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Review

Oral contraception use in *BRCA* gene mutation carriers: information for counselling in routine clinical practice

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The objective of this narrative review is to put risks and benefits for the use of oral contraception (OC) into perspective in counselling high-risk carriers of *BRCA1* or *BRCA2* gene mutations. We searched PubMed, Embase, and the Cochrane Library for studies that evaluated associations between OC use and breast or ovarian cancer among women who are carriers of *BRCA1/2* mutations. All studies concordantly demonstrated an inverse correlation between OC and ovarian cancer risk in *BRCA* mutated women. Regarding breast cancer risk, results are conflicting with some studies reporting a slightly increased risk associated with OC use, whereas others reveal no evidence of a significant association in carriers. Numerous potential cancer risk modifiers and the modern evolution of OC can partly explain these results. OC use may also reduce the risk of extra-ovarian cancers such as those of the colon and endometrium, as observed in the general population. *BRCA1/2* carriers should always receive a sensible and patient-centered contraceptive counselling because current evidence does not support recommendation against OC use, taking into account the individual profile.

Keywords

BRCA1; *BRCA2*; Oral contraceptive; Ovarian cancer; Breast cancer; Counselling

1. Introduction

Deleterious germline mutations in *BRCA1* or *BRCA2* genes represent the most significant risk factors for breast and ovarian cancer development. Lifetime risk for breast cancer reaches 72% in *BRCA1* and 69% in *BRCA2* mutation carriers, while cumulative ovarian cancer risk is estimated at 44% and 17% for *BRCA1* and *BRCA2* carriers, respectively [1]. The most effective strategy for ovarian cancer prevention in this high-risk population is represented by risk-reducing salpingo-oophorectomy (RRSO) because of the absence of effective screening methods for early detection [2], coupled with the high mortality rates of advanced disease [3, 4]. Timing of prophylactic surgery is crucial: international guidelines recommend RRSO before the age of 40 in *BRCA1* women and before the age of 45 in *BRCA2* women [5–7]. Unfortunately, surgical premature menopause increases the risk of non-cancer morbidity and mortality due to cardiovascular disease, neurological decline, metabolic dysfunction, and worsens the quality of life [8–10]. That being so, every alternative strategy that could delay iatrogenic menopause, while still maintaining cancer risk reduction, is of paramount importance. In the general population, the risk reduction rate of ovarian cancer with oral contraception (OC) use, ranges from 20% to 50% according to the duration of usage [11]. Several studies in *BRCA* mutation carriers demonstrated a similar protective effect of OC [12–14]. That being so, OC can be an ovarian chemo-preventive potential strategy until the timing of iatrogenic menopause but fears of developing breast cancer in a population already at risk at a younger age [15] impose a risk-benefit assessment on both women and health care providers (HCPs) [16]. In spite of intensive research in *BRCA* mutated carriers, the impact of different risk modifiers, such as OC composition and dosage, reproductive history, family history, and lifestyle habits is far from being clear.

In this brief narrative review, we summarize the available data in the literature on the impact of OC on ovarian and breast cancer risk in *BRCA* mutated women, offering our perspective for a tailored counselling in routine clinical practice.

2. Materials and methods

We conducted a search for relevant scientific articles updated to March 2020 using the following databases: Pubmed, EMBASE, Cochrane library. We considered clinical trials, reviews, meta-analyses, expert opinions and position statements published in the English language and limited these to human studies. Key words and MeSH terms included: "oral contraceptive(s)", "ovarian cancer", "breast cancer", "*BRCA1*"

Table 1. Oral contraception and risk of ovarian cancer in *BRCA1* and *BRCA2* mutation carriers.

