoxic metabolites produced during oxidation reactions [18–22]. The effects of oestrogens on risk modification on BRCA-related breast cancer are not clear [23]. However, there are some biological evidences of interactions between estrogens and BRCA proteins. BRCA1 expression can be induced by oestradiol in experimental models, and BRCA1 can modify the regulatory effects of the estrogen receptor $\alpha$ (ER).
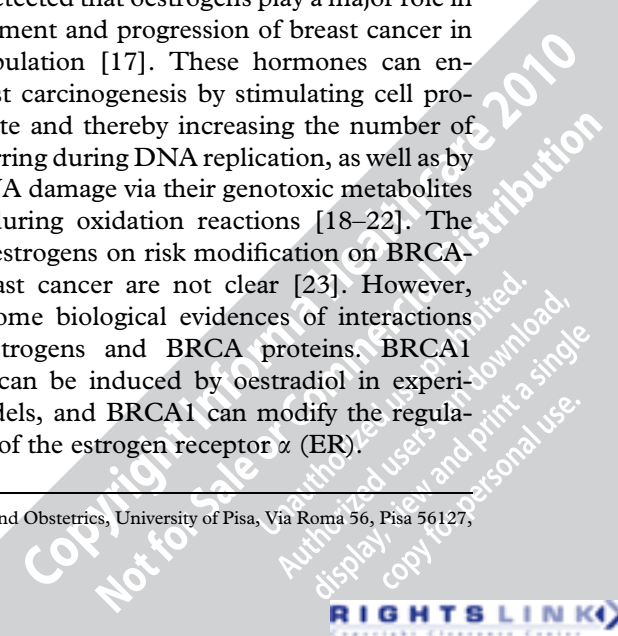
## Oral contraceptive use and ovarian cancer risk

### General population

There is good evidence that oral contraceptives (OCs) can significantly reduce the risk of ovarian cancer in general population [24–27]. A British cohort study using data of over 1 million women-years of observation reported that ever OC use was associated with a 46% reduced risk of ovarian cancer compared with never use [25]. The reduced risk was related to the duration of use, with a significant decrease among women using the pill for more than 8 years (adjusted relative risk [RR] = 0.38, 95% confidence interval [CI] = 0.16–0.88), and the protective effect persisted 15 years after stopping the use. These results were corroborated by the cumulative analysis of the data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls [26]. This study showed that that the reduction in risk of ovarian cancer increased with long-term use and persisted for 30 years after discontinuation. The risk reduction is not significantly related with histological types, although it is less consistent for mucinous tumours [24,26]. The protective effect of OCs, also considering its long-term persistence, could lead to the avoidance of 3000–5000 ovarian cancers and 2000–3000 related deaths per year in Europe [24].

Low-dose oestrogen-OCs confers substantial protection against ovarian cancer [28–31]. A U.S. population-based case–control study showed no significant difference in ovarian cancer risk between women who took low-dose oestrogen pills ($<50\ \mu g$ ethinyl estradiol or $<80\ \mu g$ mestranol) and those who received higher-dose oestrogen pills [29]. A German study reported that, per each year of use of pills containing $<35\ \mu g$, 35 to $<50\ \mu g$ and $>50\ \mu g$ ethinyl oestradiol, the odds ratio [OR]s were 0.86 (95% CI = 0.77–0.94), 0.91 (95% CI = 0.83–1.00) and 0.95 (95% CI = 0.91–0.99) [30]. Conversely, OC with high-potency progestin seemed to be more protective against ovarian cancer than those with low-potency progestin [31]. A case–control study (390 patients with ovarian cancer and 2865 controls) showed that low-potency progestin formulations were associated with a higher risk than high-potency progestin formulations (OR = 2.2; 95% CI = 1.3–3.9). These results are in agreement with the biological data showing a protective effect of progestin against ovarian carcinogenesis. In an experimental research, Rodriguez et al. [32,33] randomised female macaques to receive a diet containing no hormones, ethinyl-oestradiol, levonorgestrel or ethinyl-oestradiol plus levonorgestrel. Compared with ovaries of control monkeys and of only oestrogen-treated monkeys, the ovaries from progestin-treated animals showed an important decrease in the expression of transforming growth factor [TGF]-$\beta_1$ and a concomitant increase in the expression of TGF-$\beta_{2/3}$. The apoptotic index of the ovarian epithelium was significantly related to the changes in expression of TGF-$\beta$ isoforms induced by progestin treatment. The exposure of immortalised normal and malignant human ovarian surface epithelial cells to progesterone has been found to enhance the expression of Fas ligand (FasL) and to induce activation of caspase-8 and caspase-3 [34]. Therefore, progestin is able to stimulate ovarian epithelial cell apoptosis through both a modulation of TGF-$\beta$ isoform expression and an activation of a Fas/FasL signalling pathway. Although oestrogen may enhance cell proliferation [35,36] and prevent apoptosis through up-regulation of the anti-apoptotic Bcl-2 gene in ovarian epithelial cells [37], progestin may exert pro-apoptotic effects on these cells [32–34].

