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Contraceptives and cancer risks in *BRCA1/2* pathogenic variant carriers: a systematic review and meta-analysis

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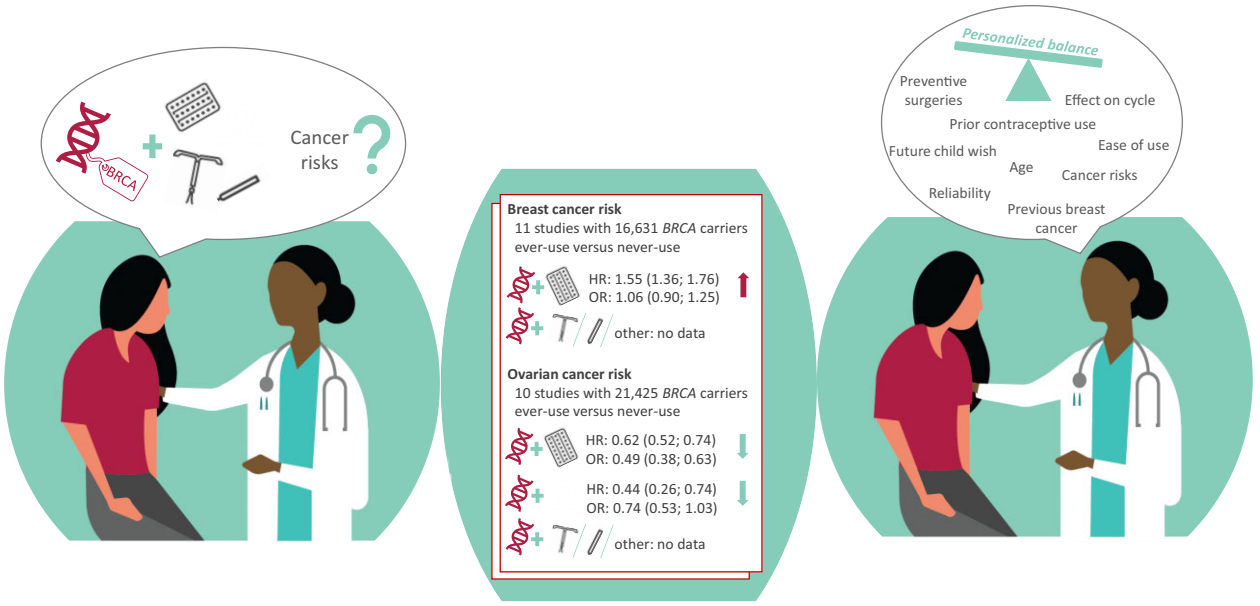
GRAPHICAL ABSTRACT



Contraceptives and cancer risks in *BRCA1/2* pathogenic variant carriers: a systematic review and meta-analysis.

BACKGROUND: Increasing numbers of BReast CAncer (*BRCA*) 1 or 2 pathogenic variant (PV) carriers, who have an inherited predisposition to breast and ovarian cancer, are being identified. Among these women, data regarding the effects of contraception on cancer risks are unclear and various guidelines provide various recommendations.

OBJECTIVE AND RATIONALE: We aim to optimize counselling regarding contraception for *BRCA1/2*-PV carriers. Therefore, we performed a systematic review and meta-analysis. We investigated the risk ratio for developing breast cancer or ovarian cancer in *BRCA1/2*-PV carriers who have used any form of contraception versus non-users. Second, we analysed breast and ovarian cancer risk among *BRCA1/2*-PV carriers as influenced by the duration of contraceptive use and by the time since last use. In addition, we provide an overview of all relevant international guidelines regarding contraceptive use for *BRCA1/2*-PV carriers.

SEARCH METHODS: A systematic search in the Medline database and Cochrane library identified studies describing breast and/or ovarian cancer risk in *BRCA1/2*-PV carriers as modified by contraception until June 2021. The search included medical subject headings, keywords and synonyms related to *BRCA* and contraceptives (any kind). PRISMA guidance was followed. Risk Of Bias In Non-randomized Studies of Interventions and Grading of Recommendations, Assessment, Development and Evaluations assessments were performed. Random-effects meta-analyses were used to estimate pooled effects for breast and ovarian cancer risk separately. Subgroup analyses were conducted for *BRCA1* versus *BRCA2* and for the various contraceptive methods.

OUTCOMES: Results of the breast cancer risk with oral contraceptive pill (OCP) analysis depended on the outcome measure. Meta-analyses of seven studies with 7525 women revealed a hazard ratio (HR) of 1.55 (95% CI: 1.36–1.76) and of four studies including 9106 women resulted in an odds ratio (OR) of 1.06 (95% CI: 0.90–1.25), heterogeneity (I^2) 0% and 52%, respectively. Breast cancer risk was still increased in ever-users compared with never-users >10 years after last OCP use. In contrast, ovarian cancer risk was decreased among OCP users: HR 0.62 (95% CI: 0.52–0.74) based on two studies including 10 981 women (I^2: 0%), and OR 0.49 (95% CI: 0.38–0.63) based on eight studies including 10 390 women (I^2: 64%). The protective effect vanished after cessation of use. Tubal ligation also protects against ovarian cancer: one study including 3319 women (I^2: 0%): HR: 0.44 (95% CI: 0.26–0.74) and three studies with 7691 women (I^2: 44%): OR: 0.74 (95% CI: 0.53–1.03). Data regarding other contraceptives were unavailable. No differences were observed between *BRCA1* and *BRCA2*-PV carriers. The quality of evidence was either low or very low.

WIDER IMPLICATIONS: The OCP potentially increases breast cancer risk, while ovarian cancer risk decreases with either the OCP and tubal ligation in *BRCA1/2*-PV carriers. Counselling of *BRCA1/2*-PV carriers should be personalized; the genetic and non-genetic factors (like prior risk-reducing surgeries, prior breast cancer and age) and patients' preferences (reversibility, ease of use, reliability and effect

on menstrual cycle) should be balanced. To further optimize counselling for high-risk women, future research should focus on other (commonly used) contraceptive methods and cancer risks in this specific population, and on the potential impact of changing formulations over time.

Key words: ovarian cancer / breast cancer / *BRCA1* gene / *BRCA2* gene / contraception / oral contraceptive pill / tubal ligation

Introduction

Female BReast CAncer (*BRCA*) *1* or *BRCA2* pathogenic variant (*BRCA1/2*-PV) carriers have an increased risk of breast and ovarian cancer, estimated to be ~70% for breast cancer and 44% and 17% for ovarian cancer, respectively, by the age of 80 years (Kuchenbaecker *et al.*, 2017). To manage these risks, timely risk-reducing salpingo-oophorectomy and either annual screening of the breasts or a risk-reducing mastectomy are recommended (IntegraalKankercentrumNederland, 2017).

Besides genetic risk factors, multiple other factors, both endogenous and exogenous, have been shown to modify cancer risks. The use of contraceptives is one of the most well-known factors. In the general population, the use of the oral contraceptive pill (OCP), which is the most frequently used hormonal contraceptive (Central Bureau for Statistics, 2013), and its effect on cancer risks are well established. While breast cancer risk is increased by OCP use (relative risk (RR): 1.20 (95% CI: 1.14–1.26)), the ovarian cancer risk decreases (odds ratio (OR): 0.73 (95% CI: 0.66–0.81)) (Havrilesky *et al.*, 2013; Mørch *et al.*, 2017). The impact of OCP on breast cancer risk depends on the duration of use and the types of hormones used (Mørch *et al.*, 2017). A similar effect was observed for the levonorgestrel-releasing intra-uterine device (LR-IUD), an increasingly popular type of hormonal contraception (Central Bureau for Statistics, 2013); in a meta-analysis, breast cancer risk was found to be higher (OR: 1.12 (95% CI: 1.02–1.22)) among LR-IUD users (Conz *et al.*, 2020), while ovarian cancer risk decreased (OR: 0.58 (95% CI: 0.47–0.71)) compared to non-users (Balayla *et al.*, 2021). Sterilization is the most frequently applied non-hormonal contraceptive method (Dietl *et al.*, 2011). Female sterilization was found to reduce ovarian cancer risk: salpingectomy reduced the risk by 42–65% (Falconer *et al.*, 2015; Madsen *et al.*, 2015; van Lieshout *et al.*, 2021), while fallopian tube occlusion resulted in a hazard ratio (HR) of 0.72 (95% CI: 0.64–0.81) relative to the ovarian cancer risk of people who had not undergone this procedure (Falconer *et al.*, 2015).

To adequately counsel *BRCA1/2*-PV carriers, data regarding the association between various contraceptives and cancer risks in these women as a population are needed. This is particularly important due to the increasing numbers of *BRCA1/2*-PV families being identified because of universal genetic tumour testing in ovarian cancer patients (Vos *et al.*, 2020). As a result, family members may discover their inherited risks at younger age, potentially increasing the need for contraceptive advice earlier in life.

Due to the lack of sufficient and uniform data, most guidelines advise (individualized) counselling about cancer risks when discussing contraception with *BRCA1/2*-PV carriers; however, different guidelines provide various recommendations. The discrepancies between the guidelines and the contradictory effects of contraceptives on cancer risks highlight the need for a re-evaluation of the current literature. Here, we aim to investigate the influence of contraceptives on breast and ovarian cancer risk in *BRCA1/2*-PV carriers, and to providing an overview of all relevant guidelines. In this manuscript, we use the term 'ovarian cancer', which covers malignancies of the fallopian tubes, ovaries and peritoneum, which are, today, considered to be one entity.

Methods

Search strategy and selection criteria

The Medline database and the Cochrane Library were systematically searched in consultation with a medical librarian. The search included medical subject headings, keywords and synonyms related to *BRCA* and contraceptives (any kind). There were no restrictions on article type, publication date or any other characteristic. Any study published before 23 June 2021 was included in the search. Studies reporting on contraception in *BRCA1/2*-PV carriers and their association with cancer risk(s) were considered eligible for inclusion. Studies were excluded when the study population did not include *BRCA1/2*-PV carriers, when the outcome measures did not include cancer risks, when the full text was unavailable in English or Dutch or when the study did not include primary data (e.g. reviews, meta-analysis, opinion letters, letters to editors). Additionally, we manually reviewed references and citation lists for all reviews and meta-analyses to check whether all relevant studies were included. After deduplication, all studies meeting the search criteria were screened by two independent researchers (M.H.D.v.B. and G.V.) using the title and abstract, and, afterwards, based on the full text using Covidence®. Discrepancies of opinion regarding the potential relevance of a study were resolved by discussion or by consultation of a third reviewer (M.G.H.). The full search strategy is provided in Supplementary Data File S1.

