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REVIEW ARTICLE

Contraception as chemoprevention of ovarian cancer in BRCA1 and BRCA2 women

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Abstract

Ovarian cancer is the seventh most common cancer in women in the world, with an estimated worldwide mortality of over 207′000 women every year. This cancer, due to the current lack of adequate screening techniques, is commonly diagnosed late and has a poor prognosis. The oral contraceptive pill is considered the most effective prevention strategy for ovarian cancer in the general population, being associated with a decreased incidence while also having a substantial positive impact on the mortality rate, which is reduced by up to 50%. BRCA1 and BRCA2 germline mutated women have an augmented risk of ovary and breast cancer: despite international guidelines that consider prophylactic surgery as the gold standard for ovarian cancer prevention, there are currently no effective non-invasive preventive methods. In BRCA1\2 mutated patients, clinicians should weigh the benefits of contraceptive pills against the risk of long-term thromboembolic side effects and hormonal malignancies such as breast and cervical cancer. A multidisciplinary team should counsel patients on the most appropriate risk-reduction strategy tailored to their needs and expectations, proposing the oral contraceptive pill to selected patients after balancing the risks of adverse effects and the benefits on both contraception and chemoprevention.

Keywords Ovarian cancer · Oral contraceptive pill · Chemoprevention · BRCA1 · BRCA2

Abbreviations

OC	Ovarian cancer
oCP	Oral contraceptive pill
BRCA1	Breast cancer type 1 susceptibility protein
BRCA2	Breast cancer type 2 susceptibility protein
HBOC	Autosomal dominant hereditary-breast-ovarian cancer syndrome
NCCN	National Comprehensive Cancer Network
RRSO	Risk-reducing bilateral salpingo-oophorectomy
BC	Breast cancer
CC	Cervical cancer
OR	Odds ratio
HR	Hazard ratio

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Methods

To identify the articles to be included in our review, we performed a literature search in the PubMed, Web of Science, and Scopus databases in June 2023. The investigation used combinations of the search terms "ovarian," "cancer," "chemoprevention," "BRCA1\BRCA2," and related synonyms. We then assessed the published papers that included these keywords in the title or the abstract, excluding publications in languages other than English. This research strategy yielded 162 publications from 1992 to 2023. Two reviewers read the abstracts and excluded all the articles that did not meet the inclusion criteria, thus excluding 49 articles related to other cancers, 27 articles without available clinical data, and 24 articles without retrievable full text.

We finally included 60 papers, 21 articles, 14 retrospective studies, 11 literature reviews, and 14 international guidelines. The review design followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [1], summarised in (Fig. 1).

Epidemiology of ovarian cancer

Global Cancer Statistics 2020 ranks ovarian cancer (OC) as the third most common for incidence and the second most common for mortality among cancers of the female reproductive system [2]. The poor prognosis of this disease is due to the usually late stage at the time of diagnosis, which leads to a 5-year survival rate of less than 36% and 17% for stage III and stage IV patients, respectively [2–4]. The Global Cancer Observatory (GLOBOCAN) estimated 313′959 new OC cases in 2020 globally in all ages, with an age-standardized rate of 6.6 per 100′000. Central and Eastern Europe, regions with a very high human development index (HDI), showed the highest incidence rate of OC, while lower incidence rates were recorded in the geographic areas with the lowest HDI. In 2020, 207′252 new deaths due to OC were reported globally, with an age-standardized mortality rate of 4.2 per 100′000. The highest mortality rate is in Polynesia, Micronesia, and Central-Eastern Europe. Despite a decreasing trend in the incidence and mortality rates of OC globally, possibly due to the widespread use of the oral contraceptive pill (oCP), a worrying increase in OC incidence is observed in females under 50 years. This evidence could be related to the change in risk factors due to the spread of the Western lifestyle [5–7]. According to GLOBOCAN's projections, by 2040, the cases of newly diagnosed OC will rise by almost 40% to over 450′000, and OC deaths will increase by over 50% in 20 years. The 5-year OC survival rates vary from 36 to 46% in the most developed

