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Oral contraceptive use and breast or ovarian cancer risk in BRCA1/2 carriers: A meta-analysis

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ABSTRACT

Background: Women with BRCA1 or BRCA2 mutations are at increased risk of breast and ovarian cancer. Oral contraceptives (OC) use has been associated with a reduction in ovarian cancer risk and with a moderately increased breast cancer risk, which tends to level off in the few years after stopping. The association between oral contraceptive and BRCA1 or BRCA2 gene mutations carriers is unclear.

Methods: We performed a comprehensive literature search updated to March 2010 of studies on the associations between OC users and breast or ovarian cancer for ascertained BRCA1/2 carriers. We obtained summary risk estimated for ever OC users, for duration of use and time since stopping.

Results: A total of 2855 breast cancer cases and 1503 ovarian cancer cases, carrying an ascertained BRCA1/2 mutation, were included in our meta-analyses, based on overall 18 studies. Use of OC was associated with a significant reduced risk of ovarian cancer for BRCA1/2 carriers (summary relative risk (SRR) = 0.50; 95% confidence interval (CI), 0.33–0.75). We also observed a significant 36% risk reduction for each additional 10 years of OC use (SRR: 0.64; 95% CI, 0.53–0.78; P trend < 0.01). We found no evidence of a significant association between OC and breast cancer risk in carriers (SRR: 1.13; 95% CI, 0.88–1.45) and with duration of use. OC formulations used before 1975 were associated with a significant increased risk of breast cancer (SRR: 1.47; 95% 1.06, 2.04), but no evidence of a significant association was found with use of more recent formulations (SRR: 1.17; 95% 0.74, 1.86).

Conclusions: OC users carrying an ascertained BRCA1/2 mutation have a reduced risk of ovarian cancer, proportional to the duration of use. There is no evidence that recent OC formulations increase breast cancer risk in carriers.

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1. Background

There is clear evidence that germ line mutation in BRCA1 (MIM #113705) or BRCA2 (MIM #600185) account for a large proportion of familial breast/ovarian cancer and confer very high lifetime risks for both cancer sites.[1] Approximately 5–10% of all epithelial ovarian carcinomas result from genetic predisposition[2] and the great majority of these are associated with BRCA genes, as opposed to 25% of all hereditary breast cancers.[3,4] The lifetime risk of breast or ovarian cancer for women who inherited a BRCA mutation is highly variable and depends on the specific mutation, on the population studied and are extremely higher than the lifetime risk in the general population.[5–10] In addition, there is evidence that cancer patients with BRCA1 and BRCA2 mutation are characterised by different pathological and clinical features, some of which have prognostic value.[11] Some studies demonstrated that breast cancers in BRCA1 carriers more likely do not express oestrogen and progesterone receptors or Her-2/neu (triple-negative breast cancer), while breast cancers in BRCA2 carriers seem to share the same pathologic characteristics as non-carriers.[12] Moreover, oral contraceptives (OC) use was associated with an increased risk of cancer among triple-negative breast cancer, but not among non-triple-negative breast cancer.[13]

In the general population long-term exposure to oestrogen may increase a woman's chance of developing breast and ovarian cancer. The level of estrogens is associated with the repair capacity of breast and ovarian epithelial cells that may result in tumour formations, instead of apoptosis.[14,15] Oestrogen levels are high in ovulating women and any factor that limit the period of ovulation (pregnancy, late onset of menstruation or early onset of menopause) decreases the lifetime exposure to oestrogen and thus the risk for both types of cancer.

The measures for ovarian cancer prevention and early detection are limited as symptoms are frequently non-specific, patients are often diagnosed with advanced disease and family history of early-onset breast/ovarian cancer remains the single most important factor in determining individual ovarian cancer risk.[17–20]

Some studies suggest that non-genetic risk factors may differ in women with hereditary breast and ovarian cancer caused by alterations in the BRCA1/2 genes. Breast cancer typically occurs in these women at a much younger age, but the risk is not influenced by the age at menarche and it is also unclear whether the relationship between parity, age at menopause and breast cancer risk holds true in women who have BRCA mutations.[1,21]

OC use has been associated with a moderately increased breast cancer risk, which tends to decline progressively after termination of use and with a reduction in ovarian cancer risk for women unselected for predisposing genetic mutations.[22,23]

The use of OC for mutation carriers could be controversial because of the increasing breast cancer risk, especially early-onset, and the contemporary protective effects for ovarian cancer.

