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Probability of detecting germline *BRCA1/2* pathogenic variants in histological subtypes of ovarian carcinoma. A meta-analysis

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HIGHLIGHTS

- Probability of finding germline *BRCA1/2* PVs varies widely among histological subtypes of ovarian carcinoma (OC).
- Germline *BRCA1/2* PVs are most frequently detected in high-grade serous OC patients.
- Limiting testing to high-grade serous histology will be insufficient to identify all OC patients with germline *BRCA1/2* PVs.

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ABSTRACT

Background. Histology restricted genetic predisposition testing of ovarian carcinoma patients is a topic of debate as the prevalence of *BRCA1/2* pathogenic variants (PVs) in various histological subtypes is ambiguous. Our primary aim was to investigate the proportion of germline *BRCA1/2* PVs per histological subtype. Additionally, we evaluated *(i)* proportion of somatic *BRCA1/2* PVs and (*ii*) proportion of germline PVs in other ovarian carcinoma risk genes.

Methods. PubMed, EMBASE and Web of Science were systematically searched and we included all studies reporting germline *BRCA1/2* PVs per histological subtype. Pooled proportions were calculated using a random-effects meta-analysis model. Subsets of studies were used for secondary analyses.

Results. Twenty-eight studies were identified. The overall estimated proportion of germline *BRCA1/2* PVs was 16.8% (95% CI 14.6 to 19.2). Presence differed substantially among patients with varying histological subtypes of OC; proportions being highest in high-grade serous (22.2%, 95% CI 19.6 to 25.0) and lowest in clear cell (3.0%, 95% CI 1.6 to 5.6) and mucinous (2.5%, 95% CI 0.6 to 9.6) carcinomas. Somatic *BRCA1/2* PVs were present with total estimated proportion of 6.0% (95% CI 5.0 to 7.3), based on a smaller subset of studies. Germline PVs in *BRIP1*, *RAD51C*, *RAD51D*, *PALB2*, and *ATM* were present in approximately 3%, based on a subset of nine studies.

Conclusion. Germline *BRCA1/2* PVs are most frequently identified in high-grade serous ovarian carcinoma patients, but are also detected in patients having ovarian carcinomas of other histological subtypes. Limiting genetic predisposition testing to high-grade serous ovarian carcinoma patients will likely be insufficient to identify all patients with a germline PV.

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Contents

1. Introduction

Recognition of heredity in ovarian carcinoma (OC) patients is crucial to reduce cancer risks among patients and family members and it may facilitate treatment decisions. About 20–25% of all OCs are caused by an underlying heritable tumor risk syndrome [1,2]. This proportion consists mainly of women harboring a germline pathogenic variant (PV) in the *BRCA1* or *BRCA2* gene [1,2]. Germline PVs in *RAD51C*, *RAD51D*, *BRIP1*, *PALB2*, *ATM*, and the mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) also confer a moderately increased risk for OC [3,4], but occur less frequently [1,5]. Germline testing plays a central role in recognition of heredity in OC patients.

Tumor DNA testing can be used as an efficient and effective prescreen to stratify germline testing and treatment options [6,7]. Tumor testing detects both germline PVs and somatic PVs (present in tumor DNA but absent in blood). The increasing importance of tumor DNA testing is underlined by developments in treatment options. For example, poly ADP ribose polymerase inhibitor (PARPi) therapy has proven to be beneficial for patients with a tumor *BRCA1/2* PV [8], either germline or somatic. Tumor DNA testing (i.e. a Tumor-First approach) detects individuals eligible for treatments options, and can simultaneously function as a prescreen to tailor genetic counseling and germline testing to patients at higher risk [6].