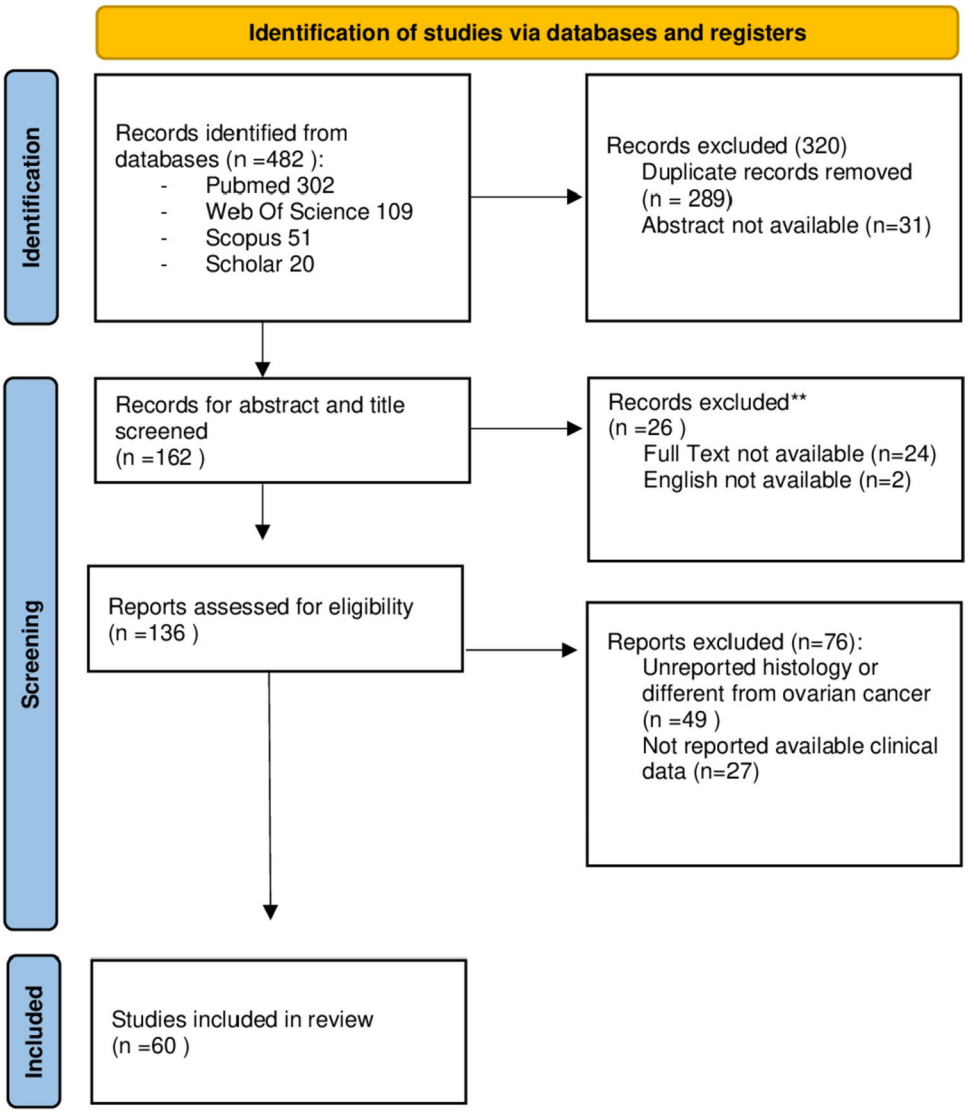

Fig. 1 Prisma 2020 flow diagram for reviews

countries, while they are much lower in less wealthy regions [8]. Analyses of the differences in incidence and mortality between high HDI and low HDI have aroused concerns regarding health disparities based on economic conditions. OC is a global health issue and a socio-economic problem that all nations should strive to address on all fronts with effective health policies [9].