The present meta-analysis was conducted to examine and clarify whether exogenous hormone in the form of OC might modify the risk of breast or ovarian cancer in BRCA mutation carriers. Furthermore we investigated the association between specific mutation (BRCA1 or BRCA2) and OC use for breast or ovarian cancers.

2. Materials and methods

2.1. Search strategy, inclusion criteria and data abstraction

We conducted a literature search updated to March 2010 using validated search strategies[23–25] on the following databases: PUBMED, EMBASE, Ovid MEDLINE®, using combinations of the following MeSH terms and keywords: 'oral contraceptives', 'cancer', 'ovarian' or 'breast', 'BRCA1' or 'BRCA2'. We also identified the most cited articles on the topic using ISI Web of Knowledge® Science Citation Index Expanded™ (Journal Citation Report). In addition we reviewed the references of all articles of interest and preceding reviews on the topic to identify additional relevant studies. The search was limited to human studies and no language or time restrictions were applied.

2.2. Meta-analysis on the impact of OC use on cancer risk in mutation carriers

Our aim was to study the association between OC use and the risk of breast/ovarian cancer in women carrying a BRCA1/2 mutation.

Published reports fulfilling the following inclusion criteria were included in the meta-analysis:

(1) Studies containing the minimum information to obtain an estimate of the relative risk (RR), with its uncertainty, of:
   (a) breast and/or ovarian cancer associated with OC use in BRCA1/2 mutation carriers ascertained by a genetic test;
   (b) ascertained BRCA1/2 mutation, in association with OC use, in patients with breast and/or ovarian cancer.
(2) Case–control, cohort studies and nested case–control studies, published as original articles.
(3) Independent studies. In case of multiple reports on the same population or sub-population, we considered the estimates from the most recent or most informative report.
(4) Study populations that were as homogeneous as possible. We excluded study performed on subjects all submitted to a surgical procedure (bilateral salphingo-oophorectomy), which could have modified the association between OC and cancer risk for affected.
(5) Case–controls studies with controls not directly tested for the mutation were excluded by the analyses evaluating cancer risk in BRCA1/2 carriers.

The exposure of interest was ever OC use, defined as any duration of OC use lifetimes. In Tables 1 and 2 we detailed definitions of the exposures as reported originally by authors.

Table 1 – Features of the studies included in the meta-analysis on the impact of OC use on cancer risk in mutation carriers.

First author (publication year)	Study design	No. of carriers[a]	Mean age	Country	Adjustments/matching	Definition of exposure for *ever OC user*	Genes with a mutation	RR and 95% CI[b]
Breast cancer								
Narod (2002)[27]	CC	2622	47	Multicentre	Adj: ethnicity, parity Match: gene mutation, year birth, residence	Any duration of use	BRCA1 BRCA2 BRCA1 or 2	1.20 (1.02–1.40) 0.94 (0.72–1.24) 1.20 (1.02–1.52)
Heimdal (2002)[28]	CC	98	42	Norway	Adj: age	>3 months users	BRCA1 BRCA2 Both BRCA1 and 2	2.00 (0.36–10.9) na na
Haile (2006)[29]	CC	800	<50	Multicentre	Adj: age, study site, family history, no. of full term pregnancies	>1 year users	BRCA1 BRCA2 Both BRCA1 and 2	0.77 (0.53–1.12) 1.62 (0.90–2.92)
Gronwald (2006)[30]	CC	696	48	Multicentre	Match: age	Any duration of use	BRCA1 BRCA2 Both BRCA1 and 2	
Brohet (2007)[31]	Retrospective cohort	1593	41	Multicentre	Adj: family clustering, parity, history of oophorectomy	Any duration of use	BRCA1 BRCA2 Both BRCA1 and 2	1.47 (1.13–1.91) 1.49 (0.80–2.70) 1.47 (1.16–1.87)
Ovarian cancer								
Runnebaum (2001)[32]	CC	663	53	Multicentre		Any duration of use	BRCA1 BRCA2 Both BRCA1 or 2	
Whittemore (2004)[33]	CC	451	50	Multicentre	Adj: parity, age, study centre Match: gene mutation, year birth, residence	>1 year users	BRCA1 BRCA2 Both BRCA1 or 2	0.65 (0.41–1.03) 0.86 (0.89–1.16) 0.85 (0.53–1.40)
Gronwald (2006)[30]	CC	300	48	Multicentre	Match: age	Any duration of use	BRCA1 BRCA2 Both BRCA1 or 2	
McLaughlin (2007)[34]	CC	3223	53	Multicentre	Adj: parity, breast feeding, tubal ligation, ethnicity; Match: gene mutation, year birth, residence	Any duration of use	BRCA1 BRCA2 Both BRCA1 and 2	0.56 (0.45–0.71) 0.39 (0.23–0.66) 0.53 (0.43–0.66)
Antoniou (2009)[35]	Retrospective CO	3181	41	Multicentre	Adj: full-term pregnancy	Any duration of use	BRCA1 BRCA2 Both BRCA1 and 2	0.52 (0.37–0.73) 1.04 (0.42–2.54) 0.55 (0.40–0.76)