Universal germline or tumor testing of all OC patients has increasingly become the norm [6,9,10]. However, OC is a heterogeneous disease and histological subtypes display varying molecular genetic landscapes and distinct precancerous lesions. Selection of histological subtypes for germline testing and tumor DNA testing (as prescreen) to reduce costs and optimize recognition of hereditary OC is still a topic of debate. Former studies and reviews have demonstrated that high-grade serous OC is the cancer associated with germline *BRCA1/2* PVs [9,11]. This is supported by the detection of serous tubal intraepithelial carcinomas (STICs) during prophylactic risk reducing salphingo-oophorectomy in individuals with a *BRCA1/2* PV [12,13]. This association with distinct histology raises the question whether genetic predisposition testing could be executed more efficiently by restricting testing to certain histological subtypes of OC.

Histology restricted genetic predisposition testing is highly dependent on the accuracy of histology typing and the proportion of PVs detected per histological subtype. In 2014 and 2020, the World Health Organization (WHO) published new criteria for histological subclassification of OC [14]. The accuracy of histology typing was of concern in older classification systems, but the WHO 2014 and 2020 are more robust [15,16]. Therefore, the proportion of PVs per histological subtype needs re-evaluation. Here, we performed a systematic review and meta-analysis of recent literature (>2015) with the primary aim to investigate the proportion of germline *BRCA1/2* PVs per histological subtype of OC. Secondarily, we evaluated *(i)* proportion and histology of somatic *BRCA1/2* PVs and (*ii*) proportion of germline PVs in moderate risk genes for OC (*BRIP1*, *RAD51C*, *RAD51D*, *ATM*, *PALB2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*) and OC histology.

2. Methods

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [17].

2.1. Search strategy and study selection

Databases PubMed/Medline, EMBASE and Web of Science were systematically searched for studies published from 1 January 2015 to 5 November 2020. A comprehensive search strategy was constructed using medical subject headings (MeSH), Embase subject headings (Emtree), keywords and synonyms related to three aspects: (i) ovarian carcinoma, (ii) *BRCA*, and (iii) germline/tumor testing. The complete search strategies are provided in supplement S1. Searches were restricted to English language and timeframe of publication 2015 (after introduction of WHO 2014 histology classification system) till "current". All references were uploaded in Endnote reference management program (Endnote™ X9). Manual removal of duplicates and selection of articles was performed by two reviewers (VW and MvB) independently, achieving agreement after discussion or by consultation of a third reviewer (NH).

2.2. Eligibility criteria

Selection of articles was performed according to predefined inclusion and exclusion criteria. Articles were included if all information required for computing the prevalence of germline *BRCA1/2* PVs per histological subtype of OC was provided. Germline *BRCA1/2* PVs were defined as class 4 and 5 variants, and OC was defined by the WHO 2014 and 2020 guidelines [15,16]. Articles were excluded when the

population did not consist of OC patients, when the number of OC patients was unclear, when no germline testing was performed, when testing was restricted to pre-specified (founder) mutations, or when the information on histology was insufficient to compute proportions per subtype. Solely articles written in English language and investigating human subjects were included. In case of overlapping cohorts, only the study with most patients was included. Review articles, case-reports, opinion pieces and letters to editors were excluded, similar to conference abstracts.

2.3. Critical appraisal

The quality of selected studies was rated using an adapted version of the critical appraisal tool for prevalence studies from the Joanne Briggs Institute [18]. The standard appraisal tool consisting of nine categories was adapted to enable scoring specifically for this systematic review. The adapted version is provided in supplement S2. Here, six (out of 13) items were considered to be essential ('answered with yes') to be included in the quantitative analysis: 1) sample frame broader than serous ovarian carcinomas, 2) total population size >50, 3) serous histology subdivided in high- and low-grade, 5) histological subgroup 'non- high-grade serous' specified, 5) germline and somatic PVs are distinguishable, and 6) variants of uncertain significance (VUS) and pathogenic variants are distinguishable. Scoring was performed by two reviewers (VW and MvB) independently, achieving agreement after discussion. The total critical appraisal score was the number of items answered with 'yes', which had no further consequences.