Author (year)	Study design	N° of cases/non cases	Adjustments/matching	Gene/s	Results
Narod (1998) [17]	Case control	207/161	Region, ethnicity	*BRCA1* and *BRCA2*	• *BRCA1*: OR = 0.5; 95% CI 0.3–0.9 • *BRCA2*: OR = 0.4; 95% CI 0.2–1.1 • Combined: OR = 0.5; 95% CI 0.3–0.8 • Inverse correlation with duration of OC (p trend < 0.001)
Modan (2001) [18]	Case control	240/592	Match: Age, area, residence in Israel	*BRCA1* and *BRCA2*	• 0.1–1.9 yrs: OR = 1.15 (95% CI 0.67–1.94) • 2–4.9 yrs: OR = 0.77 (95% CI 0.41–1.44) • >5 yrs: OR = 1.07 (95% CI 0.63–1.83)
McGuire (2004) [19]	Case control	36/568	Adj: Age, pregnancy, race Match: age and race	*BRCA1*	OR = 0.54 (95% CI 0.26–1.13)
Whittemore (2004) [20]	Case control	147/304	Adj: Parity Match: Age, residence and gene	*BRCA1* and *BRCA2*	• OR = 0.85 (95% CI 0.53–1.36) 1 year • OR = 0.62 (95% CI 0.35–1.09) 6 years • Trend per year of use OR = 0.95 (95% CI 0.9–0.99)
Gronwald (2006) [21]	Case control	150/150	None	*BRCA1*	OR = 0.4 (95% CI 0.2–1.0)
McLaughlin (2007) [22]	Case control	799/2424	Adj: Parity, breastfeeding, tubal ligation, ethnicity	*BRCA1* and *BRCA2*	• *BRCA1* mutations (OR = 0.56 [95% CI 0.45–0.71]; p < 0.0001) • *BRCA2* mutations (OR = 0.39 [0.23-0.66]; p = 0.0004)
Antoniou (2009) [23]	Cohort study	2415 exposed to OC/766 not exposed to OC	Parity, ethinicity (region)	*BRCA1* and *BRCA2*	• *BRCA1*: OR = 0.52 (95% CI 0.37–0.73) • *BRCA2*: OR = 1.04 (95% CI 0.42–2.54)
Iodice (2010) [12]	Meta-analysis	1503/6315		*BRCA1* and *BRCA2*	• General: SRR = 0.5 (95% CI 0.33–0.75) • *BRCA1*: SRR = 0.51 (95% CI 0.4–0.65) • *BRCA2*: SRR = 0.5 (95% CI 0.29–0.89) • Each additional 10 years of OC use decreased the risk by 36% (95% CI, 22–47%, p < 0.01 for trend)
Cibula (2010) [24]	Review	*BRCA1*: 2151/2121 *BRCA2*: 862/719		*BRCA1* and *BRCA2*	Relative risk decreased by 20% for each 5 years of use
Cibula (2011) [25]	Meta-analysis	*BRCA1*: 1524/1631 *BRCA2*: 458/509		*BRCA1* and *BRCA2*	OR: 0.57; (95% CI: 0.47–0.70; p < 0.001) Duration of OC use OR: 0.95; 95% CI: 0.93–0.97; p < 0.001
Moorman (2013) [13]	Meta-analysis	*BRCA1*: 1353/2310 *BRCA2*: 277/423	None	*BRCA1* and *BRCA2*	*BRCA1/2*: odds ratio [OR], 0.58; 95% CI, 0.46 to 0.73
Friebel (2014) [26]	Review and meta-analysis	1588/3365, 7 studies	Parity, age at first live birth	*BRCA1* and *BRCA2*	*BRCA1*: ES 1.85 (95% CI: 1.30–2.64)
Kotsopoulos (2014) [27]	Case control	1329/5267	Duration of use	*BRCA1* and *BRCA2*	• 5+ years of use, *BRCA1*: OR = 0.5, 95% CI 0.4–0.63 • 3+ years of use *BRCA2*: OR = 0.42, 95% CI 0.22–0.83
Perri (2015) [28]	Retrospective cohort study	175/898	Ethnicity, Jewish Israeli women	*BRCA1* and *BRCA2*	• Combined: OR 0.19; 95% CI, 0.13–0.28 (p < 0.001) • *BRCA1*: OR = 0.21; 95% CI 0.14–0.33 (p < 0.001) • *BRCA2*: OR = 0.24; 95% CI 0.09–0.61 (p < 0.001) Risk reduced with longer oral contraceptive use: for its use 1% year, OR 0.36 (95% CI, 0.16–0.84); for 1–5 years, OR 0.31 (95% CI, 0.19–0.51); and for >5 years, OR 0.10 (95% CI, 0.06–0.17).

and "*BRCA2*". Non- randomized clinical trials were found and data were reviewed independently by two investigators (CC, FZ). Duplicate studies were excluded and references identified from relevant articles were also searched. Selection of appropriate articles was carried out based on potential relevance to the key question of whether or not OC use influences breast and ovarian cancer risk in *BRCA* mutated populations in order to counsel women appropriately. The present work merely reflects our viewpoint and by no means was intended to summarize the complete literature available in this complex field of research. As a secondary analysis and review of published data, Institutional Review Board approval was not required.

3. Results

3.1 Oral contraception and ovarian cancer risk

We included 14 different publications (2 reviews, 3 meta-analyses, 7 case control studies and 2 cohort studies) on the relationship between ovarian cancer and the use of OCs in patients with a *BRCA* mutation. All studies (Table 1, Ref. [17–28]) showed a significantly decreased risk of ovarian cancer in patients with mutations among OC users.

In particular, Iodice *et al.* [12] published a meta-analysis (4 case-control studies and 1 retrospective cohort study), which included 1262 cases and 2678 controls with *BRCA1* mutation, 253 cases, and 538 controls with *BRCA2* mutation and one with both. The use of OC was defined as ever used. Apart from showing that the risk for ovarian cancer was significantly reduced in both *BRCA1* and *BRCA2* mutation carriers (general: SRR = 0.5, 95% CI 0.33–0.75) with the use of OC, such meta-analysis also pointed to a linear decrease in risk of 36% for each additional 10 years of OC usage [12].

A later meta-analysis [25] which included 3 case-control studies obtained similar results for both *BRCA1* and *BRCA2* and drew attention to the observation that 5 years of OC use was associated with a relative risk reduction of 20%. A further meta-analysis [13] comparing those that ever used OC with non-users obtained a similar ovarian cancer risk reduction (OR of 0.55 in *BRCA1* mutation carriers and OR of 0.65 in *BRCA2* mutation carriers). In addition, an inverse association between the risk of ovarian cancer and the duration of OC use was evident in every study, but the variable duration of OC use in different studies did not allow for statistical meta-analysis of the results.

That being so, protection associated with the use of OC in *BRCA* mutation carriers is well established and OC seems to have a class effect because data regarding types, doses, and regimens are lacking.

3.2 Oral contraception and breast cancer risk

We evaluated 20 different publications (2 case-only studies, 8 case-control studies, 5 cohort studies, 4 meta-analyses, and 1 review) on the relationship between breast cancer and the use of OC in *BRCA*-positive patients (Table 2, Ref. [29–40]). Overall, meta-analyses showed conflicting results depending on the design of the included studies: when case-control studies were analyzed, no association between OC and breast cancer was evident, whereas the inclusion of prospective cohort studies revealed an increased risk [26].

In particular, Iodice *et al.* [12] did not report any significant association regarding the use of OC either in *BRCA1* or in *BRCA2* individuals. In addition, there was no evidence of a possible relationship with duration of OC use. The only statistically significant finding was an increase in the relative risk of breast cancer in patients who ceased using OC at least 10 years before diagnosis when compared with those who never used OC. Similarly, another meta-analysis by Cibula *et al.* [25] showed no significant association between OC use and increased breast cancer risk for patients carrying *BRCA1* or *2*, with one exception in a subset of cohort studies in *BRCA1* mutation carriers (OR: 1.48; 95% CI: 1.14–1.92) [33]. Even Moorman *et al.* [13] published a meta-analysis of 5 studies reporting OC use and breast cancer risk in *BRCA1/2* mutation carriers. Statistical analysis was conducted separately for *BRCA1* and *2* and then combined, showing similar results: the risk was increased among those who ever used OC, without reaching statistical significance. By analyzing the duration of use in each study, there was no evidence of a trend of increasing risk with longer exposure to OC.