### BRCA mutation carriers

OC use may reduce ovarian cancer risk even in BRCA mutation carriers [6,38–42] (Table I). A Canadian case–control study (207 women with hereditary ovarian cancer and 161 sisters as controls) found that OCs protected both BRCA1 mutation carriers (OR = 0.5; 95% CI = 0.3–0.9) and BRCA2 mutation carriers (OR = 0.4; 95% CI = 0.2–1.1), and the risk of ovarian cancer decreased as the duration of use increased [38]. Many following papers reported similar results [39–42]. McGuire et al. [40] identified women with ovarian cancer in the San Francisco Bay Area from 1997 through 2001 and analysed the contraceptive and reproductive histories of 36 BRCA1 mutation carrier cases, 381 non-carriers cases and 568 controls. Ever use of OC achieved a similar reduced risk of ovarian cancer for carriers (OR = 0.54, 95% CI = 0.26–1.13) and non-carriers (OR = 0.55, 95% CI = 0.41–0.73), with a risk reduction per year of 13% ($p = 0.01$) for the former and 6% ($p < 0.001$) for the latter.

A case–control study of the Hereditary Ovarian Cancer Clinical Study Group included 799 women with ovarian cancer (670 with BRCA1 mutations, 128 with BRCA2 mutations and one with a mutation in both genes) and 2424 women without ovarian cancer (2043 with BRCA1 mutations, 380 with BRCA2 mutations and one with a mutation in both genes) [41]. OC use reduced ovarian cancer risk in both BRCA1 mutation carriers (OR = 0.56, 95% CI = 0.45–0.71) and BRCA2 mutation carriers (OR = 0.39, 95% CI = 0.23–0.66). A higher protection was seen with increasing duration of use.

Antonoiu et al. [42] retrospectively assessed 2281 BRCA1 mutation carriers and 1038 BRCA2 mutation carriers from the International BRCA1/2 Carrier Cohort Study to evaluate the effect of reproductive

Table I. OCs use and risk of ovarian cancer in BRCA1/2 mutation.

| Study | Design | No. of patients | OR for ever users | 95% CI | OR for duration of OC use (years) |
|---|---|---|---|---|---|
| Narod et al. [38] | Case–control study | 207 Hereditary ovarian cancer; 161 sisters. | 0.5 | 0.3–0.8 | <3: 0.8 (0.4–1.4)<br>3 to 6: 0.4 (0.2–0.9)<br>≥6: 0.4 (0.2–0.7)<br>Trend per year of use 0.9 (0.9–1.0) |
| Whittemore et al. [39] | Case–control study | 451 BRCA 1/2 carriers: 147 cases; 304 controls. | 0.85 | 0.53–1.4 | 1–2: 1.5 (0.82–2.9)<br>3–5: 0.69 (0.33–1.4)<br>≥6: 0.62 (0.35–1.1)<br>Trend per year of use 0.95 (0.91–0.9) |
| McGuire et al. [40] | Case-control study | 36 BRCA1 carriers; 361 non-carriers cases; 568 controls. | 0.54<br><br>0.55 | 0.26–1.13<br><br>0.41–0.73 | 1–2: 1.18 (0.50–2.75)<br>3–6: 0.46 (0.16–1.28)<br>≥7: 0.22 (0.07–0.71)<br>Trend per year of use 0.87; $p = 0.01$ |
| McLaughlin et al. [41] | Case–control study | 3223 BRCA 1/2 carriers: 799 cases; 2424 controls. | 0.53 | 0.43–0.66 | 0–1: 0.67 (0.50–0.89)<br>1–3: 0.63 (0.46–0.86)<br>3–5: 0.36 (0.25–0.53)<br>>5.0: 0.47 (0.35–0.62)<br>Trend per year of use 0.95 (0.92–0.97) |
| Antoniou et al. [42] | Retrospective study from International BRCA1/2 Carrier Cohort Study | 2281 BRCA1 carriers; 1038 BRCA2 carriers. | BRCA1 HR = 0.52 | 0.37–0.73 | |