In addition to the systematic review, we searched for relevant guidelines regarding contraceptive use among *BRCA1/2*-PV carriers. We consulted all national societies of obstetricians and gynaecologists listed on the website of the International Federation of Gynaecology and Obstetrics (FIGO) (1954) (https://www.figo.org/figos-member-societies). Societies were included if their country of origin was marked as a 'developed economy', as defined by the United Nations, in order to ensure homogeneity across the healthcare systems (UnitedNations, 2020). The websites of the included societies were searched for guidelines on 'contraception' or '*BRCA*' or 'genetic/familial/hereditary predisposition for ovarian cancer'. Guidelines were included if written in English or Dutch and if information was provided regarding contraception use by *BRCA1/2*-PV carriers. If a guideline was not found, we searched for corresponding statements embedded in other guidelines published by the respective society.

Risk of bias and quality assessment

A risk of bias assessment was conducted to score the eligible studies on methodological quality using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) questionnaire (Sterne et al., 2016). Studies were evaluated as having a 'low', 'moderate', 'serious', 'critical' or 'unclear' risk of bias based on seven domains: confounding, selection of participants, classification of intervention, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. To evaluate the quality of evidence per outcome measure, we used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework (Guyatt et al., 2008).

Data extraction

Data extraction was executed using a data-extraction form consisting of predefined topics: bibliographical data, population characteristics, methodology and study outcomes. Data extraction was performed by M.H.D.v.B. and cross-checked by G.V. In cases where the data were incompletely described in an article, we contacted the corresponding author to request the data. In cases with more than one cohort described in a study (Schrijver et al., 2018, 2021), we either included the full cohort in this meta-analysis (Schrijver et al., 2021) to be as consistent as possible with the other studies, or we included the prospective cohort when the data could not be extracted for each cohort separately (Schrijver et al., 2018).

Outcomes and statistical analysis

The primary aim was to estimate the risk ratio for developing breast cancer or ovarian cancer in *BRCA1/2*-PV carriers who have used any form of contraception versus *BRCA1/2*-PV carriers who have not. Our secondary analyses aimed to investigate the breast and ovarian cancer risks among *BRCA1/2*-PV carriers as influenced by the duration of contraceptive use and by the time since last use.

Random-effects meta-analyses were conducted to estimate the pooled effects: for the risk of developing breast cancer and for the risk of developing ovarian cancer. Data on cancer risk after hysterectomy or bilateral salpingo-oophorectomy were excluded from the meta-analysis as these surgeries are not primarily indicated for contraception. Meta-analyses were performed per outcome measure, meaning separately for ORs and HRs. Whereas a HR takes account of time (the hazard presents an instant risk during a period), an OR does not (the odds represent the cumulative risk until a defined endpoint), meaning those measures cannot usually be analysed collectively. Heterogeneity across studies was evaluated using the I^2 statistic (<25%: low, 25–75%: moderate, >75%: high), the τ^2 (Higgins et al., 2003), and the prediction interval (IntHout et al., 2016). Subgroup analyses for *BRCA1* versus *BRCA2* and for various contraceptive methods were conducted. To evaluate the potential effect of changing OCP formulations over time on cancer risks, we performed additional analyses with studies published in the last 10 years versus studies published more than 10 years ago because we expected OCP formulations to be insufficiently specified in the individual studies. The secondary objectives 'duration of use' and 'time since last use' were analysed using a meta-analysis when at least two studies had data available (like the primary outcomes) and when the studies had similarly defined their time periods. If both criteria were not met, these outcome measures were instead analysed descriptively. All analyses were performed in the statistical software R version 3.6.2 using the package 'meta' (version 4.18-0) (R, 2021). The meta-analysis used the inverse variance method, the restricted maximum-likelihood estimator for τ^2 and the Q-profile method for the CI of τ^2.

Results

Study selection

Our search yielded 447 potentially relevant studies, of which 327 were excluded based on the title and abstract and another 100 were excluded after reading the full text. Consequently, 20 studies met the eligibility criteria (Moher et al., 2009) (Fig. 1 and Table I). Of these, 10 investigated breast cancer risk, 9 evaluated ovarian cancer risk and 1 evaluated both breast and ovarian cancer risk. In total, 11 studies were included in the meta-analysis of breast cancer risk (Heimdal et al., 2002; Narod et al., 2002; Gronwald et al., 2006; Haile et al., 2006; Brohet et al., 2007; Bernholtz et al., 2011; Kotsopoulos et al., 2014; Rieder et al., 2016; Park et al., 2017; Toss et al., 2017; Schrijver et al., 2018) and 10 studies were included in the analysis of ovarian cancer risk (Narod et al., 1998, 2001; Whittemore et al., 2004; Gronwald et al., 2006; Antoniou et al., 2009; Vicus et al., 2010a; Ferris et al., 2014; Kotsopoulos et al., 2015; Perri et al., 2015; Schrijver et al., 2021), as modified by contraceptive use.

Study characteristics

The study characteristics of the 20 included studies are presented in Table I. In total, 38 056 *BRCA1/2*-PV carriers were included: 16 631 in the breast cancer risk analysis and 21 425 for analysing ovarian cancer risk. Most studies included both *BRCA1*-PV and *BRCA2*-PV carriers, the ages of whom ranged from 18 to 93 years. All studies investigated OCP, with four also evaluating tubal ligation (TL); no other methods of contraception were described. The main study designs were case–control (11 studies) and cohort (8 studies) studies, although one study used a case-only design (Bernholtz et al., 2011). The studies ended the follow-up at the time of the interview, a cancer diagnosis or risk-reducing surgery. Eleven studies had an international focus. The studies were predominantly conducted in the USA or Europe. Crude numbers per study are provided in the Supplementary Data File S2.

Risk of bias and quality of evidence

The risk of bias, according to the ROBINS-I questionnaire, was considered moderate in 15 studies, serious in 4 studies and unclear in 1 study (Table I and Supplementary Data File S3). According to the GRADE framework, the quality of evidence had an a priori ranking of 'low' for all outcomes because no randomized designs were included in our analyses. The final quality of evidence was 'low' for both the OCP-influenced breast and ovarian cancer risk with studies that used a HR. All other outcomes resulted in a final ranking of 'very low'. The rankings and reasons for downgrading are provided in Table II.

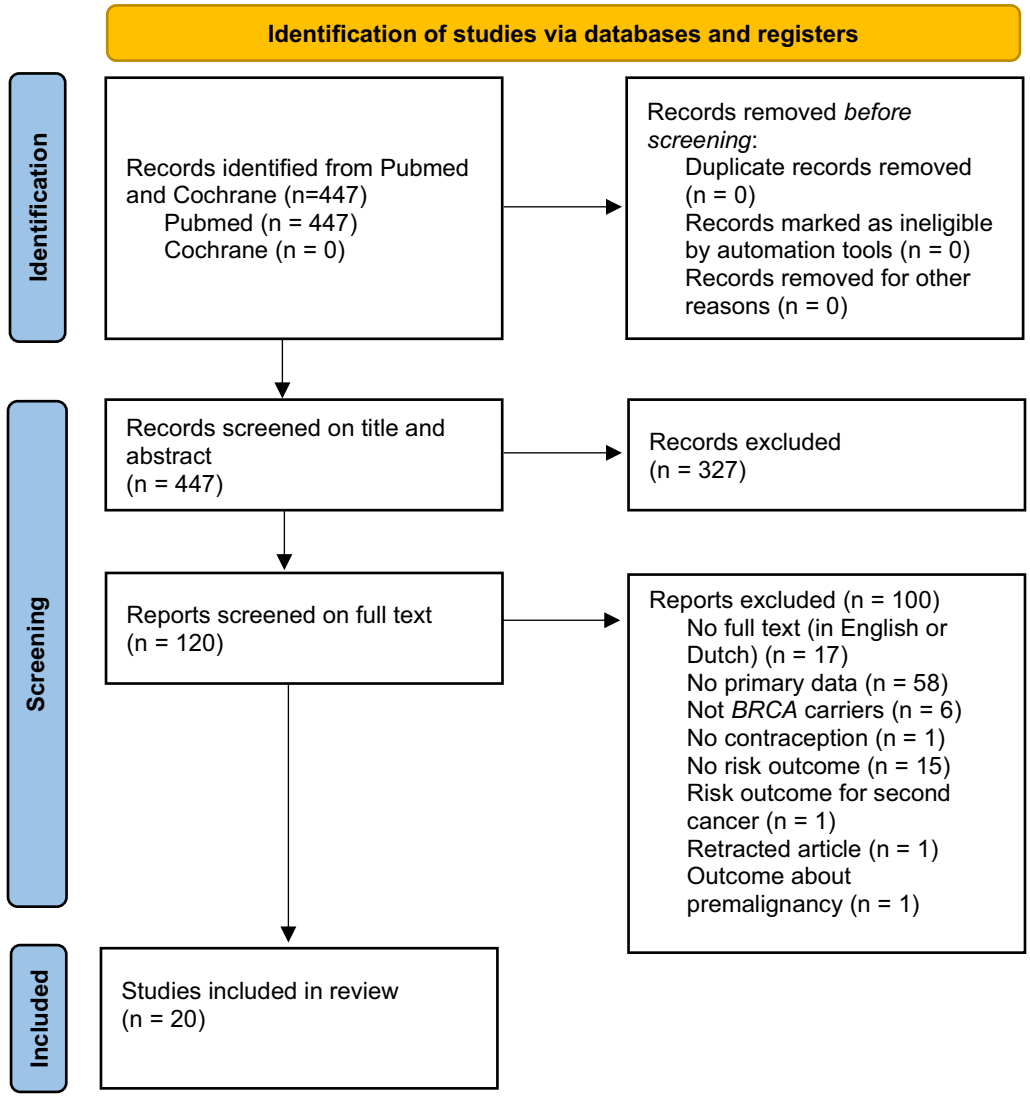


Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart of study selection.

Impact of contraceptives on breast cancer risk

Data on breast cancer risk were only available for OCP (Table I). Based on the studies that reported a HR for breast cancer risk (n = 7), the risk after using OCP was significantly increased (HR: 1.55; 95% CI: 1.36–1.76) relative to the reference group (never or a maximum of 6 months of OCP use; Table I). For the studies that reported an OR (n = 4), the pooled estimated breast cancer risk was an OR of 1.06 (95% CI: 0.90–1.25) in OCP users compared with the reference group (never or a maximum of 1 year of OCP use; Table I) (Fig. 2). Low to moderate heterogeneity was detected between studies (I^2: 0% and 52% for studies reporting HR and OR, respectively). Subgroup analyses for *BRCA1*-PV versus *BRCA2*-PV carriers revealed no significant differences in the effect of OCP on their breast cancer risks (test for subgroup differences $P = 0.54$ (studies with HR) and $P = 0.70$ (studies with OR); Supplementary Fig. S1 shows the forest plots). When analysing studies published >10 years ago versus <10 years ago, with the aim of analysing older versus more modern OCP formulations, we identified similar HRs ($P = 0.74$) of 1.48 (95% CI: 1.17–1.88) and 1.56 (95% CI: 1.30–1.88), respectively, and similar ORs ($P = 0.24$) of 1.01 (95% CI: 0.82–1.26) and 1.18 (95% CI: 1.03–1.36), respectively (Supplementary Fig. S2).