The genomic landscape of ovarian cancer: BRCA1\2 and tumorigenesis

Cancer is a very large group of diseases characterized by an accumulation of DNA damage leading to uncontrolled cell division and their spread into surrounding tissues. Advancements in current genetic oncology have led to a comprehensive understanding of the "genomic landscapes" of human cancer, attributed to approximately 140 genetic sequences that can drive tumorigenesis and are altered in a high percentage of tumours. Every cancer contains around five driver mutations classified as gain-of-function of oncogenes and loss-of-function of oncosuppressors [10, 11]. Not surprisingly, most cancer mutations abrogate cellular checkpoints (e.g. tumour protein p53, TP53) [12] and DNA-repair pathways (e.g., breast cancer susceptibility proteins type 1 (BRCA1) and type 2 (BRCA2) [13, 14]. BRCA1 [15] and BRCA2 [16] genes are chromosome custodian proteins involved in common cellular signalling of genome integrity that respond to DNA damage via repair and apoptosis pathways. Ataxia telangiectasia mutated kinase (ATM) and RAD51 are the most important proteins involved in their molecular pathway [17–19]. BRCA1\2 proteins are involved in homologous recombination, a crucial high-fidelity molecular pathway that repairs double-strand breaks using DNA sister chromatids as a template [20, 21]. Deficiency of the proteins involved in the pathway triggers the alternative pathways of single-strand annealing and non-homologous end-joining that are less precise in proof-reading function. This molecular process induces the accumulation of DNA mutations and contributes to genome instability [22]. The progressive accumulation of mutations exponentially augments the probability of developing neoplastic subclones capable of immortalize, evade host immunity, reprogram cellular metabolism, promote inflammation, and invade other tissues [23, 24]. (Fig. 2) represents the physiology and pathology of the primary DNA double-strand break repair mechanism pathways.

Hereditary breast and ovarian cancer syndrome

The germline mutation of one copy of the BRCA1\2 gene results in the autosomal dominant hereditary-breast-ovarian cancer (HBOC) syndrome associated with breast cancer

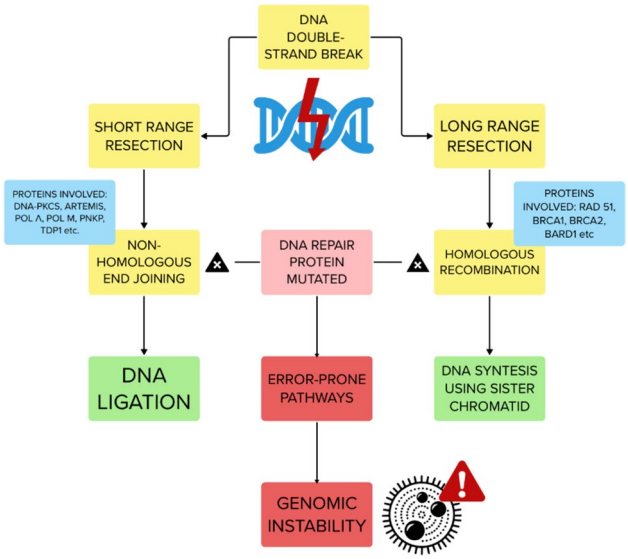

Fig. 2 Main DNA double-strand break repair mechanism pathways [25]

(BC), ovarian, fallopian tube, primary peritoneal cancer, and an increased incidence of other tumors, including melanoma, pancreatic cancer, and prostate cancers (in males). According to the NCCN Guidelines, carriers of HBOC syndrome have an augmented lifetime risk of breast and ovarian cancer: the absolute risk of BC is over 60% for both BRCA1\BRCA2 carriers, whereas the absolute risk of OC is 39–58% and 13–29% for BRCA1 and BRCA2 carriers, respectively [26–29]. HBOC should be suspected in women with a personal or family history of BC, with multiple primary localizations of early onset (before 50 years old), especially if there is triple-negative histology, and in male family members with concomitant history of pancreatic or prostate cancer [28, 30].