In 2014, Friebel *et al.* [26] analyzed 12 studies concerning breast cancer risk in *BRCA* mutations and OC use. As far as *BRCA1* was concerned, the case control studies included in the meta-analysis suggested no association between risk of breast cancer and OC use, while the cohort studies' combined hazard ratios showed an increase in risk (ES 1.59). The analysis upon the duration of use (1 year–3 years–5 years) did not show significant differences. As far as *BRCA2* was concerned, 5 studies were taken into consideration and results were similar with no difference between users and those who never used OC. However, by pooling together only the two cohort studies, Friebel *et al.* [26] showed a significant increased risk (ES 1.85) in users with no impact of duration of use.

That being so, the relationship between the use of OC in *BRCA* mutation carriers and breast cancer risk is not well established and is likely due to a large number of potential confounders.

Over the years, individual studies in patients carrying *BRCA* mutations have attempted to analyze the role of reproductive characteristics, such as parity, age at first pregnancy, age at starting OC, its dose and duration of use, in the risk of breast cancer [15, 27, 33, 38, 40].

Table 2 reports studies that have analyzed additional elements to explore the issue of OC in *BRCA* mutation carriers.

In a case-control study [15] conducted on 1156 patients (47 with *BRCA1* mutations, 36 with *BRCA2* mutations and 815 controls) with breast cancer diagnosed before age 40, at least 12 months of OC use was associated with a decreased breast cancer risk in *BRCA1* mutation carriers (OR 0.22). No association was evident in *BRCA2* carriers (OR 1.02) or in control women (OR 0.93). Adjustments were made for potential confounders.

Table 2. Oral contraception and risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers.

Author (year)	Study design	N° of CASES/NON CASES	Adjustments/matching	Gene	Results
Ursin (1997) [29]	Retrospective case–case study	14/36	Adj: Age, family history education	*BRCA1* and *BRCA2*	OC use increased the risk of BC more in patients who carry *BRCA1/2* mutations than in patients who don't
Narod (2002) [30]	Case control	*BRCA1* 981/981 *BRCA2*: 330/330	Adj: Age, parity	*BRCA1* and *BRCA 2*	*BRCA 1*: OR 1.2, 95% CI 1.02–1.4 *BRCA 2*: OR 0.94, 95% CI 0.72–1.24
Heimdal (2002) [31]	Case control	98/1325		*BRCA1*	*BRCA 1*: RR 2.00, 95% CI 0.36–10.9
Milne (2005) [15]	Case control	*BRCA1*: 47/815 *BRCA2*: 36/815 No mutation: 1073/815	Adj: Age, parity, family history, age at menarche, study location/period, education, marital status, country of birth	*BRCA1* and *BRCA2*	*BRCA1*: OR: 0.22, 95% CI 0.1–0.49 *BRCA 2*: OR: 1.02, 95% CI 0.34–3.09 No mutation: OR 0.93, 95% CI 0.69–1.24
Haile (2006) [32]	Case control	*BRCA1*: 195/302 *BRCA2*: 128/179	Adj: Age, parity, family history, study site	*BRCA1* and *BRCA2*	1 year of use: *BRCA 1*: OR 0.77, 95% CI 0.53–1.12 *BRCA 2*: OR 1.62, 95%CI 0.90–2.92
Gronwald (2006) [21]	Case control	348/348	Match: Age	*BRCA1*	OR 0.8, 95% CI 0.5–1.2
Brohet (2007) [33]	Retrospective cohort	*BRCA1*: 597/587 *BRCA2*: 249/153	Adj: Family clustering, parity, history of oophorectomy	*BRCA1* and *BRCA2*	*BRCA 1*: RR 1.47, 95% CI 1.13–1.91 *BRCA 2*: RR 1.49, 95% CI 0.80–2.70 *BRCA 1* or *BRCA 2*: RR 1.47, 95% CI 1.16–1.87
Lee (2008) [34]	Case control	94/444	Adj: Age, race, parity, family history, education, Ashkenazi Jews	*BRCA1* and *BRCA2*	OR 0.68, 95% CI 0.33–1.38 *BRCA1*: OR 0.55 (0.22–1.39) *BRCA2*: OR 0.94 (0.28–3.14)
Atchley (2008) [35]	Retrospective cohort	86/405		*BRCA1* and *BRCA2*	Past use of oral contraceptives was the same in both *BRCA1/2* mutation carriers and non-mutation carriers
Pasanisi (2009) [36]	Case only study	382 "genetic" 1333 "sporadic"			Genetic cases: OR = 1.3; 95% CI 1.0–1.7 Highest association for OC start at 18–20 years: OR = 1.6; 95% CI 1.1–2.3 (p trend = 0.18) Duration of use not statistically significant (p = 0.32)
Figueiredo (2010) [37]	Case control	*BRCA1*: 67/42 *BRCA2*: 41/31	Adj: Age	*BRCA1* and *BRCA2*	*BRCA 1*: OR 0.82, 95% CI 0.21–3.13 *BRCA 2*: OR 2.38, 95% CI 0.72–7.83
Iodice (2010) [12]	Meta analysis	*BRCA1*: 2154/2280 *BRCA2*: 707/672	Adj: Duration of use	*BRCA1* and *BRCA2*	No significant association *BRCA1*: RR = 1.09; 95% CI 0.77–1.54 *BRCA2*: RR = 1.15; 95% CI 0.61–2.18 Combined: SRR = 1.33; 95% CI 0.88–1.45. No association with duration of use (p = 0.2)
Cibula (2010) [24]	Review	*BRCA1*: 2151/2121 *BRCA2*: 94/719	Adj: Duration of use	*BRCA1* and *BRCA2*	Mild to moderate increase in risk. Further increase in risk when OC duration ≥4 years before FFT (*BRCA1*: HR = 1.49; 95% CI 1.05–2.11. *BRCA 2*: HR = 2.58; 95% CI 1.21–5.49)

Table 2. Continued.