Impact of contraceptives on ovarian cancer risk

Ovarian cancer risk data were available for OCP use and TL (Table I). A meta-analysis of the influence of OCP use on ovarian cancer risk revealed a statistically significant risk reduction relative to the reference (never or a maximum of 1 year of OCP use): HR: 0.62 (95% CI:

Table I Details of included studies.

Study characteristics			Study population										Statistics				
First author, year	Country	Study design	Inclusion criteria	Study cohort	N	*BRCA*-PV (*BRCA1* – *BRCA2* – *BRCA1* + 2)	Inclusion period	Age (years)	Birth year	Contraceptive method	Calendar year at start use	Formulation of OCP	Reference group	Follow-up period	Statistical analysis	Risk ratio	Risk of bias
Studies investigating breast cancer risk																	
Heimdal, 2002	Norway	Matched case–control	*BRCA1* mutation carriers with (cases) or relatives without (controls) breast cancer aged 40–60 years	*NA*	98	98—0—0	1989–2000	40–60	>1940	Oral contraception	Unknown	Estrogen + progestin	Never or <3 months use	*BRCA* testing—breast cancer/interview	Cox proportional hazards model	HR	Moderate
Narod, 2002	Canada*	Matched case–control	*BRCA1/2* mutation carriers with (cases) or without (controls) breast cancer	Unknown	2622	1962—660—0	1977–2001	Mean cases/controls: 46/47 (SD 10/10)	1925–1980	Oral contraception	Unknown	Unknown	Never use	Birth—interview (between 1977 and 2001, mean age at interview 47 years)	Conditional logistic regression	OR	Moderate
Haile, 2006	USA*	Case–control	*BRCA1/2* mutation carriers with (cases) or relatives without (controls) a first primary invasive breast cancer, aged < 50 years	BCFR, kConFab and Ontario Cancer Genetics Network	804	497—307—0	Unknown	<30–49	>1940	Oral contraception	Unknown	Unknown	Never or <1 year use	Birth—breast cancer/RRO/RRM/interview/in situ breast cancer	Unconditional logistic regression	OR	Moderate
Brohet, 2007	The Netherlands*	Retrospective cohort	*BRCA1/2* mutation carriers	IBCCS	1593	1181—412—0	After 1997	19–74	>1920	Oral contraception	Unknown	Unknown	Never use	Birth—age of first primary breast cancer (median 41 years)	Weighted Cox regression	HR	Moderate
Bernholtz, 2011	Israel	Retrospective case-only	Jewish *BRCA1/2* mutation carriers	*NA*	888	638—250—0	1996–2010	19–90	Unknown	Oral contraception	Unknown	Unknown	Never use	*BRCA* testing—age at breast cancer (mean age at breast cancer 50 years)	Logistic regression	HR	Moderate
Kotsopoulos, 2014	Canada*	Matched case–control	*BRCA1* mutation carriers with (cases) or without (controls) invasive breast cancer	Hereditary Breast Cancer Clinical Study Group	4984	4984—0—0	Unknown	Mean 46 (SD 9)	>1925 (mean 1958)	Oral contraception (for birth control)	Unknown	Unknown	Never use	Birth—questionnaire	Conditional logistic regression	OR	Moderate
Rieder, 2016	Austria	Retrospective cohort	*BRCA1/2* mutation carriers with breast cancer	*NA*	366	258—108—0	1995–2013	Mean around 40 years	Median 1965	Oral contraception	Unknown	Unknown	Never use	Birth—breast cancer	Uni- and multivariate Cox regression	HR	Serious
Park, 2017	Korea	Retrospective cohort	East-Asian *BRCA1/2* mutation carriers with breast cancer and their family members	KOHBRA	581	222—359—0	2007–2014	18–70+ (mean 40 years)	Unknown	Oral contraception	Unknown	Unknown	Never use	Birth—breast cancer/interview	Weighted multivariate Cox proportional hazard regression model	HR	Moderate
Toss, 2017	Italy	Retrospective cohort	*BRCA1/2* mutation carriers	*NA*	113	64—49—0	2010–2016	17–92 (mean age: 51, SD: 14)	Unknown	Combined hormonal contraceptives	Unknown	Combined	Never use	Birth—age 60	Cox proportional hazard regression	HR	Serious
Schrijver, 2018	The Netherlands*	Prospective cohort	*BRCA1/2* mutation carriers	IBCCS, kConFab, BCFR	3886	2276—1610—0	End follow-up: 2012	Mean around 40 years	1920-1992	Oral contraception	Before or after 1975	Unknown	Never or <6 months use	Recruitment/genetic testing—cancer/RRM/death/age 80/last follow-up (mean duration 5 years)	Time-dependent Cox proportional hazards regression models	HR	Moderate

(continued)

Table I Continued

Study characteristics			Study population										Statistics				
First author, year	**Country**	**Study design**	**Inclusion criteria**	**Study cohort**	**N**	***BRCA*-PV (*BRCA1* – *BRCA2* – *BRCA1* + 2)**	**Inclusion period**	**Age (years)**	**Birth year**	**Contraceptive method**	**Calendar year at start use**	**Formulation of OCP**	**Reference group**	**Follow-up period**	**Statistical analysis**	**Risk ratio**	**Risk of bias**
Studies investigating breast and ovarian cancer risk																	
Gronwald, 2006	Poland	Matched case–control	Polish founder *BRCA1/2* mutation carriers with (cases) or without (controls) breast or ovarian cancer	*NA*	BC: 696 OC: 300	996—0—0	After 1998	22–81	1917–1989 (mean 1956)	Oral contraception	Unknown	Unknown	Never use	At time of *BRCA* diagnosis—Mean age at breast/ovarian cancer: 44/49 years	Conditional logistic regression	OR	Unclear
Studies investigating ovarian cancer risk																	
Narod, 1998	Canada*	Matched case–control	*BRCA1/2* mutation carriers with (cases) or sisters without (controls) invasive epithelial ovarian cancer	Hereditary Ovarian Cancer Clinical Study Group	260	229—31—0	Unknown	patients: mean 54 (SD 8), controls: mean 52 (SD 8)	1925-1960	Oral contraception	Unknown	Unknown	Never use	Birth—interview	Unconditional logistic regression	OR	Moderate
Narod, 2001	Canada*	Matched case–control	*BRCA1/2* mutation carriers with (cases) or without (controls) invasive ovarian cancer, borderline carcinomas excluded	Hereditary Ovarian Cancer Clinical Study Group	464	346—118—0	Unknown	at diagnosis: 24-81	unknown	Oral contraception, tubal ligation (not specified)	Unknown	Unknown	Never use, no tubal ligation	Birth—questionnaire	Conditional logistic regression	OR	Serious
Whittemore, 2004	USA*	Matched case–control	*BRCA1/2* mutation carriers with (cases) or without (controls) primary invasive epithelial ovarian cancer	UKCCCR, kConFab, GRFOCR, Risk Assessment Program, BCRF	451	339—112—0	Unknown	most diagnosis 40-60	most > 1930	Oral contraception	Unknown	Unknown	Never or < 1 year use	Birth—ovarian cancer/RRSO/interview	Conditional logistic regression	OR	Moderate
Antoniou, 2009	UK*	Retrospective cohort	*BRCA1/2* mutation carriers	IBCCS	3319	2281—1038—0	1997–2005	at interview mean 46.5 (SD 12.1)	from <1940 up until ≥1965	Oral contraception, tubal ligation (not specified)	56% < 1975 44% ≥ 1975	Unknown	Never use, no tubal ligation	Birth—breast/ovarian/other cancer diagnosis/RRSO/interview (median 41 years)	Cox proportional hazards framework	HR	Moderate
Vicus, 2010a	Canada	Matched case–control	*BRCA1/2* mutation carriers with (cases) or without (controls) fallopian tube cancer	*NA*	661	661—0—0	1990–1999 and 2002–2004	at diagnosis: 38-76	1918–1965	Oral contraception, tubal ligation (not specified)	Unknown	Unknown	Never use, no tubal ligation	Birth—fallopian tube cancer/RRSO/hysterectomy/questionnaire	Uni- and multivariate conditional logistic regression	OR	Serious
Ferris, 2014	USA	Case–control	*BRCA1/2* mutation carriers with breast cancer at young age or breast and ovarian cancer (cases) or with multiple affected relatives (controls)	BCFR	639	Unknown	After 1995	mean cases 51.9 (SD 12.3), controls 47.9 (SD 16.0)	Unknown	Oral contraception	Unknown	Unknown	Never use	Birth—questionnaire	Within-family conditional logistic regression model	OR	Moderate

(continued)

Table I Continued

Study characteristics			Study population									Statistics				
First author, year	Country	Study design	Inclusion criteria	Study cohort	N	*BRCA*-PV (*BRCA1* – *BRCA2* – *BRCA1* + 2)	Inclusion period	Age (years)	Birth year	Contraceptive method	Calendar year at start use	Formulation of OCP	Reference group	Follow-up period	Statistical analysis	Risk ratio	Risk of bias
Kotsopoulos, 2015	Canada*	Matched case–control	*BRCA1/2* mutation carriers with (cases) or without (controls) invasive epithelial ovarian cancer	Hereditary Breast Cancer Clinical Study Group	6596	5386—1180—3	Unknown	26–85	1913–1982 (mean 1949)	Oral contraception (for birth control), tubal ligation (fallopian tubes tied)	Unknown	Unknown	Never use, no tubal ligation	Birth—interview (mean age at interview 54 years)	Conditional logistic regression	OR	Moderate
Perri, 2015	Israel	Historical prospective cohort	Jewish founder *BRCA1/2* mutation carriers	*NA*	1073	718—331—3 (21 unknown)	1995–2011, data update until 2013	20–93, mean 50 years	Unknown	Oral contraception	Unknown	Unknown	Never use	*BRCA* diagnosis—ovarian cancer/RRSO/death (2–18 years)	Unconditional logistic regression	OR	Moderate
Schrijver, 2021	The Netherlands*	Retrospective cohort	*BRCA1/2* mutation carriers	IBCCS	7662	4818—2844—0	End follow-up: 2012	Overall means 40–57 years	1920–1980	Oral contraception	Before or after 1975	Unknown	Never or <6 months use	Birth—ovarian cancer/RRSO/genetic testing/questionnaire (duration mean 40–55 years)	Time-dependent Cox proportional hazards regression models	HR	Moderate

*International study set up.