OR, odds ratio; 95% CI, 95% confidence interval.

and hormonal factors on ovarian cancer risk. BRCA1 carriers who had ever taken pill had a reduced risk of developing ovarian cancer (hazard ratio [HR] = 0.52; 95% CI = 0.37–0.73) and increasing duration of use was associated with a significantly reduced risk ($p = 0.0004$). The number of ovarian cancer cases in BRCA2 mutation carriers was too small to draw definitive conclusions.

## Oral contraceptive use and breast cancer risk

### General population

The correlation between OC use and breast cancer risk is still one of the most investigated topics [43–50]. In 1996, the Collaborative Group on Hormonal Factors in Breast Cancer [43] published a reanalysis of data from 54 epidemiological studies including 53,297 women with breast cancer and 100,239 controls. The relative risk (RR) of this malignancy among pill users compared with never users was 1.07 and the excess was statistically significant ($p = 0.00005$). The risk was mainly dependent on the time interval since the last administration. The RR was 1.24 (95% CI = 1.15–1.33) for current users, 1.16 (95% CI: 1.08–1.23) 1–4 years after stopping, 1.07 (95% CI: 1.02–1.13) 5–9 years after stopping and 1.01 (95% CI: 0.96–1.05) for 10 or more years after stopping. Conversely, the results from the

Women's Contraceptive and Reproductive Experience (CARE) study [44] on 4575 patients with breast cancer and 4682 controls failed to detect any increased risk for both current pill users (RR = 1.0; 95% CI = 0.8–1.3) and past users (RR = 0.9; 95% CI = 0.8–1.0).

The Norwegian-Swedish Women's Lifestyle and Health Cohort Study, which analysed 103,027 women providing information on contraception use by questionnaire, reported an increased breast cancer risk among current or recent pill users (RR = 1.6; 95% CI = 1.2–2.1) [45]. A slightly increased risk was found among short-term (i.e. <13 months) users before age 20 years (RR = 1.3; 95% CI = 1.0–1.7) and before first full-term pregnancy (RR = 1.4; 95% CI = 1.0–1.8). A subsequent Swedish population-based case–control study (245 cases and 735 controls) detected that each year of pill use before 20 years conferred a significantly increased risk (OR = 1.53; 95% CI = 1.17–1.99) for early-onset breast cancer, while there was no risk associated with use after 20 years of age [51].

Data about the clinical relevance of oestrogen and progestin types and doses are conflicting and inconclusive. Although the Collaborative Group on Hormonal Factors in Breast Cancer study [43] could not detect any difference in risk associated with the type of compound used, the Norwegian Women and Cancer study (NOWAC) study reported that the RR

of breast cancer significantly increased with higher oestrogen doses and with increasing cumulative dose of levonorgestrel [47]. In a recent U.S. population-based case–control study (1640 cases and 1492 controls), women who recently took OCs containing $> 35\ \mu g$ ethinyl oestradiol had a higher risk of breast cancer than users of lower dose oestrogen preparations when compared with never users (RR = 1.99 and 1.27, respectively, $p < 0.01$) [48]. This relationship was more significant among women $< 35$ years: the RR associated with high- and low-dose ethinyl oestradiol use was 3.62 and 1.91, respectively.

### BRCA mutation carriers

The association between OC use and breast cancer risk in BRCA mutation carriers is controversial [51–60] (Table II). In a matched case–control study including 1311 pairs of women with BRCA mutations, ever pill use was associated with a modestly increased risk of breast cancer among BRCA1 mutation carriers (OR = 1.20; 95% CI = 1.02–1.40) but not among BRCA2 mutation carriers (OR = 0.94; 95% CI = 0.72–1.24) [55]. Compared with BRCA1 mutation carriers who never used OCs, those who took pills for at least 5 years had a significantly increased risk of breast cancer (OR = 1.33, 95% CI = 1.11–1.60), as did those who took pills before the age of 30 years (OR = 1.29, 95%

CI = 1.09–1.52), those who were diagnosed with breast cancer before the age of 40 years (OR = 1.38, 95% CI = 1.11–1.72) and those who first used OCs before 1975 (OR = 1.42, 95% CI = 1.17–1.75).