Author (year)	Study design	N° of CASES/NON CASES	Adjustments/ matching	Gene	Results
Cibula (2011) [25]	Meta analysis	*BRCA1*: 1524/1631 *BRCA2*: 458/509		*BRCA1* and *BRCA2*	No significant association *BRCA1*: OR = 1.08; 95% CI 0.94–1.25 (p = 0.25) *BRCA2*: OR = 1.03; 95% CI 0.81–1.32 (p = 0.788)
Moorman (2013) [13]	Meta analysis + Systematic review	*BRCA1*: 2401/2215 *BRCA2*: 830/672 373 control: *BRCA1/2* not indicated		*BRCA1* and *BRCA2*	Non-statistically relevant increase in risk *BRCA1*: OR = 1.19; 95% CI 0.92–1.55 (p = 0.004) *BRCA2*: OR = 1.36; 95% CI 0.89–2.10 (p = 0.022) Combined: OR = 1.21; 95% CI 0.93–1.58 (p < 0.001)
Friebel (2014) [26]	Review and meta analysis	Case–control studies: Cases: 3606 *BRCA1*, 1257 *BRCA2* Controls: 3730 *BRCA1*, 1308 *BRCA2* Cohort studies: Cases: 877 *BRCA1*, 372 *BRCA2* Controls: 584 *BRCA1*, 163 *BRCA2*, 373 *BRCA1/2*		*BRCA 1* and *BRCA2*	*BRCA1*: ES = 0.78; 95% CI 0.59–1.04 *BRCA2*: ES = 1.04; 95% CI 0.81–1.3 Increase in risk *BRCA1*: ES = 1.59; 95% CI 1.32–1.92 *BRCA2*: ES = 1.85; 95% CI 1.30–2.64 No association with duration of use
Kotsoupolos (2014) [27]	Case control	2492 case control pairs	Adj: Age of beginning of OC use	*BRCA1*	Increase in risk when starting <20 years: OR = 1.45; 95% CI 1.20–1.75 (p = 0.0001) No statistically relevant increase in risk when starting at 20–25 years: OR = 1.19; 95% CI 0.99–1.42 (p = 0.06) Effect only for early-onset of cancer <40 years: OR = 1.40; 95% CI 1.14–1.70 (p = 0.001)
Rieder (2016) [38]	Case only	*BRCA1*: 258 *BRCA2*: 108	Adj: Age, duration of use	*BRCA1* and *BRCA2*	Prior or current OC associated with younger age at diagnosis: HR = 1.7; 95% CI 1.1–2.05 (p = 0.006) No association with duration of use: HR = 1.00; 95% CI 0.99–1.00
Park (2017) [39]	Retrospective cohort study	*BRCA1*: 168/54 *BRCA2*: 109/250		*BRCA1* and *BRCA2*	No significant association *BRCA1*: HR = 1.24; 95% CI 0.45–3.40 *BRCA2*: HR = 0.71; 95% CI 0.21–2.37
Schrijver (2018) [40]	Cohort study (retrospective, prospective)	Prospective cohort: Cases: 269 *BRCA1*, 157 *BRCA2* Controls: 2007 *BRCA1*, 1453 *BRCA2* Retrospective cohort, left-truncated: Cases: 1095 *BRCA1*, 752 *BRCA2* Controls: 2733 *BRCA1*, 1760 *BRCA2* Retrospective full-cohort: Cases: 2525 *BRCA1*, 1548 *BRCA2* Controls: 3180 *BRCA1*, 1973 *BRCA2*	Adj: Duration of use	*BRCA1* and *BRCA2*	Prospective cohort: *BRCA1*: HR = 1.08; 95% CI 0.75–1.5 *BRCA2*: HR = 1.75; 95% CI 1.03–2.9 Controls: *BRCA1*: HR = 1.26; 95% CI 1.06–1.51 *BRCA2*: HR 1.06; 95% CI 0.85–1.33 Retrospective cohort, left truncated: *BRCA1*: HR = 1.39; 95% CI 1.23–1.58 *BRCA2*: HR = 1.52; 95% CI 1.28–1.81 Retrospective full-cohort: Inverse correlation with duration of use, especially before FFTP (*BRCA1*: both retrospective analyses, p < 0.001 and p = 0.001; *BRCA2*: full retrospective analysis, p = 0.002)

A retrospective cohort study (1539 patients with either *BRCA1* or *BRCA2* mutations) [33] showed no evidence that the use of OC affected the risk of breast cancer by means of a weighted Cox regression analysis, even when taking into consideration age or time since stopping the use of OC. However, when adjusting for duration of use, years of OC exposure (4 or more years of use) before first full-term pregnancy, the risk was higher in mutated patients with breast cancer (HR = 1.49 for *BRCA1* and HR = 2.58 for *BRCA2*).

In 2014, Kotsopolous *et al.* [27] analyzed 2492 matched pairs of cases and controls with a mutation in the *BRCA1* gene. When OC was used before the age of 20, a significantly higher risk of breast cancer was reported. A barely significant higher risk was also evident in *BRCA1* carriers when OC was used between the ages of 20 and 25. This effect was limited to early-onset breast cancer, diagnosed before 40 years of age (OR 1.40; 95% CI 1.14–1.70; $p = 0.001$), with a risk increasing by 11% for each additional year of OC use, when started before age 20.

In a case-only study (258 *BRCA1* and 108 *BRCA2* mutation carriers), adjusted for age and duration of use [38], multivariate analysis showed an association between prior or current OC use and a younger age at diagnosis of cancer in *BRCA1* and *2* mutation carriers (HR = 1.7; 95% CI 1.1–2.05; $p = 0.006$). There was no association between the onset of cancer and the duration of OC therapy.