Abbreviations: na, not available; CC, case–control study; Cohort, cohort study; Hosp, hospital-based study; Pop, population-based study; Adj, adjustments of risk estimates for confounders; Match, variables considered for matching cases and controls. 'Ever users' included any duration of use.

[a]All studies included in the analysis tested both cases and controls for mutation.

[b] When adjusted estimates were not retrievable from the original articles we obtained unadjusted estimates from crude data.

Table 2 – Features of the studies included in the meta-analysis on association between of OC use and mutation status in cancer patients.

First author (publication year)	Study design	No. of carriers/ non-carriers	Mean age	Country	Adjustments/ matching	Definition of exposure for *ever OC user*	Genes with a mutation	RR and 95% CI
Breast cancer								
Ursin (1997)[36]	Retrospective case – case study	14/36	37	USA	Adj: age, family history education	More than a year	BRCA1 BRCA2 Both BRCA1 and 2	
Jernstrom (2005)[37]	CC	19/212	33	Sweden	Adj: age at menarche, smoking, family history and parity Match: age	Any duration of use lifetime	BRCA1 BRCA2 Both BRCA1 and 2	
Sade (2006)[38]	Retrospective case – case study	28/337	45	Israel	Adj: demographic, clinic and hormonal factors	Any duration of use	BRCA1 BRCA2 Both BRCA1 and 2	
Lee (2008)[39]	CC	94/1375	42	USA	Adj: family history, age at diagnosis, education, no. of pregnancies, race Match: age, race and neighbourhood	Any duration of use	BRCA1 BRCA2 Both BRCA1 and 2	na na 0.68 (0.33–1.38)
Atchley (2008)[12]	Retrospective cohort	86/391	42	USA		Any duration of use	BRCA1 BRCA2 Both BRCA1 and 2	
Ovarian cancer								
Modan (2001)[40]	CC	240/592	60	Israel	Match: age, area, residence in Israel	Any duration of use	BRCA1 BRCA2 Both BRCA1 and 2	
Modugno (2003)[41]	Pooled data	95/147	54	Multicentre		Any duration of use	BRCA1 BRCA2 Both BRCA1 and 2	
McGuire (2004)[19]	CC	36/568		USA	Adj: age, pregnancy and race Match: age and race	More than a year	BRCA1 BRCA2 Both BRCA1 and 2	

Abbreviations: na, not available; CC, case–control study; Cohort, cohort study; Hosp, hospital-based study; Pop, population-based study; Adj, adjustments of risk estimates for confounders; Match, variables considered for matching cases and controls.

Presence of heterogeneous exposures was investigated in a sensitivity analysis. We also explored duration of OC use, time since last use and age at start use.

When available we used fully adjusted estimates. Articles were reviewed and data were extracted and crosschecked independently by two investigators (S.I. and S.G). Any disagreement was resolved by consensus among them.

The following information were extracted and coded from the original articles: adjusted risk estimates or crude data, year of publication, type of study, country of the study, features of populations, definition of the exposure, cancer site, mutation status, adjustments and matching variables used in the analysis and study design. When dose–response estimates on duration of OC use and time since last OC use were provided, we retrieved the study-specific dose response risk estimates and frequencies for each level of exposure.

Results from unpublished data obtained in our Institute were also added in the meta-analysis and evaluated in a sensitivity analysis.

2.3. *Association between BRCA1/2 carrier status and OC use for breast or ovarian cancer patients*

We also studied the magnitude of the association between BRCA1/2 mutation and OC use in patients with breast/ovarian cancer in a case–case approach.

3. Statistical methods

When available, we retained estimates adjusted for the maximum number of confounders.

We always presented random effects models to evaluate summary relative risk (SRRs) obtained with maximum likelihood estimates, in order to be more conservative.[42] Homogeneity of effects across studies was assessed using the Chi-square statistic (which we considered statistically significant when the *P*-value was $\leqslant 0.10$)[43] and quantified by I^2, which represents the percentage of total variation across studies that is attributable to heterogeneity rather than chance.[44] When more than a single risk estimate was present in a study (i.e.