Ovarian cancer screening

Screening is a medical strategy performed in an asymptomatic or paucisymptomatic population to assess the risk of its members having a particular disease or condition [31, 32]. Common screening tests are not able to fully diagnose an illness, but they help identify a high-risk subpopulation that will then undergo further evaluation and definitive diagnostic tests and procedures. Examples of widely used screening tests in women are the Pap test for cervical cancer [33] and mammography for BC [34], which contribute to the early diagnosis and treatment of cancer, reducing the morbidity and mortality related to these diseases. An effective screening test for OC should be an easy, cost-effective diagnostic test that accurately detects the condition in order to reduce misdiagnoses and overdiagnoses. Timing is essential for a

good OC screening test because it should detect the disease at a favourable point in its natural history when a therapeutic strategy is feasible and potentially effective [35]. Screening protocols that may effectively increase early diagnosis and reduce the mortality of OC are currently lacking [36–39]. International medical organizations do not recommend screening for OC in the general, low-risk population [40–42]. The American College of Obstetricians-Gynecologists and the National Comprehensive Cancer Network (NCCN), for example, recommend stratifying women into average- and high-risk based on a detailed anamnesis for breast, colon, and gynaecologic cancer. In average-risk women, they do not recommend screening; however, in a select high-risk population, transvaginal ultrasound and the serum CA 125 or Ca125 risk of ovarian cancer algorithm may be considered every 6–12 months to localize early-stage OC [43]. The discovery of new markers and integrative proteomics and metabolomics should lead to new techniques that can be tested in large randomized controlled trials to detect preclinical OC [44]. Genetic testing of a patient's tissue should be considered to determine whether there are genetic mutations that may have a clinical impact [45]. The NCCN recommends offering genetic testing to high-risk women in two clinical scenarios, namely, if there is a blood relative with a mutation in a cancer susceptibility gene or affected by familial cancer syndromes and if there is a personal or familiar history of epithelial ovarian cancer diagnosed at any age [38]. The National Society of Genetic Counselors recommends offering genetic testing to women with OC diagnosed at a young age (less than 45 years) or with triple-negative BC. The counselor should explain to the patients all the ethical, social, and legal implications of the clinical findings and provide accurate information on the strengths and limitations of the test and the potential implications of a positive or negative result on their psychological and reproductive health [46].

The gold standard for ovarian cancer prevention: risk-reducing bilateral salpingo-oophorectomy

The NCCN panel recommend risk-reducing bilateral salpingo-oophorectomy (RRSO) for BRCA1 and BRCA2 carriers in the premenopausal age group [47]. Data from the main studies in the field indicate a substantial decrease in the incidence of both OC (by 96%) and BC (by 50%) [48] and a reduction in the all-cause mortality rate, especially among BRCA1 mutation carriers who undergo RRSO (hazard ratio 0.45, $p < 0.0001$) [49]. However, despite the indisputable advantages of the reduction of oncological risk, clinicians should counsel the patient on the hormonal consequences of the RRSO in terms of premature ovarian failure and early onset of menopause and a multidisciplinary consultation with at least a gynaecologic oncologist and a fertility specialist should precede the procedure.

Oral contraceptives as chemoprevention in the general population: a balance between benefits and potential long-term risks

RRSO is the gold standard for reducing BC and OC risk [50]. However, recent studies have investigated possible non-invasive cancer prevention strategies to reduce the risk of cancer development. The ideal chemopreventive medication should be efficacious, risk-free, easy to administer, and cost-effective [51]. There are two types of chemoprevention: blocking and suppressing agents. Blocking agents act on the initial phase of carcinogenesis while suppressing agents delay the progression of premalignant cells to an invasive tumour [52, 53]. Several drugs have been proposed to prevent OC, but oral contraceptives alone have robust data in support. The oCP is the most effective non-surgical prevention strategy for high-risk populations, having an inverse association with the incidence of OC with an odds ratio (OR)•0.58, 95% CI 0.46–0.73 [54–56] and resulting in a concomitant decrease in mortality rate and a lifetime reduction in OC of approximately 54% [57–61]. The chemopreventive potential of oCP may originate from its ability to suppress ovulation and consequently reduce oxidative stress and accumulation of DNA damage; another chemopreventive action may arise from progestin's ability to promote differentiation in hormone-sensitive cells. (Table 1) lists the main studies and findings on the effect of oral contraception on OC risk. Some authors attribute the recorded reduction in mortality (23%) and incidence (26%) of OC recorded in the USA and in Europe since 1975 [62] to the introduction and growing popularity of oral contraceptive pills, suggesting a chemopreventive effect of the medication in women younger than 60 [63–65]. There should be increasing focus on the stratification of oCP risks and benefits for different ages of use.