A recent publication [40] included 6030 *BRCA1* and 3809 *BRCA2* mutation carriers who were analyzed according to different designs (prospective, left-truncated retrospective and full-cohort retrospective). The prospective cohort included patients with no history of cancer or risk-reducing mastectomy; the left-truncated cohort included *BRCA* mutation carriers without cancer history or risk-reducing mastectomy in the 5 years that preceded the inclusion in the study. In the case of *BRCA1* mutations, the prospective analysis found no association with OC use and breast cancer, when factors such as age, generic duration of use or duration of use before first full term pregnancy were analyzed. The other two cohorts, (left-truncated and full-cohort retrospective analysis) found an increase in risk of breast cancer (HR 1.39, 95% CI 1.23–1.58). An inverse correlation was evident between increase in risk and both first full-term pregnancy and lifetime duration of use in both cohorts. The results were then stratified by age and the left-truncated cohort analysis revealed that the OC use before first full-term pregnancy posed a significant risk only if restricted to women under 35 years of age (p-value 0.001). Even the full cohort analysis showed an increased risk with younger age at first OC use and longer duration of use after first full-term pregnancy.

The majority of studies did not consider characteristics of OC. An attempt was published in 2008 [34] considering contraceptive products used $<$(high-dose) or $\geq$ 1975 (low-dose) in *BRCA1/2* mutated women (94 with breast cancer 444 controls). The study showed that use of OC, duration of use, and time since last OC use were not associated with breast cancer risk in patients carrying both *BRCA1* and *BRCA2* mutations. When *BRCA1* patients who had undergone low-dose OC therapy were considered alone the OR was 0.55, whereas the OR was 0.94 in *BRCA2* patients. This would suggest that low-dose OC use would be protective in *BRCA1* mutation carriers. None of the other adjustments, such as early age of OC use, showed a significant association with breast cancer risk.

Collectively, the effect of OC on breast cancer risk in women carrying *BRCA1/2* mutations remains uncertain but available evidence does not point to a safety issue. Women should be counselled about strengths and limitations of the current level of evidence to allow an informed choice.

4. Discussion

Effective contraceptive counselling is the result of a shared decision making approach which has the aim to plan reproductive goals taking into account the best medical evidence available and the levels of women's knowledge on modern contraception [41]. Breast cancer risk associated with the use of OC is an area of controversy in the medical community [42], whereas the efficacy of OC in reducing ovarian cancer risk over time of use is supported by good evidence [11]. As we stated above, a similar picture emerges by examining the literature in *BRCA* mutation carriers. These facts should be part of our routine counselling in high-risk women that needs a balanced view on the benefits of OC use in preventing ovarian cancer and on the possible negative effects in promoting breast cancer risk. However, in communicating the uncertainties HCPs have to consider selection bias in studies and meta-analyses conducted so far [43]. Special populations with prevalent cancer cases, inclusion of specific ethnic subgroups, presence of controls not genetically tested and lack of exclusion of other possible cancer modifying factors such as BMI, diet and exercise features, cigarette smoking, anti-inflammatory medications, radiation exposure, menarche age, reproductive-life history and breastfeeding are likely to explain the conflicting results [26]. Ethical barriers prevent the use of randomized controlled trials with the aim of elucidating the interactions between OC use and other potential cancer modifiers. Therefore, we hope that well-designed national and regional clinical registries will assist HCPs in elucidating the risk of breast cancer associated with OC use in *BRCA* carriers.

A useful element for counselling these women may be the age at first OC prescription, as well as the age at first full-term pregnancy. Indeed, in *BRCA* mutation carriers, who started OC before 20 years and/or before first full-term pregnancy, an increased breast cancer risk, mostly early-onset breast cancer, has been reported [27, 34, 36, 40]. These data are in line with those reported in the general population [44–47]. Interestingly, older age at first live birth seemed to be associated with a lower risk of breast cancer in women carriers of *BRCA* mutations, suggesting some sort of higher vulnerability to hormone exposure at a younger age [26]. On the other hand, even duration of OC use in *BRCA1/2* patients may be

a key element to consider in contraceptive counselling since the increased breast cancer risk progressively reduced following discontinuation of OC [24, 40]. An observational retrospective study among women at increased genetic or familial breast cancer risk analyzed reproductive characteristics including the use of several combined hormonal contraceptive options and did not confirm an increased risk of breast cancer over time of hormone exposure [48, 49]. That being so, the increased risk of breast cancer, if any, should be limited to the oldest OC formulations [12] and should not discourage *BRCA* carriers that request effective contraception to use OC because this choice represents a reliable opportunity for ovarian cancer prophylaxis until surgical risk reduction is planned. Indeed, a recent expert opinion by Grandi *et al.* [50] argued that the possible increased breast cancer risk associated with OC use has much less an impact than the protection against ovarian cancer, taking into account preventive measures and different outcomes. Indeed, effective early detection strategies recommended for all *BRCA* carriers who do not undergo prophylactic mastectomy could successfully manage the theoretical small additional breast cancer risk derived from the use of OC. Moreover, we know very little about the effects of different OC formulations stratified by type and dose of estrogen, type and dose of progestogens and regimen, on the oncologic risk of *BRCA* populations. The routes of administration of combined estrogen-progestogen formulations, as well as of progestogen-only options, have also been poorly investigated with the aim of assessing potential differences in the long-term risks attributed to their use.

Finally, it is worth mentioning that effective counselling should consider that OC may offer non-contraceptive benefits also in *BRCA* carriers who should not be denied an effective option to counteract dysmenorrhea, heavy menstrual bleeding and other reproductive and non-reproductive conditions which may be effectively managed with adequate counselling [51].