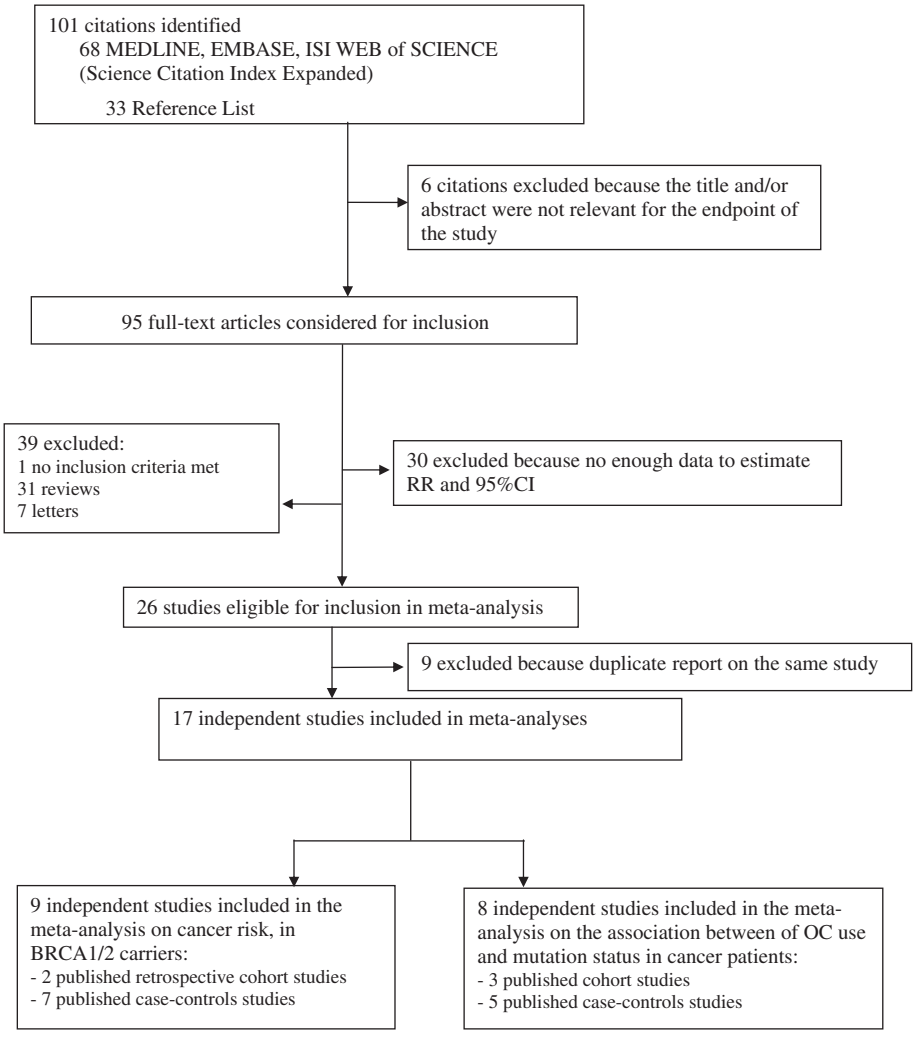


Fig. 1 – Flow chart of selection of studies.

separate estimates for BRCA1 and BRCA2), we adjusted the pooled estimates for intra-study variation. When possible we performed separate analyses for type of mutation by using a bivariate approach. Sub-group and meta-regression analyses were carried out to investigate potential sources of between-study heterogeneity.[45] Many studies reported estimates for first use of OC in or after 1975, when dose of oestrogen in OC formulation was reduced substantially. We performed meta-regression by year at start OC, assuming that women who started their OC after 1975 have used low-dose OC.

In the dose–response analysis, we considered duration of OC use and time since last use as explanatory variables. In pooling dose–response data, we took into account correlation between RRs categories within the same study, using Greenland and Longnecker method.[46]

We also studied the magnitude of the association between BRCA1/2 mutation and OC use in patients with breast/ovarian cancer with a case–case comparison. Following this approach, cancer patients with the mutation formed the 'pseudo-cases' and patients without the genotype formed the 'pseudo-controls' group. The two groups were then compared with respect to the prevalence of each exposure. The SRRs obtained reflects the association between the exposure (OC use) and the genotype (BRCA1/2 mutation), assuming the independence of genotype and exposure in the source population.