Hailed et al. [56] reported an association of elevated breast cancer risk with OC use for at least 5 years (OR = 2.06; 95% CI = 1.08–3.94) and with duration of use (OR per year of use = 1.08, $p = 0.008$) among BRCA2 mutation carriers.

An International retrospective cohort study of 1593 BRCA1 mutation carriers reported that ever OC use has an HR for breast cancer of 1.47 (95% CI = 1.16–1.87) [57]. Duration of use before first full-term pregnancy had a positive association with breast cancer risk in both BRCA1 and BRCA2 mutation carriers ($\geq 4$ years of use, HR = 1.49, 95% CI = 1.05–2.11 for BRCA1 carriers and HR = 2.58, 95% CI = 1.21–5.49 for BRCA2 carriers).

An Italian study assessed 3123 patients with a diagnosis of breast cancer before the age of 45 years; the patients were classified according to their probability of carrying a BRCA mutation on the basis of their family history [60]. The analysis included 382 breast cancer cases with high probability of BRCA mutation (genetic cases) and 1333 cases with a low probability of BRCA mutation (sporadic cases). We found a borderline significant interaction between genetic breast cancer incidence and oral contraception for ever users compared with never users (OR = 1.3; 95% CI = 1.0–1.7). The

Table II. OCs use and risk of breast cancer in BRCA1/2 mutation.

| Study | Design | No. of patients | BRCA1 OR (95% CI) for ever users | BRCA2 OR (95% CI) for ever users | OR (95% CI) for duration of OC use (years) BRCA1* BRCA2+ |
|---|---|---|---|---|---|
| Milne et al. [54] | Case–control study | 47 BRCA1 carriers; 36 BRCA2 carriers; 1073 controls | 0.22 (0.1–0.49) | 1.02 (0.34–3.09) | 1–4: 0.25 (0.09–0.7)* 0.97 (0.26–3.56)+ 5–9: 0.22 (0.09–0.58)*, 1.34 (0.41–4.45)+ $\geq$10: 0.20 (0.08–0.54)*, 0.73 (0.20–2.65)+ |
| Vessey et al. [55] | Cohort study | 1311 pairs if BRCA mutations | 1.20 (1.02–1.40) | 0.94 (0.72–1.24) | |
| Haile et al. [56] | Case–control study on women $< 50$ years | 497 BRCA1 carriers; 307 BRCA2 carriers. | 0.77 (0.53–1.12) | 1.62 (0.90–2.92) | 1–4: 0.68 (0.43–1.08)*, 1.16 (0.58–2.34)+ $\geq$5: 0.80 (0.54–1.18)*, 2.06 (1.08–3.94)+ Trend per year of use 0.99 ($p = 0.62$)*; 1.08 ($p = 0.008$)+ |
| Brohet et al. [57] | Retrospective study | 1.181 BRCA1 carriers; 412 BRCA2 carriers. | 1.47 (1.13–1.91) | 1.49 (0.8–2.70) | 1–3: 1.36 (0.99–1.88)*, 1.23 (0.64–2.35)+ 4–8: 1.51 (1.10–2.08)*, 2.27 (1.10–4.65)+ >9: 1.63 (1.17–2.29)*, 1.47 (0.66–3.28)+ |
| Pasanisi et al. [60] | Case-only study | 3123 breast cancer women $< 45$ years: 382 genetic cases; 1333 sporadic cases | 1.3 (1.0–1.7) in genetic cases | OC at 18–20 years; OR = 1.6 (1.1–2.3) | |

OR, odds ratio; 95% CI, 95% confidence interval.

strongest interaction was found for women who started using OCs at 18–20 years (OR = 1.6; 95% CI = 1.1–2.3).

However, other studies failed to detect that OC use increases breast cancer risk in BRCA 1 mutation carriers [54,56,58] and/or BRCA2 mutation carriers [54,58].