In counselling high-risk women, another issue to be considered is that germline mutations in *BRCA* suppressor genes have been associated over time with several malignancies, in addition to breast and ovarian cancers. The Breast Cancer Linkage Consortium and The Hereditary Breast Cancer Study Group showed an increased risk for endometrial cancer in *BRCA1* mutated women (relative risk = 2.65; 95% CI, 1.69–4.16; $p < 0.001$ and standardized incidence ratio = 1.91; 95% CI, 1.06–3.19; $p = 0.03$) [52, 53]. In addition, a prospective multicenter cohort study highlighted an increased risk for serous and/or serous-like uterine cancer in this high-risk population [54]. Recently, Oh *et al.* [55] in their systematic review (18 studies) and meta-analysis (14 studies) found that the risk of colorectal cancer is moderately elevated in *BRCA1* (OR = 1.49, 95% CI = 1.19 to 1.85, $p < 0.001$), regardless of study design, specific type of cancer, method of detection, or age. Therefore, OC may offer a protective benefit against endometrial and colorectal malignancies [56]. According to the most recently published data from the Royal College of General Practitioners' Oral Contraception Study including nearly 1.3 million women-years of observation among general population, OC users appeared to be protected from colorectal and endometrial cancer for many years after stopping OC [57]. This extra-ovarian chemo-preventive benefit of OC use has to be taken into account when counselling high-risk populations, even if specific data obtained in *BRCA* mutated women are still not available.

Finally, *BRCA1* and *BRCA2* populations included in published studies are carriers of many hundreds of mutations with different effects on protein coding and function and with possible different effects on breast and ovarian cancer risk. To date, we are not aware of any study that has evaluated the potential interaction between this mutational heterogeneity and OC use in term of cancer prevalence and phenotypes of lesions.

5. Conclusions

OC reduces the risk of ovarian cancer in *BRCA1* and *BRCA2* mutation carriers. Protective effects increase with duration of use. On the other hand, there is not a clear consensus on the possible increase of breast cancer risk in special populations already at high-risk. *BRCA1/2* carriers should always receive a sensible and patient-centered contraceptive counselling because they have to struggle from an early age with the multifaceted burden of being previvors. They really need special care to foster their ability to make life-changing decisions throughout their reproductive lifetime. Notwithstanding this, when they are asking for reliable contraception, HCPs have to consider that there is no evidence to recommend against the use of OC, but rather there is a chemopreventive potential in such a choice that needs to be tailored based on each individual profile.

Author contributions

CC and FZ conceived and designed the analysis, collected data, performed the analysis, wrote and reviewed the manuscript; CAC, DP, MU contributed to data collection and analysis; SS, ADV, SM contributed to analysis and interpretation of results; EA, AS reviewed the manuscript, REN revised for intellectual content and finally all authors read and approved the manuscript.

Ethics approval and consent to participate

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Conflict of interest

The authors declare no conflict of interest.

References

[1] Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips K, Mooij TM, Roos-Blom M, *et al.* Risks of breast, ovarian, and contralateral breast cancer for *BRCA*1 and *BRCA*2 mutation carriers. Journal of the American Medical Association. 2017; 317: 2402–2416.

[2] Jacobs IJ, Menon U, Ryan A, Gentry-Maharaj A, Burnell M, Kalsi JK, *et al.* Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet. 2016; 387: 945–956.

[3] Chirlaque MD, Uhry Z, Salmerón D, Sánchez-Zapata MI, Zannoni GF, Navarro C, *et al.* Trends in net survival from ovarian cancer in six European Latin countries: results from the SUDCAN population-based study. European Journal of Cancer Prevention. 2017; S107–S113.

[4] Malvezzi M, Carioli G, Rodriguez T, Negri E, La Vecchia C. Global trends and predictions in ovarian cancer mortality. Annals of Oncology. 2016; 27: 2017–2025.

[5] Daly MB, Pilarski R, Yurgelun MB, Berry MP, Buys SS, Dickson P, *et al.* Genetic/familial high-risk assessment: breast, ovarian, and pancreatic. Version 1.2020. 2019.

[6] Paluch-Shimon S, Cardoso F, Sessa C, Balmana J, Cardoso MJ, Gilbert F, *et al.* Prevention and screening in *BRCA* mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. Annals of Oncology. 2016; 27: v103–v110.

[7] Walker JL, Powell CB, Chen L, Carter J, Bae Jump VL, Parker LP, *et al.* Society of Gynecologic Oncology recommendations for the prevention of ovarian cancer. Cancer. 2015; 121: 2108–2120.

[8] Kingsberg SA, Larkin LC, Liu JH. Clinical effects of early or surgical menopause. Obstetrics & Gynecology. 2020; 135: 853–868.

[9] Rocca WA, Gazzuola-Rocca L, Smith CY, Grossardt BR, Faubion SS, Shuster LT, *et al.* Accelerated accumulation of multimorbidity after bilateral oophorectomy: a population-based cohort study. Mayo Clinic Proceedings. 2016; 91: 1577–1589.

[10] Rocca WA. Difficult decisions in women at high genetic risk for cancer: toward an individualized approach. Menopause. 2020; 27: 727–729.

[11] Collaborative Group on Epidemiological Studies of Ovarian Cancer, Beral V, Doll R, Hermon C, Peto R, Reeves G. 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: 303–314.

[12] Iodice S, Barile M, Rotmensz N, Feroce I, Bonanni B, Radice P, *et al.* Oral contraceptive use and breast or ovarian cancer risk in *BRCA1/2* carriers: a meta-analysis. European Journal of Cancer. 2010; 46: 2275–2284.

[13] Moorman PG, Havrilesky LJ, Gierisch JM, Coeytaux RR, Lowery WJ, Peragallo Urrutia R, *et al.* Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis. Journal of Clinical Oncology. 2013; 31: 4188–4198.

[14] Huber D, Seitz S, Kast K, Emons G, Ortmann O. Use of oral contraceptives in *BRCA* mutation carriers and risk for ovarian and breast cancer: a systematic review. Archives of Gynecology and Obstetrics. 2020; 301: 875–884.