Sensitivity analysis was carried out in order to evaluate whether overall results were influenced by a single or a group of studies.[47] Publication bias was evaluated by funnel plots and quantified by the Egger's test.[48,49] All analyses were performed with SAS Software using PROC MIXED (SAS, 8.02 for Windows, Cary, NC).[50]

4. Results

Details on the search strategy and the data extrapolation are described in Fig. 1. The main characteristics of the studies included in the analyses are shown in Table 1.

4.1. OC-associated breast cancer risk

The analysis was based on five studies (2855 breast cancer cases, 2954 healthy carriers). Breast cancer risk estimates for various categories of OC use are described in Table 3.

For BRCA1/2 carriers, we found that breast cancer risk was not significantly increased by OC use (SRR = 1.13; 95% confidence interval (CI): 0.88–1.45). Similarly, no significant association was found when we limited the analysis to BRCA1 or BRCA2 carriers (Fig. 2 left).

There was no evidence of a dose–response relationship with duration of OC use ($P = 0.20$).

The association between time since stopping OC use and breast cancer was assessed basing on three studies and overall 2109 cases. Compared to never users, BRCA1/2 carriers who stopped OC at least 10 years before diagnosis were at significant increased risk of breast cancer (SRR = 1.46; 95% CI, 1.07–2.07). By contrast, no significant association was observed

Table 3 – Summary risk estimates of the association between OC use and cancer risk in mutation carriers.

Exposure	Genes with mutation	Categories of exposure[a]	No. of studies	No. of cases [b]	SRR (95% CI)[c]	P-value[d]
Breast cancer						
OC users	BRCA1/2	Ever users	5	2855	1.13 (0.88, 1.45)	
	BRCA1	Ever users	5	2148	1.09 (0.77, 1.54)	0.70
	BRCA2		3	707	1.15 (0.61, 2.18)	
Duration of use	BRCA1/2	1 year	4	2828	1.01 (0.99, 1.03)	0.20[e]
		5 years			1.06 (0.95, 1.18)	
		10 years			1.13 (0.91, 1.40)	
Time since stopping	BRCA1/2	< 10 years	3	2109	1.14 (0.83, 1.56)	0.03
		>10 years	3		1.46 (1.07, 2.07)	
Year at start	BRCA1/2	Before 1975	3	2160	1.47 (1.06, 2.04)	0.07
		After 1975			1.17 (0.74, 1.86)	
Age at start	BRCA1/2	<20 years	3	2229	1.28 (0.91, 1.79)	0.53
		>20 years			1.24 (0.80, 1.90)	
Ovarian cancer						
OC users	BRCA1/2	Ever users	5	1503	0.50 (0.33, 0.75)	
	BRCA1	Ever users	5	1251	0.51 (0.40, 0.65)	0.88
	BRCA2		4	286	0.52 (0.31, 0.87)	
Duration of use	BRCA1/2	1 year	4	1336	0.96 (0.94, 0.97)	<0.01[e]
		5 years			0.80 (0.73, 0.88)	
		10 years			0.64 (0.53, 0.78)	

Abbreviations: SRR, summary relative risk; CI, confidence intervals; OC, oral contraceptives.

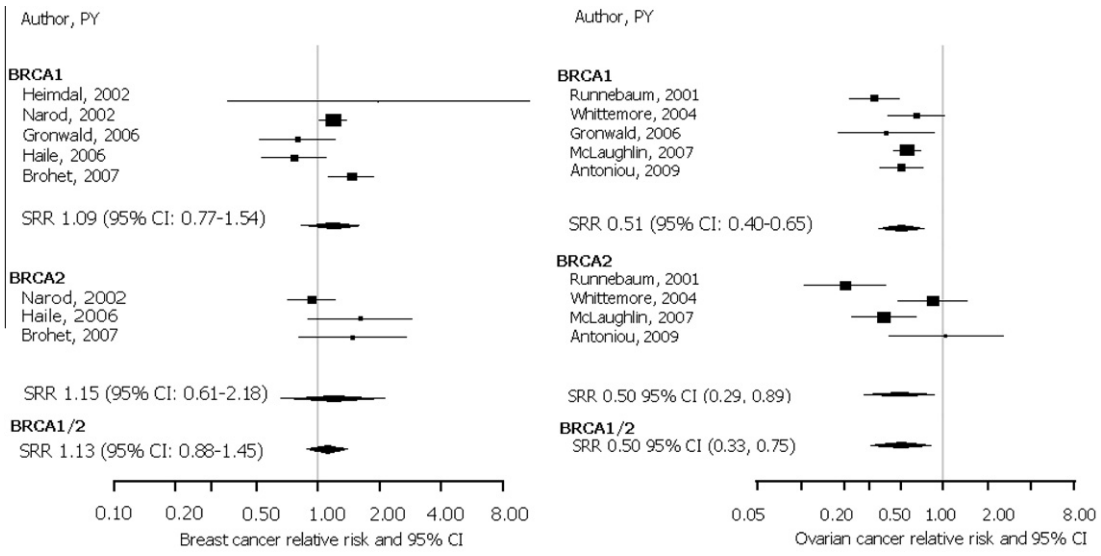
[a] 'Ever users' defined as OC users for any duration lifetime.