Clinicians should balance oCP benefits against undesirable side effects [78]. The most commonly reported minor side effects, such as headaches, nausea, breast tenderness, and weight gain, have been reported as being at the same rate as placebo in controlled clinical trials [79, 80]. Irregular bleeding is one of the most troubling side effects. It occurs in about 25% of cases in the first month of use, consistently decreasing in the third [81]. Unintended pregnancy is also a side effect of oCP: the overall median failure rate of oCP is estimated at 5.5, 10.8, and 15.1 per 100 episodes of typical use in 12, 24, and 36 months, respectively [82]. One of the most feared side effects of the oCP is thromboembolism. The incidence of this complication progressively decreased over

Table 1 Main studies and findings on the effect of oral contraception on oc risk, modified and integrated from cibula [66] and van bommel [67]

Author (year)	Number of cases BRCA1	Number of cases BRCA2	Number of cases BRCA1\2	*Overall estimated effect of oCP (95%Cl)*	*Statistical analysis*	Study design	Study Cohort	Measured outcome
Narod et al. *(1998)* [68]	179	28	\	BRCA1\2 0.5 (0.3–0.8)	OR	Case–control	Ever oCP use	Invasive OC
Narod et al. *(2001)* [69]	346	118	\	BRCA1\2 0.28 (0.15–0.52)	OR	Matched case–control	Ever oCP use	Invasive OC
Runnebaum et al. *(2001)* [70]	595	183	195	BRCA1\2 0.8;(0.5–1.3)	OR	Case–control	Ever oCP use	OC
Whittemore et al. *(2004)* [71]	339	112	451	BRCA1 0.65 (0.41–1.03) BRCA1\2 0.85 (0.53–1.36)	OR	Case–control	Ever oCP use	OC
McGuire et al. *(2004)* [72]	36	\	\	BRCA1 0.54 (0.26, 1.13)	RR	Case–case studies	oCP use > 1 year	Invasive OC
Gronwald et al. *(2006)* [73]	300	\	\	BRCA1 0.40 (0.20–1.00)	OR	Case–control	Ever oCP use	OC
McLaughlin et al. *(2007)* [56]	2713	508	3223	BRCA1 0.56 (0.45–0.71) BRCA2 0.39 (0.23–0.66) BRCA1\2 0.53 (0.43–0.66)	OR	Case–control	Ever oCP use	Invasive OC
Antoniou et al. *(2009)* [74]	3989	2445	\	BRCA1 0.51 (0.36–0.71) BRCA2 0.65 (0.35–1.19)	HR	Retrospective cohort	Ever oCP use	OC
Vicus et al. *(2010)* [75]	661	\	\	BRCA1 0.91 (0.83–0.99) BRCA2 OR = 0.94 (0.80–1.11)	OR	Matched case–control	Ever oCP use	OC
Kotsopoulos et al. *(2015)* [76]	5386	1180	\	BRCA1 0.50 (0.40–0.63) BRCA2 0.42 (0.22–0.83)	OR	Matched case–control	Ever oCP use	OC
Perri et al. *(2015)* [77]	718	331	3	BRCA1\2 0.19 (0.13–0.28)	OR	Historical prospective cohort	Ever oCP use	OC
Schrijver et al. *(2021)* [74]	4818	2844	\	BRCA1\2 0.67 (0.40–1.12)	HR	Retrospective cohort	Ever oCP use	OC