BC: breast cancer; BCFR: breast cancer family registry; *BRCA*-PV: *BRCA* pathogenic variant; GRFOCR: Gilda Radner Familial Ovarian Cancer Registry; HR: hazard ratio; IBCCS: International *BRCA1/2* Carrier Cohort Study; kConFab: Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer; KOHBRA: Korean Hereditary breast cancer study; N: number; NA: not applicable; not specified: no information available whether this includes salpingectomy as a contraceptive procedure; OC: ovarian cancer; OCP: oral contraceptive pill; OR: odds ratio; RRM: risk-reducing mastectomy; RRO: risk-reducing oophorectomy; RRSO: risk-reducing salpingo-oophorectomy; SD: standard deviation; UKCCCR: United Kingdom Consortium for Clinical Cancer Research.

Risk of bias has been assessed using the ROBINS-I questionnaire.

Table II **Quality of evidence for all outcomes that have been analysed using a meta-analysis, according to the GRADE framework.**

Quality assessment							Number of patients			Effect	Quality of evidence
Number of studies	Study design	A-priori ranking	Inconsistency	Indirectness	Imprecision	Other considerations	Total	*BRCA1*	*BRCA2*	Relative (95% CI)	
Primary outcomes											
Breast cancer risk and the oral contraceptive pill—hazard ratio											
7	5 cohort, 1 case–control, 1 case-only	Low	Not serious	Not serious	Not serious	None	16 631	7525	9106	1.55 (1.36–1.76)	⊕⊖⊖⊖ low
Breast cancer risk and the oral contraceptive pill—odds ratio											
4	Case–control	Low	Serious[a]	Not serious	Not serious	None	9106	8139	967	1.06 (0.90–1.25)	⊖⊖⊖⊖ very low
Ovarian cancer risk and the oral contraceptive pill—hazard ratio											
2	Cohort	Low	Not serious	Not serious	Not serious	None	10 981	7099	3882	0.62 (0.52–0.74)	⊕⊖⊖⊖ low
Ovarian cancer risk and the oral contraceptive pill—odds ratio											
8	7 case–control, 1 cohort	Low	Serious[a]	Not serious	Not serious	None	10 390[*]	7640	598	0.49 (0.38–0.63)	⊖⊖⊖⊖ very low
Ovarian cancer risk and tubal ligation—hazard ratio											
1	Cohort	Low	Not serious	Not serious	Serious[b]	None	3319	2281	1038	0.44 (0.26–0.74)	⊖⊖⊖⊖ very low
Ovarian cancer risk and tubal ligation—odds ratio											
3	Case-control	Low	Serious[a]	Not serious	Serious[b]	None	7691	6393	1298	0.74 (0.53–1.03)	⊖⊖⊖⊖ very low
Secondary outcomes											
Breast cancer risk and time since last use of the oral contraceptive pill—hazard ratio											
2	cohort	Low	Not serious	Not serious	Serious[b]	None	5479	3457	2022	1.40 (1.13–1.73)	⊖⊖⊖⊖ very low
Breast cancer risk and time since last use of the oral contraceptive pill—odds ratio											
3	case-control	Low	Serious[a]	Not serious	Not serious	None	7750	7443	307	1.38 (1.13–1.68)	⊖⊖⊖⊖ very low

GRADE: Grading of Recommendations, Assessment, Development, and Evaluation Working Group.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.
Non-randomized studies have the a-priori ranking 'low',
[a]downgraded 1 level for inconsistency: moderate or high heterogeneity;
[b]downgraded 1 level for imprecision: small studies and/or wide CIs;
[*]Total number of participants is higher than the number of BRCA1 plus the number of BRCA2 pathogenic variant carriers, as the studies of Ferris *et al.*, 2014 and Perri *et al.*, 2015 did not specify the number of BRCA1 and BRCA2 pathogenic variant carriers separately.

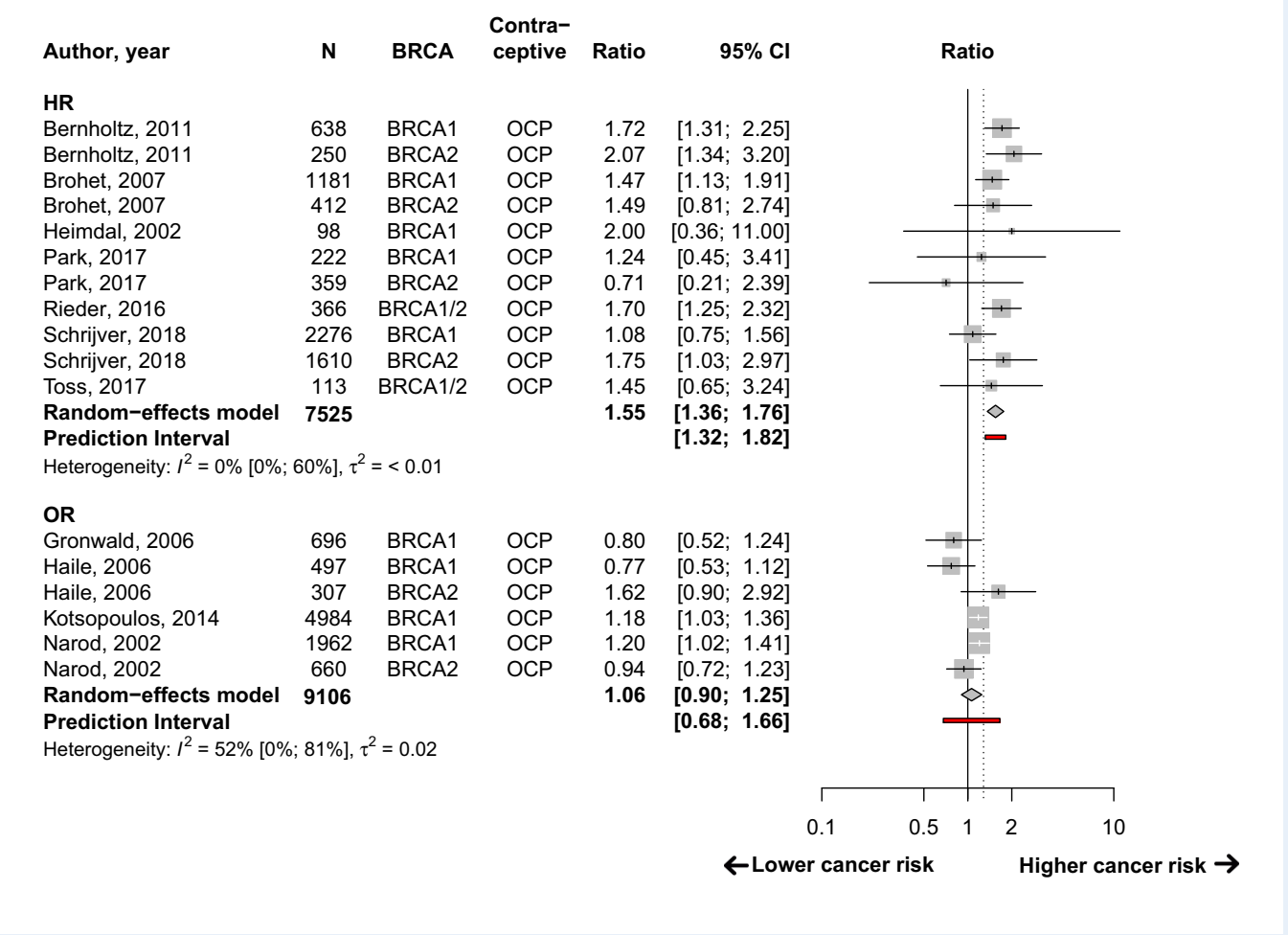


Figure 2. Forest plots presenting meta-analysis of breast cancer risk as modified by ever use of the OCP. Analysis split on effect size, i.e. studies reporting a HR versus studies reporting an OR. HR: hazard ratio; N: number of participants; OCP: oral contraceptive pill; *BRCA*-PV: *BRCA1/2* pathogenic variant; OR: odds ratio.

0.52–0.74) based on two studies including 10 981 women, and OR: 0.49 (95% CI: 0.38–0.63) based on eight studies with 10 390 women (Fig. 3). Heterogeneity was low (I^2: 0%) for studies reporting a HR and moderate (I^2: 64%) for studies reporting an OR. No differences were observed between *BRCA1*-PV and *BRCA2*-PV carriers in the studies that reported a HR ($P = 0.41$) (Supplementary Fig. S3). Among the studies with an OR, we found a difference between the results of studies that did and did not distinguish between *BRCA1*-PV or *BRCA2*-PV carriers ($P = 0.04$), but we found no difference for *BRCA1*-PV versus *BRCA2*-PV (Supplementary Fig. S3). When analysing studies published >10 years ago versus <10 years ago, we found HRs of 0.65 (95% CI: 0.34–1.21) and 0.64 (95% CI: 0.52–0.80), respectively, and ORs of 0.54 (95% CI: 0.41–0.69) and 0.45 (95% CI: 0.27–0.75), respectively (Supplementary Fig. S4). No significant differences were found between studies published >10 years ago versus <10 years ago ($P > 0.99$ and $P = 0.55$ for studies using HRs and ORs, respectively).

Figure 4 presents the meta-analysis of ovarian cancer risk after TL, revealing that this procedure reduces the risk of ovarian cancer in comparison with *BRCA1/2*-PV carriers who did not undergo TL: HR: 0.44 (95% CI: 0.26–0.74) and OR: 0.74 (95% CI: 0.53–1.03). Heterogeneity was low (I^2: 0%) and moderate (I^2: 44%) for studies using a HR or an OR, respectively. The effect of TL on ovarian cancer risk did not notably differ between *BRCA1*-PV and *BRCA2*-PV carriers ($P = 0.85$ and $P = 0.58$ for studies reporting HR and OR, respectively) (Supplementary Fig. S5).