[b] When the number of cases was not available for subgroups, we reported the overall amount.

[c] Reference category never OC users.

[d] P-values test homogeneity between strata.

[e] P-values test the linear trend associated with increments of 1-year exposure.



Forest plot and summary relative risk on the association between OC use and breast cancer (left) and ovarian cancer (right) in carriers.

PY: publication year; SRR: Summary Relative Risk; CI confidence intervals

Fig. 2 – Association between oral contraceptives (OC) use and breast or ovarian cancer in BRCA1/2 carriers.

for women who stopped OC use within the last 10 years. Difference between the two estimates was statistically significant ($P = 0.03$).

We also found that OC formulations used before 1975 were associated with increased risk of breast cancer (SRR = 1.47; 95% CI, 1.06–2.04). On the contrary no evidence of an association was found with use of recent formulations (SRR = 1.17; 95% CI, 0.74–1.86).

4.2. *OC-associated ovarian cancer risk*

Overall the meta-analysis was based on five studies (1503 ovarian cancer cases, 6315 healthy carriers).

In Table 3, we present risk estimates for ovarian cancer associated with different exposures to OC. We found a significant protective association between OC use and the risk of ovarian cancer (SRR = 0.50; 95% CI, 0.33–0.75).

When we performed separate analyses by type of mutation, OC use was associated with a significant reduced risk of cancer for both BRCA1 (SRR = 0.51; 95% CI, 0.40–0.65) and BRCA2 mutations carriers (SRR = 0.50; 95% CI, 0.29–0.89) (Fig. 2 right).

We found a significant linear decrease in risk for carriers with increasing duration of OC use: each additional 10 years of OC use the risk decreased by 36% (95% CI, 22–47%, $P < 0.01$ for trend).

5. Sensitivity analysis, meta-regression and publication bias

In this meta-analysis, the term 'ever OC use' was referred to any use of OC reported during lifetime. This is a general definition, which includes all meanings considered by the authors: Haile[29] included in that definition OC users for at least 1 month, Heimdal[28] for at least 3 months, while Whittemore[33] evaluated OC users for at least 1 year. The influence of these different definitions of exposure was evaluated in sensitivity analyses with no substantial differences for breast/ovarian cancers risk.

Among the studies included in the analysis on breast cancer, one study[27] has a very large weight. Similarly, McLaughlin[34] could drive the analysis on ovarian cancer and it is also the only study with no histological confirmation of cancer diagnosis. Testing whether the exclusion of these studies may have potentially biased the estimates, we did not observe any change in the overall results.

In order to prevent from inclusion of prevalent cases, two studies[31,34] reported separate estimates limiting the cohort to subjects with a diagnosis within 5 and 3 years since diagnosis, respectively, in order to prevent from survival bias. We investigated the possible effect of inclusion of prevalent cases performing the analysis including the estimates form the cohorts restricted to incidence cases, where the survival bias is likely to be smaller, without marked change in breast (SRR = 1.10; 95% CI: 0.93–1.29) or ovarian cancer estimates (SRR = 0.49; 95% CI: 0.32–0.75).

The core of our meta-analysis included case–controls, both hospital and population based, and cohort studies. However, we performed in a sensitivity analysis a separate analysis for case–controls and cohort studies, without any difference in the estimates. Our main analysis on the effect of OC on cancer for mutation carriers comprised only one cohort[31] for breast cancer. Excluding the latter from the analysis the summary estimate remains similar (SRR = 1.04; 95% CI: 0.79–1.38).

Some studies included patients who had undergone salphingo-oophorectomy. Most of them presented estimates adjusted for this effect or used it as a matching variable. We performed separate analysis for studies taking into account this risk modifier, with lower estimates for studies taking into

account this factor, but no differences in the estimates for both breast and ovarian cancer ($P = 0.19$ and $P = 0.19$; respectively).