OR: odds ratio, HR: hazard ratio, RR: relative risk, OC: ovarian cancer

the years as a consequence of the progressive reduction of the total dose of oestrogen in the oral formulation. There are an estimated 8–10 cases in 10′000/year of venous embolism and 1–4 cases in 10′000/year of arterial embolism [83–85]. The relative risk of venous thromboembolism and arterial thromboembolism are three-fold and two-fold, respectively, compared to that for non-users, but the absolute risk of these adverse events for oCP users remains low. During the counselling, which precedes contraception prescription, the clinical should also inform the patient of the oncological risk for BC and cervical cancer (CC). Compared to women without a personal history of use of hormonal contraceptives assumption, patients with at least one prescription of oCP had a significantly increased incidence of BC with an OR•1.33, 95% CI 1.26–1.41 $p < 0.001$. In a nested case–control study that included almost 10,000 women aged under 50 years old and with a diagnosis of BC, those prescribed any form of hormonal contraceptives were shown to have an increased risk of BC. The average time between the last prescription and the BC diagnosis is about 3 years. The results were similar regardless of the type of oCP [86]. Women who use the oCP have a time-dependent increase also in CC risk of about 10% for use during fewer than 5 years, 60% in 5–9 years, and doubling with ten or more years of use [87]. The gynaecologist should balance the data on the augmented risk of BC and CC with the documented beneficial effects

on OC and other cancers like endometrial and colon cancer, reduced by 30% and 15–20%, respectively [88–90].

The role of oral combined contraception in ovarian cancer risk in BRCA1\2 mutated patients

A recent meta-analysis of BRCA1\2 carriers found that oCP has a chemopreventive function in both BRCA1 and BRCA2-mutated patients, OR•0.55, 95% CI 0.47- 0.66 and OR•0.65, 95% CI 0.34–1.24, respectively. These results suggest that the oCP reduces the risk of OC in BRCA1\ BRCA2 mutation carriers, similar to the data in the general population [47, 55]. In a study based on data from 3989 BRCA1-mutated patients, a statistically significant reduction of OC was still present more than 15 years after the discontinuation. The risk reduction related to the use of the oCP in BRCA1\BRCA2 mutation carriers is directly proportional to the duration of use, as follows: use during fewer than ten years has an OR•0.40 95%, CI, 0.22–0.71 in BRCA1 and OR•0.36 95% CI, 0.14–0.92 in BRCA2, while prolonged use (over 20 years) has an OR•0.61 95% CI, 0.43–0.87 for BRCA1 and OR•0.78, 95% CI, 0.40–1.52 for BRCA2. An important finding is that the protective effect of contraception on OC risk continued for longer than 15 years after discontinuing use [74, 76]. Because of the smaller sample size, further studies are necessary to evaluate the impact of the oCP in BRCA2-mutated cohorts. All the evidence suggests that women who have ever used the oCP in their lives have a significant reduction of OC risk by over 42%; this strong effect increases with long-term use and remains also after discontinuing use [66]. Oral contraceptives should be discussed as an effective contraceptive option and cancer chemoprevention during counselling among the high-risk BRCA1\2 mutated population.

New chemoprevention strategies

There are few published clinical studies on alternative chemopreventive strategies for the general population and for BRCA1\2 mutated women [52]. Multiple chemopreventive medications have been proposed based on studies on molecular science, but there is a lack of robust translational and clinical data in support.

NSAID

One of the main fields of study is nonsteroidal anti-inflammatory drugs (NSAIDs) because of their low cost, high availability, and known pharmacological safety. All the NSAIDs significantly reduce the risk of OC (OR•0.72, 95% CI 0.53–0.98). Women reporting daily use of aspirin, compared with non-daily use and non-use, had a 10% lower risk of having OC (HR•0.90, 95% CI = 0.82 to 1.00, $P = 0.05$). This association was statistically significant for use up to 10 years duration (HR•0.88, 95% CI = 0.65 to 1.18), whereas 10 or more years of aspirin use led to an augmented risk of OC (HR •1.27, 95% CI = 0.99 to 1.62) [7]. In contrast, other studies found no correlation between using analgesics and developing OC, especially in a multiethnic population [91].