Duration of contraceptive use and cancer risks

Data regarding duration of use and cancer risks were only available for OCP. The risk ratios for developing breast cancer per evaluated time period per study are shown in Table III. Of the 11 studies that investigated breast cancer risk, 8 described the association with duration of OCP use. In one study, breast cancer risk was found to increase with prolonged duration of use (Brohet *et al.*, 2007). Another study reported a higher risk in *BRCA2*-PV carriers after prolonged use, but not in *BRCA1*-PV carriers (Haile *et al.*, 2006). Two studies showed varying ratios per time period (Narod *et al.*, 2002; Kotsopoulos *et al.*, 2014). In four studies, duration of use was shown to have no

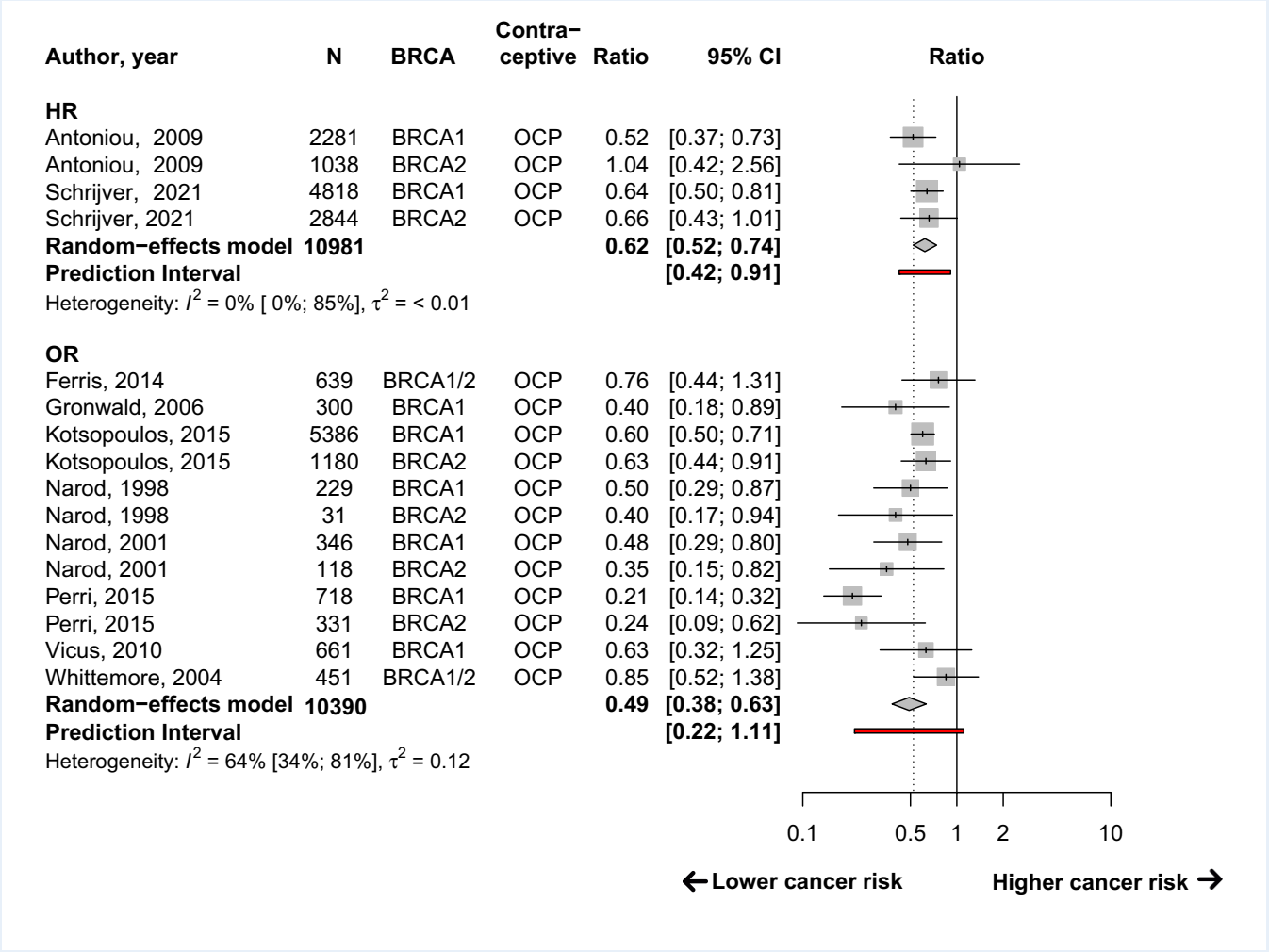


Figure 3. Forest plots visualizing the meta-analysis of the influence of ever OCP use on ovarian cancer risk. Analysis split on effect size, i.e. studies reporting a HR versus studies reporting an OR. HR: hazard ratio; N: number of participants; *BRCA*-PV: *BRCA1/2* pathogenic variant; OCP: oral contraceptive pill.

significant effect on breast cancer risk (Gronwald *et al.*, 2006; Rieder *et al.*, 2016; Toss *et al.*, 2017; Schrijver *et al.*, 2018).

Regarding ovarian cancer risk, 8 of the 10 evaluated studies explored the association with duration of OCP use. As shown in Table III, these studies evaluated varying periods of time. Of these eight studies, three found that the longer the OCP use, the lower the risk of ovarian cancer for *BRCA1*-PV and *BRCA2*-PV carriers (Narod *et al.*, 1998; Kotsopoulos *et al.*, 2015; Perri *et al.*, 2015). In four other studies, this association was reported to be significant for *BRCA1*-PV carriers, but not for *BRCA2*-PV carriers (Gronwald *et al.*, 2006; Antoniou *et al.*, 2009; Vicus *et al.*, 2010a; Schrijver *et al.*, 2021). One study did not split *BRCA1/2*-PV carriers and found a significant protective trend with prolonged OCP use, but no significant risk reductions when categorizing duration (Whittemore *et al.*, 2004).

Time since last use and cancer risks

OCP use was also described in terms of time since last use. The results of the five studies that reported the time since last OCP use are presented in Table III. A meta-analysis revealed a HR of 1.40 (95% CI: 1.13–1.73) and an OR of 1.38 (95% CI: 1.13–1.68) for developing breast cancer more than 10 years since the last use of OCP compared with having never used OCP (Supplementary Fig. S6), with no significant differences between *BRCA1*-PV and *BRCA2*-PV carriers ($P = 0.47$ and $P = 0.32$ for studies with HR and OR, respectively).

Two studies reported on ovarian cancer risks as influenced by the time since the last use of OCP (Antoniou *et al.*, 2009; Schrijver *et al.*, 2021). Both found that the reduced risk of ovarian cancer vanished with increasing time since last OCP use, whether after 10 years (Antoniou *et al.*, 2009) or 20 years (Schrijver *et al.*, 2021) (Table III).

Guidelines

A total of 132 national societies for gynaecologists and obstetricians were listed on the FIGO website in June 2021, of which 34 societies were founded in a nation with a developed economy, as determined by the United Nations. Four internationally collaborative societies were added, as was one society in which two nations (Australia and

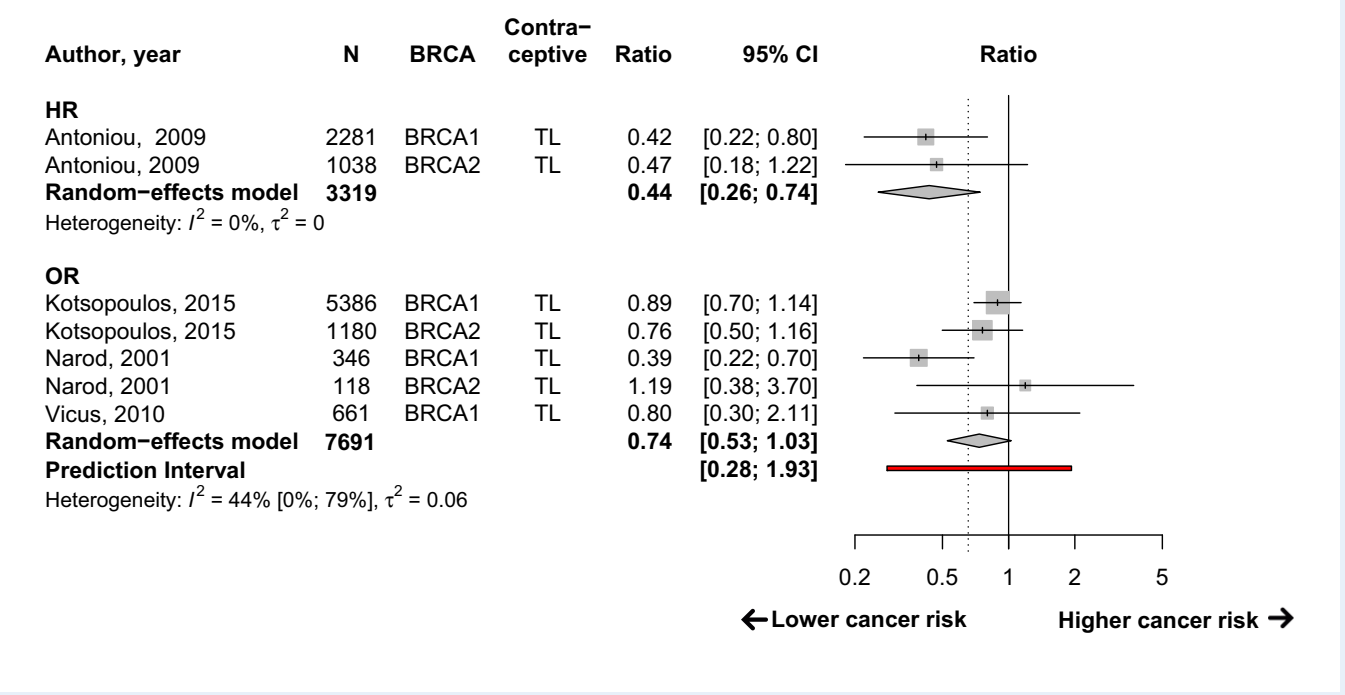


Figure 4. Forest plots of the meta-analysis of the influence of TL on ovarian cancer risk. Analysis split on effect size, i.e. studies reporting a HR versus studies reporting an OR. HR: hazard ratio; N: number of participants; *BRCA*-PV: *BRCA1/2* pathogenic variant; TL: tubal ligation.

New Zealand) collaborate, resulting in 37 societies with 50 potentially eligible guidelines. Guidelines were excluded because they were either about *BRCA* or contraceptives but not both topics (n = 22), due to language (n = 11) or because they were unavailable (n = 5). Twelve guidelines from six nations met the inclusion criteria. We also searched for relevant guidelines written for general practitioners in these six nations and found two additional guidelines; thus, a total of 14 guidelines were included.

Table IV presents the recommendations of each guideline. As shown, most guidelines recommend (individualized) counselling about cancer risks when discussing contraception with *BRCA1/2*-PV carriers. One guideline stands out as it describes an absolute contraindication for hormonal contraception in *BRCA1/2*-PV carriers aged 35 years or older, and a relative contraindication for carriers aged 25 to 35 years (Barnhoorn, 2020).

Discussion

Main findings

In this systematic review using meta-analyses, we investigated the impact of contraceptive use on breast and ovarian cancer risk among *BRCA1/2*-PV carriers. Regarding breast cancer risk, the data were limited to the OCP, and the results were heterogenous between the reported outcome measures: breast cancer risk was either increased (HR: 1.55, 95% CI: 1.36–1.76) or unaffected (OR: 1.06, 95% CI: 0.90–1.25) by use of the OCP. This increased breast cancer risk was even found 10 years after the last OCP use; however, no clear association was identified between breast cancer risk and duration of OCP use. By contrast, OCP use reduced ovarian cancer risk, with a HR of 0.62 (95% CI: 0.52–0.74) and an OR of 0.49 (95% CI: 0.38–0.63), and longer usage of OCP might lower ovarian cancer risk. These beneficial effects seem to vanish over time following the cessation of OCP use, however. TL was found to decrease ovarian cancer risk as well, with a HR of 0.44 (95% CI: 0.26–0.74) and an OR of 0.74 (0.53–1.03). The impacts of these contraceptives on cancer risks were similar for *BRCA1*-PV and *BRCA2*-PV carriers. No data were available regarding other types of contraception and their effects on cancer risks in *BRCA1/2*-PV carriers.