### Prophylactic oophorectomy

Bilateral prophylactic oophorectomy reduces the risk of ovarian cancer [13,61–71] and breast cancer [61–63,65–67,69–71] in women with BRCA mutations (Table III).

Rebbeck et al. [62] analysed the incidence of ovarian cancer among 551 BRCA mutation carriers: 259 patients underwent bilateral prophylactic oophorectomy and 292 matched controls did not. The follow-up was at least 8 years for both groups. Six (2.3%) women who underwent prophylactic oophorectomy were found to have a stage I ovarian cancer at the time of the procedure, and two (0.8%) additional women were diagnosed to have a primary serous peritoneal carcinoma 3.8 and 8.6 years after prophylactic surgery. Among the controls, 58 (19.9%) developed an ovarian cancer during the follow-up. With the exclusion of the six women whose cancer was diagnosed at surgery, prophylactic oophorectomy significantly reduced the risk of coelomic epithelial cancer (HR = 0.04; 95% CI = 0.01–0.16). Oliver et al. [13] assessed the histopathological findings of women at high risk for ovarian cancer who underwent bilateral prophylactic oophorectomy. Thirty-eight women underwent a bilateral oophorectomy (26 BRCA1, 3 BRCA2 and 9 belonging to hereditary breast/ovarian cancer family, respectively) and 90 women underwent bilateral salpingo-oophorectomy (58 BRCA1, 6 BRCA2, one BRCA1 and 2 and 25 belonging to hereditary breast/ovarian cancer family, respectively). In the former group no occult carcinomas were found, whereas five (8.6%) occult tumours were found among 58 BRCA1 mutation carriers of the latter group. All five tumours were only detected at microscopic pathological examination. Of the 38 patients who underwent a bilateral oophorectomy, 3 of 26 BRCA1 mutation carriers developed peritoneal papillary serous carcinoma during a mean follow-up of 45 months. No primary peritoneal carcinoma occurred in the 90 women who underwent a salpingo-oophorectomy after a mean follow-up of 12 months.

In a large prospective study, including 1828 BRCA mutation carriers, the HR for BRCA-related gynaecological cancer after prophylactic salpingo-oophorectomy was 0.20 (95% CI = 0.07–0.58) [68]. It is noteworthy that the estimated cumulative incidence of primary peritoneal cancer was 4.3% at 20 years after prophylactic surgery.

Kauff et al. [70], who analysed 1079 BRCA mutation carriers found that salpingo-oophorectomy significantly reduced the risk of BRCA1-associated gynaecologic cancer risk (HR = 0.15; 95% CI: 0.04–0.56) but offered no protection against BRCA2-associated gynaecologic cancer.

A meta-analyses of 10 studies on BRCA mutation carriers who had undergone bilateral salpingo-oophorectomy showed that this prophylactic surgery was associated with a significant reduction in the risk of ovarian or fallopian tube cancer (HR = 0.21; 95% CI = 0.12–0.39), although the data were insufficient to obtain separate estimates for risk reduction in BRCA1 versus BRCA2 mutation carriers [71].

Bilateral oophorectomy decreases breast cancer risk of approximately 50% in BRCA mutation carriers [61–63,65–67,69–71]. In the study of Rebbeck et al. [62], this malignancy developed in 21.2% of the women who underwent bilateral oophorectomy versus 42.3% of those who did not (HR = 0.47; 95% CI = 0.29–0.77).

Kauff et al. [70] reported that salpingo-oophorectomy achieved a 72% reduction in BRCA2-associated breast cancer risk (HR = 0.28; 95% CI = 0.08–0.92), with no statistically significant protection against BRCA1-associated breast cancer (HR = 0.61; 95% CI = 0.30–1.22).