[15] Milne RL, Knight JA, John EM, Dite GS, Balbuena R, Ziogas A, *et al.* Oral contraceptive use and risk of early-onset breast cancer in carriers and noncarriers of *BRCA*1 and *BRCA*2 mutations. Cancer Epidemiology, Biomarkers & Prevention. 2005; 14: 350–356.

[16] Del Pup L, Codacci-Pisanelli G, Peccatori F. Breast cancer risk of hormonal contraception: counselling considering new evidence. Critical Reviews in Oncology/Hematology. 2019; 137: 123–130.

[17] Narod SA, Risch H, Moslehi R, Dørum A, Neuhausen S, Olsson H, *et al.* Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. The New England Journal of Medicine. 1998; 339: 424–428.

[18] Modan B, Hartge P, Hirsh-Yechezkel G, Chetrit A, Lubin F, Beller U, *et al.* Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a *BRCA*1 or *BRCA*2 mutation. New England Journal of Medicine. 2001; 345: 235–240.

[19] McGuire V. Relation of contraceptive and reproductive history to ovarian cancer risk in carriers and noncarriers of *BRCA*1 gene mutations. American Journal of Epidemiology. 2004; 160: 613–618.

[20] Whittemore AS, Balise RR, Pharoah PD, Dicioccio RA, Oakley-Girvan I, Ramus SJ, *et al.* Oral contraceptive use and ovarian cancer risk among carriers of *BRCA*1 or *BRCA*2 mutations. British Journal of Cancer. 2004; 91: 1911–1915.

[21] Gronwald J, Byrski T, Huzarski T, Cybulski C, Sun P, Tulman A, *et al.* Influence of selected lifestyle factors on breast and ovarian cancer risk in *BRCA*1 mutation carriers from Poland. Breast Cancer Research and Treatment. 2006; 95: 105–109.

[22] McLaughlin JR, Risch HA, Lubinski J, Moller P, Ghadirian P, Lynch H, *et al.* Reproductive risk factors for ovarian cancer in carriers of *BRCA*1 or *BRCA*2 mutations: a case-control study. The Lancet. Oncology. 2007; 8: 26–34.

[23] Antoniou AC, Rookus M, Andrieu N, Brohet R, Chang-Claude J, Peock S, *et al.* Reproductive and hormonal factors, and ovarian cancer risk for *BRCA*1 and *BRCA*2 mutation carriers: results from the international *BRCA1/2* carrier cohort study. Cancer Epidemiology Biomarkers & Prevention. 2009; 18: 601–610.

[24] Cibula D, Gompel A, Mueck AO, La Vecchia C, Hannaford PC, Skouby SO, *et al.* Hormonal contraception and risk of cancer. Human Reproduction Update. 2010; 16: 631–650.

[25] Cibula D, Zikan M, Dusek L, Majek O. Oral contraceptives and risk of ovarian and breast cancers in *BRCA* mutation carriers: a meta-analysis. Expert Review of Anticancer Therapy. 2011; 11: 1197–1207.

[26] Friebel TM, Domchek SM, Rebbeck TR. Modifiers of cancer risk in *BRCA*1 and *BRCA*2 mutation carriers: systematic review and meta-analysis. Journal of the National Cancer Institute. 2014; 106: dju091.

[27] Kotsopoulos J, Lubinski J, Moller P, Lynch HT, Singer CF, Eng C, *et al.* Timing of oral contraceptive use and the risk of breast cancer in *BRCA*1 mutation carriers. Breast Cancer Research and Treatment. 2014; 143: 579–586.

[28] Perri T, Lifshitz D, Sadetzki S, Oberman B, Meirow D, Ben-Baruch G, *et al.* Fertility treatments and invasive epithelial ovarian cancer risk in Jewish Israeli *BRCA*1 or *BRCA*2 mutation carriers. Fertility and Sterility. 2015; 103: 1305–1312.

[29] Ursin G, Henderson BE, Haile RW, Pike MC, Zhou N, Diep A, *et al.* Does oral contraceptive use increase the risk of breast cancer in women with *BRCA*1/*BRCA*2 mutations more than in other women? Cancer Research. 1997; 57: 3678–3681.

[30] Narod SA, Dubé M, Klijn J, Lubinski J, Lynch HT, Ghadirian P, *et al.* Oral contraceptives and the risk of breast cancer in *BRCA*1 and *BRCA*2 mutation carriers. Journal of the National Cancer Institute. 2002; 94: 1773–1779.

[31] Heimdal K, Skovlund E, Møller P. Oral contraceptives and risk of familial breast cancer. Cancer Detection and Prevention. 2002; 26: 23–27.

[32] Haile RW, Thomas DC, McGuire V, Felberg A, John EM, Milne RL, *et al.* *BRCA*1 and *BRCA*2 mutation carriers, oral contraceptive use, and breast cancer before age 50. Cancer Epidemiology, Biomarkers & Prevention. 2006; 15: 1863–1870.

[33] Brohet RM, Goldgar DE, Easton DF, Antoniou AC, Andrieu N, Chang-Claude J, *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. Journal of Clinical Oncology. 2007; 25: 3831–3836.

[34] Lee E, Ma H, McKean-Cowdin R, Van Den Berg D, Bernstein L, Henderson BE, *et al.* Effect of reproductive factors and oral contraceptives on breast cancer risk in *BRCA1/2* mutation carriers and noncarriers: results from a population-based study. Cancer Epidemiology, Biomarkers & Prevention. 2008; 17: 3170–3178.

[35] Atchley DP, Albarracin CT, Lopez A, Valero V, Amos CI, Gonzalez-Angulo AM, *et al.* Clinical and pathologic characteristics of patients with *BRCA*-positive and *BRCA*-negative breast cancer. Journal of Clinical Oncology. 2008; 26: 4282–4288.