Interpretation

The impact of contraceptives on cancer risks has been investigated for some time, and previous systematic reviews and meta-analyses have been published about their effects on the *BRCA1/2*-PV population (Cibula *et al.*, 2010, 2011a,b; Iodice *et al.*, 2010; Rice *et al.*, 2012; Friebel *et al.*, 2014; Huber *et al.*, 2020). Our study is the most up to date, however, and is based on the largest sample sizes thus far. We also summarized the evidence using meta-analyses, in contrast to some others (Cibula *et al.*, 2010; Moorman *et al.*, 2013; Huber *et al.*, 2020). Furthermore, unlike previous meta-analyses, we specifically searched for contraceptive methods in our systematic search, instead of factors influencing cancer risks in general (Friebel *et al.*, 2014). We did not restrict our search strategy to either OCP or TL, as others have done (Iodice *et al.*, 2010; Cibula *et al.*, 2011a,b; Rice *et al.*, 2012; Huber *et al.*, 2020). Despite these differences, the results of the previous reviews and meta-analyses are highly comparable to ours.

Table III Outcome data per included study.

First author, year	Contra-ceptive	Risk ratio	Primary outcome			Secondary outcomes					
			Risk at cancer for ever-use of contraception			Duration of use			Time since last use		
			BRCA1	*BRCA2*	Total *BRCA*	*BRCA1*	*BRCA2*	Total *BRCA*	*BRCA1*	*BRCA2*	Total *BRCA*
Studies investigating breast cancer risk											
Heimdal, 2002	OCP	HR	2.00 (0.36–10.9)	.	.	.	.	.	.	.	.
Narod, 2002	OCP	OR	1.20 (1.02–1.40)	0.94 (0.72–1.24)	.	Never: 1 0–4y: 1.10 (0.92–1.31) 5–9y: 1.36 (1.11–1.67) 10–14y: 1.27 (0.99–1.64) 15–30y: 1.30 (0.91–1.87)	Never: 1 0–4y: 0.90 (0.67–1.20) 5–9y: 0.82 (0.56–1.91) 10–14y: 1.16 (0.75–1.78) 15–30y: 1.35 (0.71–2.56)	.	Never: 1 Current: 0.83 (0.66–1.04) 1–5y: 1.03 (0.81–1.32) 6–10y: 1.10 (0.87–1.38) >10y: 1.59 (1.30–1.94) Trend: $P = 0.05$	.	.
Gronwald, 2006	OCP	OR	0.8 (0.5–1.2)	.	.	Never: 1 <2y: 0.9 (0.5–1.5) >2y: 0.8 (0.5–1.4)	.	.	.	.	.
Haile, 2006	OCP	OR	0.77 (0.53–1.12)	1.62 (0.90–2.92)	.	Never or <1y: 1 1–4y: 0.68 (0.43–1.08) 5>y: 0.80 (0.54–1.18) Trend per year: not significant	Never or <1y: 1 1–4y: 1.16 (0.58–2.34) 5>y: 2.06 (1.08–3.94) Trend per year: 1.08 ($P = 0.008$)	.	Never or <1y: 1 <10y: 0.63 (0.42–0.95) ≥10y: 1.00 (0.64–1.57) Trend per year: 1.04 ($P = 0.002$)	Never or <1y: 1 <10y: 1.62 (0.91–2.87) ≥10y: 1.92 (0.97–3.82) Trend per year: 1.02 ($P = 0.034$)	.
Brohet, 2007	OCP	HR	1.47 (1.13–1.91)	1.49 (0.8–2.70)	1.47 (1.16–1.87)	Never: 1 1–3y: 1.36 (0.99–1.88) 4–8y: 1.51 (1.10–2.08) >9y: 1.63 (1.17–2.29)	Never: 1 1–3y: 1.23 (0.64–2.35) 4–8y: 2.27 (1.10–4.65) >9y: 1.47 (0.66–3.28)	Never: 1 1–3y: 1.34 (1.00–1.78) 4–8y: 1.59 (1.19–2.13) >9y: 1.61 (1.18–2.20) Trend per year $P = 0.257$	Never: 1 <1y: 1.35 (0.94–1.94) 1–10y: 1.56 (1.13–2.14) >10y: 1.50 (1.09–2.05)	Never: 1 <1y: 1.75 (0.76–4.00) 1–10y: 1.69 (0.80–3.55) >10y: 1.39 (0.73–2.64)	Never: 1 <1y: 1.39 (1.00–1.94) 1–10y: 1.56 (1.17–2.09) >10y: 1.48 (1.12–1.96)
Bernholtz, 2011	OCP	HR	1.715 (1.307–2.251)	2.07 (1.338–3.20)	1.842 (1.465–2.314)	.	.	.	.	.	.
Kotsopoulos, 2014	OCP	OR	1.18 (1.03–1.36)	.	.	Never: 1 0 to <5y: 1.14 (0.97–1.35) 5 to <10y: 1.19 (0.99–1.43) 10 to <15y: 1.27 (1.02–1.60) 15 to <30y: 1.23 (0.92–1.65) Trend per year: 1.01 (1.00–1.03)	.	.	Never: 1 Current: 0.80 (0.66–0.97) <5y: 1.42 (1.13–1.77) 5–10y: 1.55 (1.25–1.77) >10y: 1.27 (1.06–1.53) Trend: $P = 0.38$	.	.
Rieder, 2016	OCP	HR	.	.	1.7 (1.1–2.05)	.	.	Trend per year: 1.00 (0.99–1.00)	.	.	.
Park, 2017	OCP	HR	1.24 (0.45–3.40)	0.71 (0.21–2.37)	.	.	.	.	.	.	.
Toss, 2017	OCP	HR			1.45 (0.65–3.25)	.	.	<10y: 1 >10y: 0.78 (0.18–3.34)	.	.	.
Schrijver, 2018	OCP	HR	1.08 (0.75–1.56)	1.75 (1.03–2.97)	.	Never or <6m: 1 <5y: 1.13 (0.75–1.71) 5–9y: 0.93 (0.60–1.43) 10>y: 1.16 (0.77–1.73)	Never or <6m: 1 <5y: 1.83 (1.04–3.25) 5–9y: 1.40 (0.75–2.61) 10>y: 1.75 (0.98–3.16)	.	Never or <6m: 1 <3y: 0.96 (0.60–1.55) 3–10y: 1.14 (0.72–1.80) ≥10y: 1.11 (0.75–1.65) Trend per year: $P = 0.30$	Never or <6m: 1 <3y: 1.56 (0.77–3.17) 3–10y: 1.60 (0.78–3.30) ≥10y: 1.77 (1.02–3.06) Trend per year: $P = 0.75$	.
Studies investigating ovarian cancer risk											
Narod, 1998	OCP	OR	0.5 (0.3–0.9)	0.4 (0.2–1.1)	0.4 (0.2–0.7)	.	.	Never: 1 <3y: 0.4 (0.3–0.9) 3 to <6y: 0.4 (0.1–1.0) 6>y: 0.3 (0.1–0.7) Trend per year: 0.9 (0.9–1.0)	.	.	.

(continued)

Table III Continued

First author, year	Contra-ceptive	Risk ratio	Primary outcome			Secondary outcomes					
			Risk at cancer for ever-use of contraception			Duration of use			Time since last use		
			BRCA1	*BRCA2*	Total *BRCA*	*BRCA1*	*BRCA2*	Total *BRCA*	*BRCA1*	*BRCA2*	Total *BRCA*
Narod, 2001	OCP	OR	0.48 (0.29–0.80)	0.35 (0.15–0.83)	0.44 (0.28–0.68)	.	.	.	.	.	.
	TL	OR	0.39 (0.22–0.70)	1.19 (0.38–3.68)	.	.	.	.	.	.	.
Whittemore, 2004	OCP	OR	.	.	0.85 (0.53–1.4)	.	.	Never or <1y: 1 1–2y: 1.5 (0.82–2.9) 3–5y: 0.69 (0.33–1.4) 6>y: 0.62 (0.35–1.1) Trend per year: 0.95 (0.91–0.99)	.	.	.
Gronwald, 2006	OCP	OR	0.4 (0.2–1.0)	.	.	Never: 1 <2y: 0.8 (0.2–2.5) >2y: 0.2 (0.1–0.7)	.	.	.	.	.
Antoniou, 2009	OCP	HR	0.52 (0.37–0.73)	1.04 (0.42–2.54)	0.55 (0.40–0.76)	Never: 1 0–1y: 1.03 (0.64–1.65) 1–3y: 0.51 (0.28–0.93) 3–5y: 0.40 (0.17–0.91) 5>y: 0.34 (0.21–0.54)	Never: 1 0–1y: NA 1–3y: 1.33 (0.52–3.39) 3–5y: NA 5>y: 0.59 (0.16–2.24)	Never: 1 0–1y: 1.04 (0.66–1.62) 1–3y: 0.60 (0.35–1.03) 3–5y: 0.41 (0.19–0.87) 5>y: 0.35 (0.22–0.55) Trend per year: $P = 0.0003$	Never: 1 current/<10y: 0.28 (0.17–0.48) ≥10y: 0.80 (0.55–1.18)	Never: 1 current/<10y: 0.38 (0.10–1.45) ≥10y: 1.76 (0.63–4.94)	Never: 1 current/<10y: 0.29 (0.18–0.48) ≥10y: 0.85 (0.59–1.21)
	TL	HR	0.42 (0.22–0.80)	0.47 (0.18–1.21)	0.43 (0.24–0.75)	.	.	.	.	.	.
Vicus, 2010a	OCP	OR	0.63 (0.32–1.26)	.	.	Never: 1 <5 y: 0.84 (0.40–1.78) 5>y: 0.47 (0.19–1.14) Trend per year: 0.91 (0.83–0.99)	Trend per year: 0.94 (0.80–1.11)	.	.	.	.
	TL	OR	0.80 (0.3–2.08)	.	.	.	.	.	.	.	.
Ferris, 2014	OCP	OR	.	.	0.76 (0.44–1.31)	.	.	.	.	.	.
Kotsopoulos, 2015	OCP	OR	0.60 (0.50–0.71)	0.63 (0.44–0.92)	.	Never: 1 <1y: 0.82 (0.64–1.05) 1 to <3y: 0.56 (0.41–0.75) 3 to <5y: 0.54 (0.39–0.75) 5>y: 0.50 (0.40–0.63)	Never: 1 <1y: 1.09 (0.68–1.79) 1 to <3y: 0.62 (0.36–1.08) 3 to <5y: 0.42 (0.22–0.83) 5>y: 0.51 (0.32–0.81)	Trend per year: 0.93 (0.90–0.97)	.	.	.
	TL	OR	0.89 (0.69–1.13)	0.76 (0.50–1.16)	.	.	.	.	.	.	.
Perri, 2015	OCP	OR	0.21 (0.14–0.33)	0.24 (0.09–0.61)	0.21 (0.14–0.31)	.	.	Never: 1 1<y: 0.36 (0.16–0.84) 1–5y: 0.31 (0.19–0.51) >5y: 0.10 (0.06–0.17)	.	.	.
Schrijver, 2021	OCP	HR	Full cohort: 0.64 (0.50–0.81)	Full cohort: 0.66 (0.43–1.00)	.	Never/<6m: 1 <5y: 0.84 (0.61–1.14) 5–9y: 0.74 (0.53–1.04) 10>y: 0.44 (0.31–0.61) Trend per year: significant	Never/<6m: 1 <5y: 0.81 (0.46–1.43) 5–9y: 0.62 (0.34–1.14) 10>y: 0.59 (0.35–0.99) Trend per year: non-significant	.	Never/<6m: 1 <10y: 0.53 (0.37–0.77) 10–19y: 0.70 (0.51–0.95) ≥20y: 0.73 (0.54–1.00) Trend per year: $P = 0.113$	Never/<6m: 1 <10y: 0.44 (0.22–0.86) 10–19y: 0.70 (0.39–1.26) ≥20y: 0.76 (0.45–1.26) Trend per year: $P = 0.162$	.