Table III. Bilateral salpingo-oophorectomy and risk of ovarian/fallopian tube and breast cancer in BRCA1/2 mutation carriers.

| Study | Design | No. of BRCA1/2 carriers with salpingo-oophorectomy | No. of BRCA1/2 carriers without salpingo-oophorectomy | Gynaecologic cancers HR (95% CI) | Breast cancer HR (95% CI) |
|---|---|---|---|---|---|
| Kauff et al. [65] | Prospective | 98 | 72 | 0.15 (0.02–1.31) | 0.32 (0.08–1.20) |
| Rebbeck et al. [62] | Retrospective | 261 | 292 | 0.04 (0.01–0.16) | 0.53 (0.33–0.84) |
| Rutter et al. [64] | Case–control | 5 | 223 | 0.29 (0.12–0.73) | NA |
| Eisen et al. [66] | Case–control | 166 | 3139 | NA | 0.46 (0.32–0.65) |
| Domchek et al. [67] | Prospective | 155 | 271 | 0.11 (0.03–0.47) | 0.36 (0.20–0.67) |
| Finch et al. [68] | Combined | 1041 | 779 | 0.20 (0.07–0.58) | |
| Chang-Claude et al. [69] | Retrospective | 55 | 1601 | NA | 0.56 (0.29–1.09) |
| Kauff et al. [70] | Prospective | 509 | 283 | 0.12 (0.03–0.41) | 0.53 (0.29–0.96) |
| Rebbeck et al. [71] | Meta-analysis of 10 studies | | | 0.21 (0.12–0.39) | 0.49 (0.37–0.65) |

OR, odds ratio; 95% CI, 95% confidence interval; NA, not available.

The case–control study of Eisen et al. [66] showed that bilateral oophorectomy was associated with a reduction in breast cancer risk of 56% for BRCA1 mutation carriers (OR = 0.44; 95% CI = 0.29–0.66) and of 46% for BRCA2 mutation carriers (OR = 0.57; 95% CI = 0.28–1.15). The risk reduction was greater if oophorectomy was performed in women younger than 40 years (OR = 0.36; 95% CI = 0.20–0.64 for BRCA1 carriers) than in older ones (OR = 0.53; 95% CI = 0.30–0.91). In a prospective cohort study including 155 BRCA mutations carriers who had bilateral salpingo-oophorectomy and 271 controls Domchek et al. [67] found that the HR of the former for breast-cancer-specific mortality was 0.10 (95% CI = 0.02–0.71) and for ovarian-cancer-specific mortality was 0.05 (95% CI = 0.01–0.46).

In the meta-analysis of Rebbeck et al. [71], salpingo-oophorectomy was associated with a statistically significant reduction in breast cancer risk for both BRCA1 mutation carriers (HR = 0.47; 95% CI = 0.35–0.64) and BRCA2 mutation carriers (HR = 0.47; 95% CI = 0.26–0.84).

There is much debate about the need of removal the uterus at the time of salpingo-oophorectomy. Even if careful ligation of the fallopian tube at the uterine origin is performed, a small interstitial portion of the tube is left in the uterine fundus. However, a large clinical-pathological study revealed that 92% of 105 tubal carcinomas developed in the distal-or mid portion of the tuba [72]. Therefore, according to some authors [10], there is little evidence to suggest the systematic performance of hysterectomy to prevent tubal carcinoma. However, hysterectomy can be taken into consideration for other reasons, such as the reduction of endometrial cancer risk associated with tamoxifen treatment for a previous breast cancer [73] or the elimination of the low risk of uterine serous papillary carcinoma [14–16].

There is a good evidence from observational and randomised trials of a higher risk of breast cancer in women receiving oestrogen plus a progestin compared with those receiving estrogen alone as postmenopausal hormone replacement therapy (HRT) [74–80]. Therefore, oestrogen replacement therapy is preferable when breast cancer risk is particularly high as in BRCA mutation carriers, which could suggest the performance of hysterectomy at the time of bilateral salpingo-oophorectomy. However, different progestins may exert different effects on breast carcinogenesis. Recent trials showed that the association of natural progesterone with oestrogen confers less or even no risk of breast cancer when compared with other synthetic progestins [81–85].

### HRT in BRCA mutation carriers

Surgical menopause in young women can result in severe hot flashes, vaginal dryness, sexual dysfunction, sleep disturbances and cognitive changes that may significantly affect quality of life. Non-hormonal therapies may palliate some of these symptoms. For instance, centrally active agents (i.e. venlafaxine, paroxetine, gabapentin) are regarded as the most promising non-hormonal treatments for hot flashes in breast cancer survivors [86]. Venlafaxine reduces hot flashes score, but it often causes toxic effects leading to premature treatment discontinuation and, moreover, it is non-effective in a substantial number of women [87–89]. HRT represents the gold standard treatment for the menopausal symptoms, but its use can be dangerous for women at risk of breast cancer such as BRCA mutation carriers.