No indication of publication bias was found when assessing OC effect on both cancer sites: *P*-values from weighted Egger's test for funnel plot were 0.90 for breast cancer and 0.73 for ovarian cancer.

Since our analysis includes studies based on familial cancer cases, we evaluated in breast cancer analyses whether there was any difference between estimates adjusted or not for family history. No difference was found between them through meta-regression ($P = 0.41$). The estimates used for ovarian cancer analysis were not adjusted for this factor.

6. Association between OC use and mutation status in cancer patients

Features of the studies included in the analysis are detailed in Table 2. We evaluated estimates from case–case approaches to study whether mutation carriers were more likely than non-carriers to use OC.

The estimates were based on a total of 241 breast cancer cases and 371 ovarian cancer cases with a BRCA1/2 mutation. We found no significant associations between BRCA1/2 mutation status and use of OC for breast/ovarian cancer, even separately investigating the cancer sites and mutations (Fig. 3).

7. Discussion

Our meta-analysis was based on 2855 breast and 1503 ovarian cancer cases with a BRCA1/2 mutation. We found no evidence of a significant increased breast cancer risk in OC users overall, for recent formulation of OC and in the first 10 years after cessation.

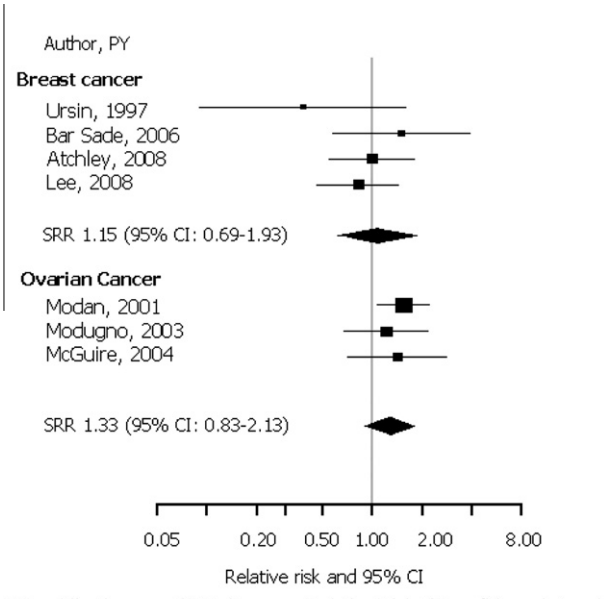


Fig. 3 – Association between BRCA1 and BRCA2 combined carrier status and oral contraceptives (OC) use in cancer patients.

Our outcomes differ from results obtained in a previous pooled-analysis, based on 54 studies. The authors investigated the association between OC use and breast cancer risk in the general population, showing a significant association between OC use and breast cancer. However, the estimate in this pooled analysis was slightly above the unit (RR = 1.07; SD = 0.02)[22] and the risk progressively declines, disappearing during the 5 years after stopping. Our study on mutation carriers was based on ever OC users, and it suggests evidence of an increased risk of breast cancer of 46% only for women who ceased OC use more than 10 years before diagnosis. This increasing risk could be explained by the effect of age as women who ceased in more distant time are supposed to be older than recent quitters. To some extent these results could also be explained by differences in OC formulations: most women who stopped OC use 10 or more years before diagnosis tend to have used higher dose preparation. In fact, in our analyses OC formulations used before 1975 (when drugs were likely to contain high doses of hormones) were associated with a 46% increased risk of breast cancer, on the contrary no association was found with use of recent formulations.

We also confirmed that carriers who use OC are at a significant reduced risk of ovarian cancer. The reduction is associated with ovarian cancer in a dose–response relationship: risk is greater the longer women used OC.

The reduction in ovarian cancer risk of 50% for BRCA1/2 carriers ever OC users was consistent with, and higher than, the reduction observed in the general population: in a pooled meta-analysis, based on 45 epidemiological studies, the reduction observed for ever OC users was 27%. Similarly, in our results the overall risk decreased by a 20% for mutation carriers for each five years of use, consistent with the 20% reduction observed in the general population.[23]

We carried out a separate analysis by type of mutation, based on the rationale that cancer patients with BRCA1 and BRCA2 mutation are characterised by different cancer subtypes in terms of oestrogen, progesterone or Herb2 status. In fact we could suppose that the risk for triple negative breast cancer, which is more frequent in BRCA1, due to hormonal risk factors, such as OC use, could be higher.[12,13] However, we did not find significant differences between BRCA1 and BRCA2 mutation carriers.