All data are represented as risk ratio (95% CI).
HR, hazard ratio; m, months; OCP: oral contraceptive pill; OR: odds ratio; TL: tubal ligation; y: years; .: data not available.

Table IV Overview of current guidelines regarding contraception in BRCA1/2-PV carriers.

	Country, society	Guideline	Year	Recommendations/summary	Conclusion
1	Slovakia, SAGO	Guidelines for complex genetic analysis of hereditary breast ovarian cancer syndrome in Slovak population	2015	– Hormonal contraception is not necessarily contraindicated in carriers of a mutation; however, the benefits need to be considered.	Not contraindicated
2	The Netherlands, NVOG	Erfelijk en familiair ovariumcarcinoom (in English: Hereditary and familial ovarian carcinoma)	2015	– No reason to advise against OCP in healthy women with a *BRCA1/2* mutation aged 25 years or below – Data regarding LR-IUD and the risk of breast cancer in healthy *BRCA1/2* mutation carriers is lacking, therefore no statement can be made on the safety of these IUDs in this specific group – There is some data showing that the use of LR-IUD after breast cancer does not increase the risk of recurrence of breast cancer.	Not contraindicated
3	USA, AGOC	US Medical Eligibility Criteria for Contraceptive Use	2016	– Evidence does not suggest that the increased risk for breast cancer among women with either a family history of breast cancer or breast cancer susceptibility genes is modified by the use of combined oral contraceptives.	Not contraindicated
4	Spain, SEGO	Clinical guidelines in hereditary breast and ovarian cancer	2016	– Oral contraceptives in *BRCA1/2* mutation carriers can reduce the risk of ovarian cancer by 50%, with the benefit being greater with longer duration of treatment. Their use is not contraindicated, although there is a possibility of an increased risk of breast cancer.	Not contraindicated
5	Canada, SOGC	Canadian Contraception Consensus	2017	The use of combined oral contraception in *BRCA1/2* carriers is controversial but appears to be associated with a decreased risk of ovarian cancer and no increase in the risk of breast cancer – Women with a history of breast cancer >5 years ago: benefit for expert consultation prior to advising against contraceptive use – In general: adequate counselling prior to OCP initiation to ensure an informed choice and improve adherence and continuation	Ambivalent, counsel
6	United Kingdom, NICE*	Surveillance proposal for *BRCA*	2017	– Women <35 years with a family history of breast cancer: in keeping with general health advice on the use of the OCP – Women >35 years with a family history of breast cancer: inform on an increased breast cancer risk associated with taking the OCP, and that their absolute risk increases with age – *BRCA1* carriers: conflicting effects of a potential increased risk of breast cancer under the age of 40 years and the lifetime protection against ovarian cancer risk from taking the OCP should be discussed – The OCP should not be prescribed purely for prevention of cancer	Ambivalent, counsel
7	USA, ACOG	Clinical management guidelines for Obstetrician-Gynecologists: Hereditary Breast and Ovarian Cancer Syndrome	2017	– Given the magnitude of the potential benefits (e.g. ovarian and endometrial cancer risk reduction, pregnancy, prevention, cycle regulation), it is appropriate for women with mutations in *BRCA1* or *BRCA2* to use oral contraceptives if indicated, and use for cancer prophylaxis is reasonable. Although there have been conflicting reports in the literature on the effect of oral contraceptives on breast cancer risk. – In high-risk women who are undergoing tubal sterilization for contraception, bilateral salpingectomy followed by future oophorectomy may be a reasonable option to offer, but ovarian cancer risk reduction remains under evaluation.	Not contraindicated
8	Canada, SOGC	Gynaecologic management of hereditary breast and ovarian cancer	2018	– Combined hormonal contraceptive use is an effective method of chemoprevention for ovarian/tubal/peritoneal cancer in the general population and women with *BRCA1/2*. – The use of OCP in young *BRCA1* variant carriers should be individualized, taking into account the risks and benefits.	Ambivalent, individualize

(continued)

Table IV Continued

	Country, society	Guideline	Year	Recommendations/summary	Conclusion
9	United Kingdom, FSRH	Guideline-combined-hormonal-contraception	2019	– Amongst *BRCA* carriers, use of OCPs is associated with reduced risk of ovarian cancer with use, proportional to the duration of use. The evidence is stronger for *BRCA1* carriers but exists for both *BRCA1* and *BRCA2*. This advantage would need to be weighed against the potential increased risk of breast cancer. – Women with a *BRCA* mutation should be advised that current use of combined hormonal contraception is associated with a small increased risk of breast cancer which reduces with time after stopping combined hormonal contraception.	Ambivalent, counsel
10	United Kingdom, FSRH	UK Medical Eligibility Criteria (UKMEC) for contraceptive use	2019	Carriers of a known gene mutations associated with breast cancer (e.g. *BRCA1/BRCA2):* – Copper IUD: no restriction for use – LR-IUD, progestogen-only-implant, medroxyprogesterone acetate, progestogen-only-pill, combined hormonal contraception: the advantages generally outweigh the theoretical or proven risks	Not contra-indicated
11	USA, NCCN	Genetic/familial high-risk assessment: Breast and ovarian cancer	2019	– The use of oral contraceptives significantly reduced the risk of ovarian cancer by approximately 50% for both the *BRCA1* and *BRCA2* mutation carriers. Studies on the effects of oral contraceptive use on breast cancer risk among *BRCA1/2* mutation carriers have reported conflicting data.	No advice reported
12	The Netherlands, NHG*	Anticonceptie (in English: Contraception)	2020	– *BRCA* ≥35 years: absolute contra-indication for hormonal contraceptives – *BRCA* 25-35 years: relative contra-indication for hormonal contraceptives – BRCA <25 years: no contra-indication for hormonal contraceptives	Contra-indicated, depending on age
Collaborative societies					
13	WHO	Medical eligibility criteria for contraceptive use	2015	Women with a family history of cancer or with breast cancer susceptibility genes (such as *BRCA1* and *BRCA2):* – Combined oral contraceptive, combined contraceptive patch, vaginal ring or injectable contraceptive: no restriction for use	Not contra-indicated
14	EMSO	Prevention and screening in *BRCA* mutation carriers	2016	– The use of the OCP may be considered as a risk-reducing measure for ovarian cancer. It should however be noted that there are conflicting data whether OCP increases breast cancer risk among *BRCA1/2* carriers	Not contra-indicated

*Guideline of the society of general practitioners.
LR-IUD: levonorgestrel releasing intra-uterine device; OCP: oral contraceptive pill.

Moreover, the preventive effect of OCP on ovarian cancer risk was consistently found in the previous meta-analyses (Iodice *et al.*, 2010; Cibula *et al.*, 2011b; Moorman *et al.*, 2013; Friebel *et al.*, 2014), and the results from meta-analyses regarding TL and the reduced ovarian cancer risk were consistent with ours (Cibula *et al.*, 2011a; Rice *et al.*, 2012; Friebel *et al.*, 2014). Regarding breast cancer risk, the results of earlier meta-analyses are less consistent. Some studies revealed differing results between outcome measures and across study designs, similar to our findings (Cibula *et al.*, 2011b; Friebel *et al.*, 2014). Others found no statistically significant effect of OCP on breast cancer risk (Iodice *et al.*, 2010; Moorman *et al.*, 2013), which might be explained by the variation in the included study populations.

The negative impact of OCP on breast cancer risk and the beneficial effect on ovarian cancer risk identified here in *BRCA1/2*-PV carriers are similar to previous findings in the general population (Beral *et al.*, 2008; Mørch *et al.*, 2017); however, the impact on cancer risks may be more clinically relevant for people who already have a high risk of cancer, such as *BRCA1/2*-PV carriers, although this is personal. One patient might want to avoid every additional risk, while another one might question the relevance of additional increased risk when the baseline risk of breast cancer is already as high as ~70% (Kuchenbaecker *et al.*, 2017). Importantly, as we investigated risk ratios, the increase in absolute percent points will be higher in case of a high baseline risk than in case of a low baseline risk. Regarding ovarian cancer, reliable screening is unavailable, and mortality rates are high as it is generally diagnosed at an advanced stage (Oei *et al.*, 2006; Siegel *et al.*, 2019). This might favour the usage of OCP among high-risk women, but the advice to undergo a risk-reducing salpingo-oophorectomy around the age of 40 years (and its high uptake) may reduce the relevance of the beneficial effect of OCP use (Harmsen *et al.*, 2016; Metcalfe *et al.*, 2019). Furthermore, *BRCA1/2*-PV carriers can choose to undergo a risk-reducing mastectomy, the uptake of which varies greatly across cultures (Metcalfe *et al.*, 2019). After mastectomy, which greatly reduces breast cancer risk by at least 90–95% (Rebbeck *et al.*, 2004; Heemskerk-Gerritsen *et al.*, 2019), the influence of OCP on breast cancer risk may be negligible. Previous risk-reducing surgeries should therefore be taken into account in the contraceptive advice for *BRCA1/2*-PV carriers. In other cases, the use of contraceptives might influence breast cancer management strategies; for example, OCP might increase breast density, as was previously described for hormone replacement therapy, although the data are inconsistent (van Barele *et al.*, 2021; Evans, 2002; Lundström *et al.*, 2002). Higher breast density negatively affects the evaluability of imaging techniques. Furthermore, magnetic resonance imaging (MRI) is aimed to be performed between Days 5 and 15 of the menstrual cycle of premenopausal women to optimize evaluability; thus, the optimal timing of an MRI can be challenging in non-menstruating women, for example when using an LR-IUD.