2.4. Outcomes and data-extraction

Our primary outcome was defined as the proportion of germline *BRCA1/2* PVs per histological subtype of OC. Our secondary outcomes were: *(i)* proportion of somatic *BRCA1/2* PVs and *(ii)* proportion of germline PVs in other risk genes for OC (*BRIP1*, *RAD51C*, *RAD51D*, *PALB2*, *ATM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*). We defined somatic *BRCA1/2* PVs as variants that are present in tumor DNA but absent in normal tissue or blood. We extracted data from eligible studies using a data extraction table consisting of predefined topics: bibliographical data, population data, methodological data, and outcome data. Data on histology of tested population and data on histology of *BRCA1/2* positive cases were essential items in data extraction. We recorded whether tumor testing was performed in addition to germline testing and which genes other than *BRCA1/2* were tested. Data extraction was split between two reviewers, who cross-checked each other's work. In case any discrepancies in original articles were identified during data extraction, we considered data from tables to be most reliable.

2.5. Data analysis and statistics

We performed meta-analyses of the proportion of germline and somatic *BRCA1/2* PVs in all OCs. Additionally, we performed meta-analyses of the proportion of germline *BRCA1/2* PVs per histological subtype of OC: high-grade serous (HGS), endometrioid, clear cell, low-grade serous (LGS), mucinous, carcinosarcoma, and 'other'. The group 'other' was a merge of the histological types seromucinous, transitional cell, Brenner, undifferentiated, mixed, and other. We did not calculate an average proportion for (ovarian) carcinoma not specified, adenocarcinoma not specified and serous carcinoma not specified. Data analysis was performed at study level.

Pooled proportions were calculated by a random intercepts logistic regression model (GLMM) using a maximum likelihood estimation (ML) [19,20]. Heterogeneity across studies was estimated using the I^2 statistic (<25% low level of heterogeneity, 50% moderate level of heterogeneity, >75% high level of heterogeneity) [21]. Subgroup analysis was undertaken based on ethnicity (country where study was performed) to assess potential differences.

Data was examined for the presence of outliers, defined as studies in which the individual confidence interval (CI) did not overlap with the meta-analysis CI. Outliers were not excluded from analyses, but these articles were screened for potential reasons for variation. In addition, the data was examined for influential studies, defined as studies for which exclusion leads to changes in result of the meta-analysis [22]. Also, removing studies one-by-one was performed and the effect on pooled proportion was evaluated to assess sensitivity of the meta-analysis model.

All analyses were conducted using statistical software R version 3.6.2 (2019-12-12) using the packages "*meta*" and "*metafor*".

3. Results

3.1. Study selection

Database searches generated a total of 4756 records, of which 2941 remained after removal of duplicates. Exclusion based on screening of title and abstracts ($n = 2708$) and full text ($n = 135$) resulted in 98 articles who were subjected to a critical appraisal. Then, another 69 articles were excluded which resulted in a total of 29 articles. During data extraction two articles were merged as they presented results of the same cohort [23,24]. The critical appraisal scores of the included articles are presented in supplement S3. In total, this systematic review and meta-analysis is based on 28 studies (Fig. 1).

3.2. Characteristics of the included studies

Table 1 presents an overview of the study characteristics and main outcome data of the included studies. The included studies were conducted either in Asian or European countries, with the exception of one study which was conducted in the United States [1]. Details on selected OC patients are also provided; most studies included all OC patients, with mucinous ovarian carcinoma being the predominant exclusion criterium. The number of included OC patients in individual studies ranged from 56 to 1915 (patients with known germline or somatic mutation status and known histology of OC). In total, we include 11,351 OC patients from 28 studies. The individual study results on total number of *BRCA1/2* PVs and *BRCA1/2* PVs per histological subtype of OC are presented in Table 1. Table 1 also marks that nine studies performed somatic tumor testing in addition to germline testing, this subset was used to analyze the proportion and histology of somatic *BRCA1/2* PVs. Another subset of nine studies could be used to evaluate proportion and histology of other risk genes for OC as they tested for these in addition to *BRCA1/2*.