We also conducted a separate meta-analysis to determine whether OC use differs in breast/ovarian cancer cases with or without a mutation. Oral contraceptive use was not significantly more common for carriers compared with cases without any mutation.

Relative risk estimates of case–case approach are based on the assumption of independence between presence of a mutation and OC. This seems to be reasonable in all studies we included in the analyses, even if there may be a possibility of a violation of this assumption. If there were a positive association between genotype and exposure in the underline population, this could lead to some bias in the estimates, when compared to the ratio of the relative risk that the authors are attempting to estimate. Only analyses on case–controls and cohort studies would address this limitation. Therefore, we based our conclusions mainly on the latter results.

Studies included in the analyses are based on different study designs and analyses, different types of mutations

and baseline cancer risk. We investigated how these aspects could have influenced the estimates through subgroup analyses and meta-regressions.

The studies that formed the basis of our meta-analysis included case–controls, both hospital and population based, and cohort studies. We found no difference in the estimates obtained from separate analyses on case–controls and cohort studies.

Some studies included patients who had undergone salphingo-oophorectomy, a cancer prevention strategy that could have an impact on the magnitude of the protection afforded by oral contraceptives use. Most of these studies presented adjusted estimates for this effect or used it as a matching variable. We evaluated whether this could have overestimated the protective association, performing separate analysis for studies taking into account this risk modifier, with no differences in the estimates for both cancer sites.

One possible source of bias is that the studies we included in the analyses reported different definitions of exposure. In fact, the majority of the authors defined ever OC users as women with any duration of use. We investigated differences in the estimates by types of definitions reported by the authors and we found no substantial variations.

Another possible limitation of the present analysis could arise from the inclusion of prevalent cases which may result in survival bias. If OC use is associated with a higher mortality in women with breast or ovarian cancer, the selection of prevalence cases might operate to reduce the risk. However, the investigation of heterogeneity and sensitivity analyses did not show any substantial effect of this factor, suggesting that survival bias was limited.

Most of the published evidence related to BRCA1/2 was based on large families with many individuals affected by breast/ovarian cancer. Because family members share heritable and probably environmental factors, it is possible that an amount of cancer cases diagnosed in these families may be partly due to other genetic or environmental factors.

Moreover, the inclusion of studies conducted on members of families with multiple cases of cancer may bias the risk estimates as oral contraceptives use in these carriers may not pertain to the general population of carriers. However, the study with the highest weight, used for breast cancer analysis,[27] selected participants from previous trials and research protocols; therefore, cohort selection from clinical genetic centres should not be the main issue of this analysis.

There has been a change in the formulation of OC over the past several decades. In the recent formulations there is a substantial reduction in the oestrogen content. Typical oestrogen doses in the 1960s were more than double the typical doses in the 1980s and later, so that recent formulations may be considered less hazardous than the older. Calendar year (before or after 1975) is used in many studies as an indicator of the average oestrogen dose of the preparations. We found that OC formulations used before 1975 were associated with increased risk of breast cancer. On the contrary no association was found with use of recent formulations.

This is the first meta-analysis addressing breast or ovarian cancer risk for OC users for BRCA1/2 carriers. The study involved overall 5809 and 7818 mutation carriers in the analysis on breast and ovarian cancer, respectively. The main strength of our meta-analysis is the large number of cases included, with a known mutation in one of the BRCA1 or BRCA2 genes, and the possibility to investigate the association with duration of use, age at start, time since quitting and calendar time.

Even if the ideal would be to present all the estimates of risk by types of mutation, we could not carry out all our analyses by BRCA status because many authors presented only estimates for BRCA carriers combined, presumably due to limited statistical power.

Another possible limitation of this meta-analysis is the lack of published prospective studies. In fact all but two retrospective cohort studies were case–controls, and even if we try to investigate the effect of study design, we were not able to completely address the issue of potential presence of recall bias. However, in the pooled analysis on observational studies, there was no difference in the association of OC use with breast cancer between prospective cohort studies and case–controls studies.

Our investigation of the potential effect of different study designs and adjusting factors did not show any impact on the summary estimates, however, possible sources of unexplained bias could remain and influence our results.

Our meta-analysis provides evidence that OC reduces ovarian cancer risk and no evidence that recent formulation of OC increases breast cancer risk for women with a germ line mutation in BRCA1 or BRCA2.

Further prospective studies on carriers may have to confirm our results and could also evaluate the additive effect of post-hormone use or types of OC that we could not deeply investigate in this setting.

Conflict of interest statement

None declared.

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