Other factors to be included in counselling are age, reversibility of contraception and whether contraceptives have been used already (e.g. is stopping/switching indicated?). Moreover, the benefit of adequate contraception could be considered to outweigh the very low risk of developing a certain type of cancer at a young age (<25 years). Because of the protective effect of TL on ovarian cancer risk, this might be the optimal approach to combine contraception with ovarian cancer prevention; however, TL is not suitable for young women who have (latent) child wish because it is irreversible. For women who have already been using contraceptives, it is important to include the effect of prolonging contraceptive use on cancer risks in counselling, which was also concluded in a recent investigation in which absolute cancer risks as influenced by OCP were estimated in a hypothetical cohort of *BRCA1/2*-PV carriers (Schrijver *et al.*, 2022). We found that, with increasing time since last OCP use, the preventive effect on ovarian cancer disappears, whereas the increased breast cancer risk remains for more than 10 years after last use.

We should take into account that women who stopped OCP more than 10 years ago are potentially older than those who have never used these contraceptives, and that the formulation of OCPs has changed over time (lower hormonal dosages, different steroid types). An earlier meta-analysis suggested that breast cancer risk is lower in users of newer OCP formulations (after 1975) than those who used OCPs formulated before 1975 (Iodice *et al.*, 2010). Regarding ovarian cancer risk, Schrijver *et al.* (2021) reported a reduced ovarian cancer risk for *BRCA1*-PV carriers using OCP formulations initiated before 1975 and no significant effect for formulations initiated after 1975, compared with the risk for women who had never used these OCPs. For *BRCA2*-PV carriers, a pre-1975 initiation did not significantly reduce ovarian cancer risk, whereas a post-1975 initiation did, compared with those who never used these OCPs (Schrijver *et al.*, 2021). We also evaluated the effect of modernity of OCP on cancer risks in the present study. As OCP formulations were poorly described in the individual studies, we performed analyses with studies published more than 10 years ago versus those published in the last 10 years, in which we found consistent results as those obtained in the analyses of all studies combined. The lack of clear data regarding age at first or last use and formulation of OCP may be one explanation for the remaining increased breast cancer risk after the cessation of OCP use. Additional research regarding the potential impact of changing formulations over time is therefore needed.

Both OCP and TL reduce ovarian cancer risk, but the underlying aetiology remains unclear. One hypothesis is that ovarian cancer risk increases with increasing numbers of ovulations, which is counteracted by the prevention of ovulation by OCPs (Fathalla, 1971, 2013). The hypothesis that (serous) ovarian cancer originates in the fallopian tubes is increasingly accepted (Piek *et al.*, 2001; Labidi-Galy *et al.*, 2017). Potentially, the traumatized ovarian surface epithelium (as during ovulation) is more prone to the attachment of premalignant cells from the fallopian tube, which may then undergo further malignant transformation on the ovary. The preventive effect of TL might support the hypothesis of a central role for the fallopian tube in the origin of ovarian cancer as well; for example, TL may act as a mechanical barrier against malignant or premalignant cells moving from the tubes towards the ovaries (Cibula *et al.*, 2011a; Rice *et al.*, 2012). One study investigated the impact of contraceptives on premalignant lesions of ovarian cancer and found no significant association between either OCP or TL on either p53 signatures or on tubal intraepithelial carcinogenic lesions (Vicus *et al.*, 2010b). Further hypotheses regarding TL preventing ovarian cancer include: the inhibition of retrograde menstruation (Cibula *et al.*, 2011a; Rice *et al.*, 2012); a decreased blood flow towards the ovaries, which could alter the levels of growth factors and hormones (Cramer and Xu, 1995; Riman *et al.*, 1998; Cibula *et al.*, 2011a); the inhibition of the spread of infections from the external genitalia upwards (Cibula *et al.*, 2011a; Rice *et al.*, 2012); and TL surgery enabling the removal of suspicious ovarian tissue. These theories may apply to

salpingectomy as well. Nowadays, most gynaecologists perform salpingectomy instead of TL as a surgical sterilization method. Of the four studies included in the meta-analysis of TL, one stated that it focussed on the tying of the fallopian tubes (Kotsopoulos et al., 2015), while the others did not specify whether the sterilization included salpingectomy (Narod et al., 2001; Antoniou et al., 2009; Vicus et al., 2010a). In the general population, salpingectomy was found to be more effective than sterilization (TL) in reducing ovarian cancer risk (Falconer et al., 2015). Based on the findings of Falconer et al. (2015) and the pathogenesis of (serous) ovarian cancer in which the fimbriated ends seem crucial (Labidi-Galy et al., 2017), it is possible that, among *BRCA1/2*-PV carriers, salpingectomy might be more effective than TL in reducing ovarian cancer risk. Currently, salpingectomy is being investigated as a method to reduce ovarian cancer risk in *BRCA1/2*-PV carriers in ongoing trials (NCT04294927, ISRCTN 25173360, NCT04251052).

Data were unavailable regarding the impact of other contraceptive methods (e.g. copper IUD, LR-IUD, transdermal contraceptive patch, vaginal ring, contraceptive injection, progestogen-only contraceptive pill and contraceptive implant) on cancer risks among women at high inherited risk for breast and ovarian cancer at the time we performed our systematic search. Nevertheless, in early 2022, the first study that investigated progestin only contraceptives including the implant, the injection and the IUD among *BRCA1/2*-PV carriers was published (Xia et al., 2022), revealing a preventive effect of the implant on ovarian cancer risk but no significant effects on ovarian cancer risk were found for the injection, the hormonal IUD and the non-hormonal IUD. As we found comparable results in the general population and the *BRCA1/2*-PV population regarding OCP and TL, one could imagine that other contraceptives may similarly impact cancer risks as well (Madsen et al., 2015; Mørch et al., 2017). For the general population, data regarding breast cancer risk and other contraceptives are available; an increased RR of breast cancer was found for the LR-IUD and the levonorgestrel-only pill, whereas no significant influence was found for the contraceptive patch, vaginal ring, contraceptive injection and contraceptive implant (Mørch et al., 2017; Conz et al., 2020). Regarding ovarian cancer risk, the use of an IUD (both copper-bearing and levonorgestrel-releasing) or a contraceptive implant was found to be protective (Urban et al., 2012; Wilailak et al., 2012; Wheeler et al., 2019; Balayla et al., 2021; Phung et al., 2021). To fully counsel *BRCA1/2*-PV carriers about the contraceptive options, data regarding the impact of contraceptive methods other than OCP and TL on cancer risks in the *BRCA1/2*-PV population are needed.

For clinical practice, it would be interesting to translate our outcomes into absolute risks. However, we should be aware that for both the HR and the OR this is difficult. The HR corresponds to different RRs at different time points and the OR represents the ratio of cumulative risks (expressed as odds) at a certain timepoint and those timepoints as well as the ages of the participating women vary across studies. Also, data regarding the risk of breast and ovarian cancer in women without contraceptives are unclear as earlier studies that calculated cumulative lifetime risks of breast and ovarian cancer among *BRCA1/2*-PV carriers do not provide information about whether those women did or did not use contraceptives (Kuchenbaecker et al., 2017; Chen et al., 2020). It is highly likely that the populations included in those studies consist of a mixture of users and non-users. Taking into account those limitations, our results suggest that compared to a breast cancer risk of 70% for *BRCA1/2*-PV carriers in general (Kuchenbaecker et al., 2017), the breast cancer risk in those who used OCP lies between 68% and 75% based on our OR, and between 76% and 80% based on our HR. Regarding ovarian cancer, overall, *BRCA1*-PV carriers have a risk of 44% (Kuchenbaecker et al., 2017); based on our OR, this risk would be between 23% and 33% for OCP users and based on our HR between 29% and 37%. Compared to the risk of 17% in *BRCA2*-PV carriers in general (Kuchenbaecker et al., 2017), for OCP users, a risk between 7% and 11% (based on OR) or between 10% and 13% (based on HR) would be suggested. For TL and ovarian cancer risk, compared to the overall risk of 44% for *BRCA1*-PV carriers, TL would result in a risk between 29% and 45% based on our OR, or between 17% and 37% based on our HR. Compared to the risk of 17% for *BRCA2*-PV carriers, our OR suggest that TL leads to a risk between 10% and 17% and our HR suggest a risk between 5% and 13%.

Strengths and limitations

The main strengths of our study include the large number of more than 38 000 *BRCA1/2*-PV carriers and the performance of meta-analyses, which heighten the level of evidence. We also broadly investigated cancer risks and current recommendations across nations by providing an overview of all relevant international guidelines. In contrast to most previous studies, we did not limit our research to certain types of contraceptives, and we investigated both breast and ovarian cancer risk. Unfortunately, data regarding the formulations of OCPs were unavailable in most of the included studies. The wide variety in age of the included women, and therefore probably the variety of OCP formulations used, may have influenced our results, as OCPs prescribed between the 1960s and 1990s were significantly different from the OCPs used today. We tried to increase the generalizability to modern OCP formulations by conducting additional analyses with studies published >10 years ago versus <10 years ago. Due to the retrospective design of the majority of the included studies, recall and survival bias may influence our results. Furthermore, the analysis of the association between duration of use and cancer risks was limited due to the availability of aggregate data only, as well as the heterogeneity in the way duration of use was categorized across studies. For the same reasons, we were also unable to provide age- or dosage-related effects.

Conclusion

In conclusion, among *BRCA1/2*-PV carriers, breast cancer risk was found to be increased by OCP usage compared with those who had never used these contraceptives, with the risk remaining increased for more than 10 years after cessation of use. Ovarian cancer risk was lower among OCP users, but this effect vanishes after cessation of use. TL protects against ovarian cancer. No data are available for other kinds of contraceptives. We should be aware that OCP formulations have changed with time, and we will not know the safety profile of newer OCP formulations for a few years yet. Counselling *BRCA1/2*-PV carriers regarding contraceptives should be personalized, balancing both genetic and non-genetic individual risk factors (such as prior risk-reducing surgeries, prior breast cancer and age), as well as taking into account patients' preferences (such as reversibility, ease of use, reliability and effect on the menstrual cycle). To optimize counselling and provide clear recommendations for women at high risk for breast and

ovarian cancer, future (prospective) research should focus on other (commonly used) contraceptive methods and cancer risks in this specific population.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

Data availability

The data underlying this study are available in the article and in its online supplementary material. Further supportive material is available upon reasonable request to the corresponding author.

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Authors' roles

All authors critically revised the manuscript and provided final approval of the version to be published. M.H.D.v.B. and G.V. performed the data collection and critical appraisal. M.H.D.v.B. wrote the original draft of the manuscript. M.H.D.v.B. and J.I. were involved in analysing the data. M.H.D.v.B., J.I., C.M.K., J.A.d.H., A.M.v.A. and M.G.H. contributed to the study design and data interpretation. M.G.H. supervised the study.

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Conflict of interest

The authors declare no conflicts of interest.

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