3.3. Proportion of germline BRCA1/2 PVs per histological subtype

Meta-analysis of 28 studies resulted in an estimated proportion of 16.8% (95% CI 14.6 to 19.2) for germline *BRCA1/2* PVs in a population of OC patients as is illustrated in Fig. 2A. Considerable (high level) heterogeneity was present ($I^2 = 88\%$), representing differences in results among studies. Subgroup analysis for studies conducted in Asian versus European/American countries (predominantly Asian versus predominantly Caucasian women) revealed no differences in proportions and heterogeneity between these two groups (supplement S4). More specifically, the estimated proportion of germline *BRCA1* PVs was 10.7% (95% CI 8.8 to 12.9, $I^2 = 88\%$) and the proportion of *BRCA2* PVs was 5.5% (95% CI 4.7 to 6.3, $I^2 = 51\%$).

Fig. 3A presents a pie chart of the OC histological subtypes of all patients and Fig. 3B presents a pie chart of the OC histological subtypes of women with *BRCA1/2* PVs. It appears that OC patients with a germline *BRCA1/2* PV are relatively more likely to develop HGSOC compared to the general OC population in this meta-analysis: in women with *BRCA1/2* PVs this percentage is 91% (1738 / 1907), whereas around 75% (7914 / 10,487) of all OCs are of HGS histology.