In a Dutch observational study including 162 premenopausal women at high risk of hereditary ovarian cancer who had undergone bilateral salpingo-oophorectomy, an 18-item functional assessment of cancer therapy, endocrine symptoms was used to evaluate menopausal symptoms [90]. As indicated by the mean scores, the HRT users reported significantly fewer climacteric symptoms than the nonusers ($p < 0.05$). Both groups reported comparable levels of sexual functioning, as measured by the pleasure, discomfort and habit scales of the sexual activity questionnaire.

A prospective multicentre cohort study on BRCA mutation carriers determined the incidence of breast cancer in 155 women who had undergone bilateral oophorectomy and in 307 women who had not [91]. With a median follow-up of 3.6 years, this prophylactic surgery significantly reduced breast cancer risk (HR = 0.40; 95% CI = 0.18–0.92) and short-term HRT of any type did not significantly change this protective effect (HR = 0.37; 95% CI = 0.14–0.96).

A Markov decision analytic model was developed to calculate the impact of prophylactic oophorectomy and HRT on breast cancer, ovarian cancer, coronary disease, osteoporosis and venous thrombosis [92]. According to this model BRCA mutation carriers who undergo prophylactic oophorectomy between 30 and 40 years will obtain a significant gain in life expectancy, irrespective of whether HRT is given after oophorectomy [93]. This gain in life decreases as age at the time of oophorectomy increases, ranging from 4.65 years in 30-year-old women who do not take HRT to 2.63 years for 40-year-old women who take HRT for life.

Gabriel et al. [94] retrospectively assessed 73 BRCA mutation carriers who had bilateral salpingo-oophorectomy between 1972 and 2005 and who had no history of breast or ovarian cancer at the time of surgery. Forty (55%) of these also underwent total abdominal hysterectomy and 33 (45%) took HRT following prophylactic surgery. There was no difference in HRT use between women who underwent

hysterectomy and those who did not (43% vs. 48%). However, the use of HRT, especially combined oestrogen-progestin therapy, has declined after 2002, the year of the publication of Women's Health Initiative studies, even if not in statistically significant manner.

## Discussion

OC use has been associated with a small increase in breast cancer risk and a substantial decrease in ovarian cancer risk in general population. The effects of OCs on BRCA mutation carriers are not yet completely defined. OCs appear to protect against ovarian carcinogenesis but could enhance breast carcinogenesis in these women.

A review of the literature data appear to show that prophylactic surgery, i.e mastectomy and salpingo-oophorectomy, leads to better survival than surveillance alone in BRCA mutation carriers [95–97]. Salpingo-oophorectomy reduces the risk of coelomic epithelial cancer of 80–95% and the risk of breast cancer of approximately 50%. After removal of the fallopian tubes and ovaries, the peritoneum is still at risk for developing malignancy, reflecting its common embryologic origin with the ovarian epithelium [98]. Piver et al. [99] reported that a primary peritoneal carcinoma occurred in 6 (1.9%) of 324 women with a family history of ovarian cancer after a lead time of 1–27 years following prophylactic oophorectomy.

The protection against breast carcinogenesis may differ between BRCA1 and BRCA2 mutation carriers, probably because BRCA1- and BRCA2-related breast cancers have a distinct morphologic and molecular signature [100,101]. BRCA2 tumours are more likely to exhibit the luminal phenotype and to be ER+, while BRCA1 tumours often exhibit a basal phenotype and are ER−. BRCA1 and BRCA2 mutation carriers should be encouraged to undergo prophylactic bilateral salpingo-oophorectomy at the age of 35–40 years or when childbearing is complete. Multiple factors may influence decisions regarding whether or not total abdominal hysterectomy is done at the time of salpingo-oophorectomy, whether HRT is taken after prophylactic surgery, and if so, which type of HRT is chosen. The risk and benefits of concomitant hysterectomy should be discussed with each individual woman. Short-term use of HRT may relieve menopausal symptoms and does not appear to affect the breast cancer risk reduction obtained with salpingo-oophorectomy. Therefore, the decision making process about HRT use should be based largely on quality-of-life issues rather than life expectancy. According to Armstrong et al. [93], HRT could be administered until the time of expected natural menopause, approximately age of 50 years.

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