[36] Pasanisi P, Hédelin G, Berrino J, Chang-Claude J, Hermann S, Steel M, *et al.* Oral contraceptive use and *BRCA* penetrance: a case-only study. Cancer Epidemiology Biomarkers & Prevention. 2009; 18: 2107–2113.
[37] Figueiredo JC, Haile RW, Bernstein L, Malone KE, Largent J, Langholz B, *et al.* Oral contraceptives and postmenopausal hormones and risk of contralateral breast cancer among *BRCA*1 and *BRCA*2 mutation carriers and noncarriers: the WECARE Study. Breast Cancer Research and Treatment. 2010; 120: 175–183.
[38] Rieder V, Salama M, Glöckner L, Muhr D, Berger A, Tea M, *et al.* Effect of lifestyle and reproductive factors on the onset of breast cancer in female *BRCA* 1 and 2 mutation carriers. Molecular Genetics & Genomic Medicine. 2015; 10: 172–177.
[39] Park B, Hopper JL, Win AK, Dowty JG, Sung HK, Ahn C, *et al.* Reproductive factors as risk modifiers of breast cancer in *BRCA* mutation carriers and high-risk non-carriers. Oncotarget. 2017; 8: 102110–102118.
[40] Schrijver LH, Olsson H, Phillips KA, Terry MB, Goldgar DE, Kast K, *et al.* Oral contraceptive use and breast cancer risk: retrospective and prospective analyses from a *BRCA*1 and *BRCA*2 mutation carrier cohort study. JNCI Cancer Spectrum. 2018; 2: pky023.
[41] Dehlendorf C, Krajewski C, Borrero S. Contraceptive counseling: best practices to ensure quality communication and enable effective contraceptive use. Clinical Obstetrics and Gynecology. 2014; 57: 659–673.
[42] Hunter DJ. Oral contraceptives and the small increased risk of breast cancer. The New England Journal of Medicine. 2017; 377: 2276–2277.
[43] Gadducci A, Biglia N, Cosio S, Sismondi P, Genazzani AR. Gynaecological challenging issues in the management of *BRCA* mutation carriers: oral contraceptives, prophylactic salpingo-oophorectomy and hormone replacement therapy. Gynecological Endocrinology. 2010; 26: 568–577.
[44] Jernström H, Loman N, Johannsson OT, Borg A, Olsson H. Impact of teenage oral contraceptive use in a population-based series of early-onset breast cancer cases have undergone *BRCA* mutation testing. European Journal of Cancer. 2005; 41: 2312–2320.
[45] Kumle M, Weiderpass E, Braaten T, Persson I, Adami H, Lund E. Use of oral contraceptives and breast cancer risk: the Norwegian-Swedish women's lifestyle and health cohort study. Cancer Epidemiology, Biomarkers & Prevention. 2002; 11: 1375–1381.
[46] Althuis MD, Brogan DD, Coates RJ, Daling JR, Gammon MD, Malone KE, *et al.* Breast cancer among very young premenopausal women (United States). Cancer Causes &Control. 2003; 14: 151–160.
[47] Mørch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard Ø. Contemporary hormonal contraception and the risk of breast cancer. New England Journal of Medicine. 2017; 377: 2228–2239.
[48] Toss A, Grandi G, Cagnacci A, Marcheselli L, Pavesi S, De Matteis E, *et al.* The impact of reproductive life on breast cancer risk in women with family history or *BRCA* mutation. Oncotarget. 2017; 8: 9144–9154.
[49] Grandi G, Toss A, Cagnacci A, Marcheselli L, Pavesi S, Facchinetti F, *et al.* Combined hormonal contraceptive use and risk of breast cancer in a population of women with a family history. Clinical Breast Cancer. 2018; 18: e15–e24.
[50] Grandi G, Sammarini M, Chiara Del Savio M, Toss A, Facchinetti F. Combined hormonal contraceptives in *BRCA* gene mutation carriers: why not? The European Journal of Contraception & Reproductive Health Care. 2019; 24: 417–419.
[51] Maguire K, Westhoff C. The state of hormonal contraception today: established and emerging noncontraceptive health benefits. American Journal of Obstetrics and Gynecology. 2011; 205: S4–S8.
[52] Thompson D, Easton DF. Cancer Incidence in *BRCA*1 mutation carriers. Journal of the National Cancer Institute. 2002; 94: 1358–1365.
[53] Segev Y, Iqbal J, Lubinski J, Gronwald J, Lynch HT, Moller P, *et al.* Hereditary Breast Cancer Study Group. The incidence of endometrial cancer in women with *BRCA*1 and *BRCA*2 mutations. Gynecologic Oncology. 2013; 130: 127–131.
[54] Shu CA, Pike MC, Jotwani AR, Friebel TM, Soslow RA, Levine DA, *et al.* Uterine cancer after risk-reducing salpingo-oophorectomy without hysterectomy in women with *BRCA* mutations. JAMA Oncology. 2016; 2: 1434–1440.
[55] Oh M, McBride A, Yun S, Bhattacharjee S, Slack M, Martin JR, *et al. BRCA*1 and *BRCA*2 gene mutations and colorectal cancer risk: systematic review and meta-analysis. Journal of the National Cancer Institute. 2018; 110: 1178–1189.
[56] Davidson BA, Moorman PG. Risk-benefit assessment of the combined oral contraceptive pill in women with a family history of female cancer. Expert Opinion on Drug Safety. 2014; 13: 1375–1382.
[57] Iversen L, Sivasubramaniam S, Lee AJ, Fielding S, Hannaford PC. Lifetime cancer risk and combined oral contraceptives. 2017; 216: 580.e1–580.e9.
[58] Bernholtz S, Laitman Y, Kaufman B, Paluch Shimon S, Friedman E. Cancer risk in Jewish *BRCA*1 and *BRCA*2 mutation carriers: effects of oral contraceptive use and parental origin of mutation. Breast Cancer Research and Treatment. 2011; 129: 557–563.