Retinoids

Retinoids demonstrated a significant cytotoxic effect on OC in murine cell lines grown in vitro, but studies on clinical applications are limited. A clinical trial on chemoprevention with retinoids in patients with a history of BC reported a transient decrease in the incidence of OC. However, other studies are needed to assess these medications' safety and clinical applicability [92].

Phytochemicals

Plant-derived antioxidants and phytochemicals can induce autophagy and apoptosis, reduce proliferation, and induce cytotoxicity in cancer cells in vitro. In vivo experiments are required [93].

Anti-angiogenic drugs

In the past 15 years, anti-angiogenic drugs have been approved for treating OC. In the multicentre phase III GOG-0218 trial, patients treated with bevacizumab (upfront and maintenance) improved by 3.8 months progression-free survival (PFS) compared with the control group. There was no improvement in overall survival (OS) except among patients at advanced stage IV doing upfront and maintenance therapy, who had an OS of 42.8 months, vs 32.6 months of the controls. Further studies should examine the feasibility of angiopreventive agents such as chemoprevention, particularly in high-risk women and especially those with BRCA1\2 mutations [94].

PARP inhibitors

Poly-ADP ribose polymerase (PARP) inhibitors are safe and effective chemotherapies proposed as chemopreventive agents for high-risk populations, but preclinical and clinical studies are very limited [95]. In 2014, Ciric to et al. tested the effect of the PARP inhibitors veliparib and olaparib on tumour development in the mammary glands of BRCA1-deficient mouse models; this study demonstrated a significant delay in the age of the first detectable tumour of 2.4 weeks in veliparib-treated mice and 6.5 weeks in

olaparib-treated mice, compared to the controls [96]. The authors also reported an increased average lifespan of 7 weeks in olaparib-treated mice. The main limits of using PARP inhibitors as chemoprevention are long-term toxicity, drug resistance, and the lack of data on the possible pro-cancerogenic effect of this medication on the disease-free population [97]. Potential future directions in the field of PARP inhibitors may be to design and conduct more robust preclinical studies on selected animal models to determine the capacity of these drugs to delay tumour onset.

Conclusions

Ovarian cancer is prevalent among women who carry the BRCA1\2 gene mutation. However, there are currently few non-invasive preventive methods available. The epidemiologic evidence supports a significant preventive effect of oCP use on the risk of developing OC in women with a BRCA1 or BRCA2 mutation [55, 74, 76]. When considering the best chemopreventive options, both patient and clinician must be fully aware of the chemoprevention agents' potential risks, benefits, and side effects. A match between the candidate agent and risk group would be essential for successful OC chemoprevention. Successful chemoprevention programs will likely involve physicians with expertise in patient risk stratification and having a clear understanding of the agent's pharmacology. There is no absolute contraindication of the use of the oCP in BRCA1\2 mutated patients. A multidisciplinary team should counsel women on the most appropriate risk-reduction strategy available for the BRCA1\2 population, basing selection of the best treatment on family history, anamnesis, and the patient's needs and expectations regarding OC chemoprevention.

Author contributions The authors confirm their contribution to the paper as follows: study conception and design: Vera Loizzi (VL), Gennaro Cormio (GC), and Ettore Cicinelli (EC); data collection: Marco Cerbone (MC), Francesca Arezzo (FA), and Erica Silvestris (ES); analysis and interpretation of results: MC, FA, ES, Gianluca Raffaello Damiani (GRD), Gerardo Cazzato (GeC), and VL; draft manuscript preparation: MC, VL, FA, GRD, GeC, GC, and EC; writing—review & editing of the manuscript: MC, VL, FC, ES, GC, GeC, GRD, GC, and EC. All authors reviewed the results and approved the final version of the manuscript.

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