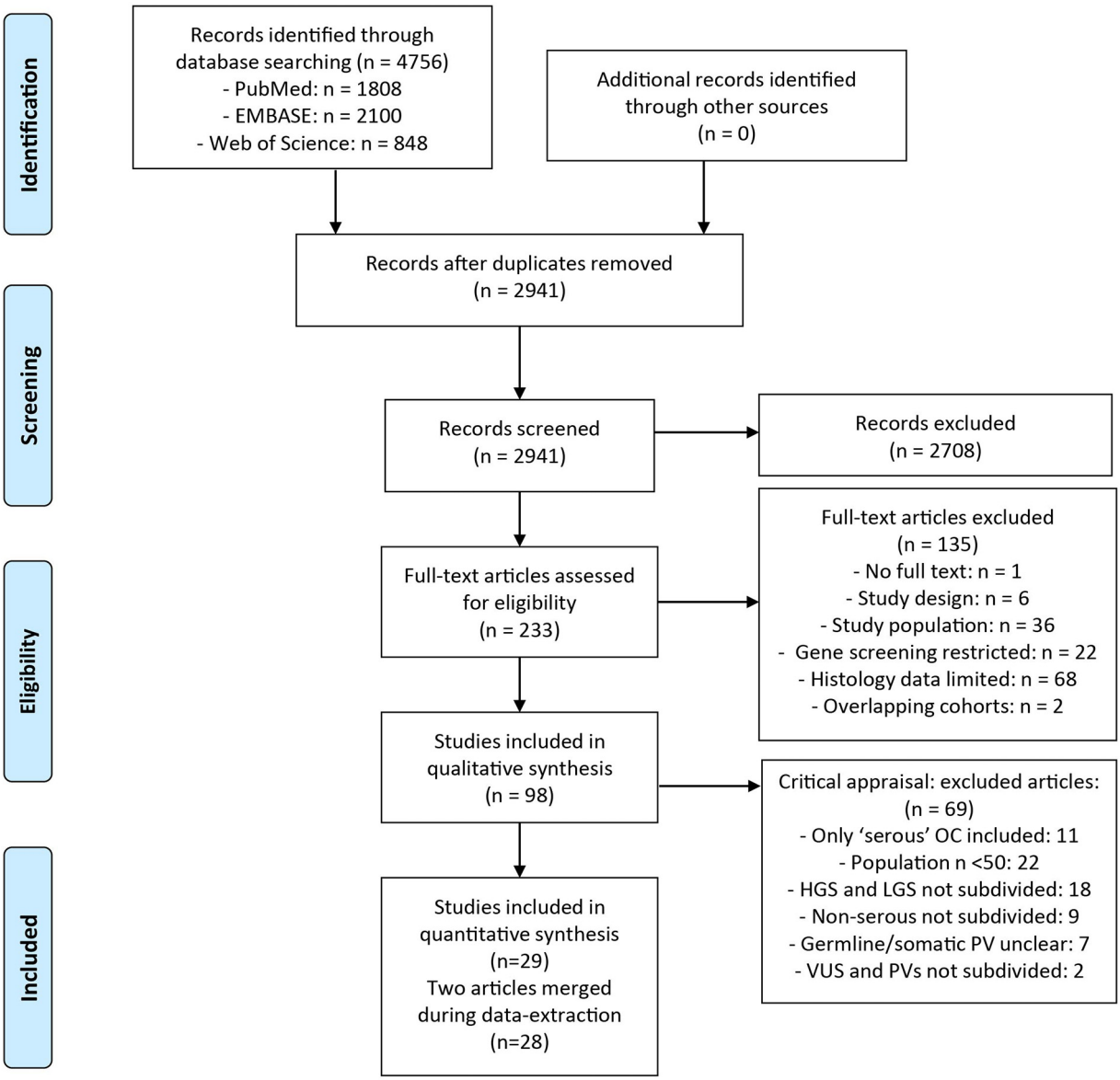

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of study selection. After several rounds of selection, 28 articles remained from the initial database searches.
Abbreviations: OC: ovarian carcinoma, HGS: high-grade serous, LGS: low-grade serous, PV: pathogenic variant, VUS: variant of uncertain significance.

Proportions of germline *BRCA1/2* PVs per histological subtype of OC are presented in Table 2 and Fig. 4. Presence of germline *BRCA1/2* PVs varied substantially among patients having various histological subtypes of OC. The proportion of germline *BRCA1/2* PVs was highest in patients with HGSOC (22.2%, 95% CI 19.6 to 25.0), and also the proportion in ovarian carcinosarcoma patients was found to be relatively high (11.9%, 95% CI 5.8 to 22.6). The probability of detecting a germline *BRCA1/2* PV was lower in patients having endometrioid OC (5.8%, 95% CI 3.3 to 9.9), LGSOC (5.2%, 95% CI 2.3 to 11.3), clear cell OC (3.0%, 95% CI 1.6 to 5.6) or mucinous OC (2.5%, 95% CI 0.6 to 9.6). Thus, for all OC patients, irrespective of the histological subtype, there is a probability that the patient is carrying a germline *BRCA1/2* PV, but the number of patients needed to test to identify one *BRCA1/2* PV vary substantially as is presented in Table 2.

Heterogeneity was low in all non-HGS histological subtypes, indicating here that the CIs of individual study estimates overlap, potentially due to rarity of these subtypes. We assessed the sensitivity of the meta-analysis by removing studies one-by-one and analyzing their influence on the pooled proportion. The pooled proportion of germline *BRCA1/2* PVs in patients with non-HGSOC were more sensible to the effect of removing single studies compared to HGS. Therefore, the pooled proportion of germline *BRCA1/2* PVs in patients with non-HGSOC are more uncertain, especially for carcinosarcoma, LGS, and mucinous OC. This uncertainty in the pooled proportion is also visible from the wider CIs of the pooled proportions. Despite this uncertainty in the estimate proportion, germline *BRCA1/2* PVs were detected in all histological subtypes of OC. Also, in seven studies that incorporated an extra round of pathological revision in their study design, germline *BRCA1/2* PVs were identified in all histological subtypes [1,28,31,34,42,47,48].

3.4. Proportion and histology of somatic BRCA1/2 PVs

Meta-analysis of a subset of nine studies that performed tumor testing in addition to germline testing indicated that the estimated proportion of somatic (non-germline) *BRCA1/2* PVs in a population of OC

Table 1
General study characteristics and primary outcome data.

Study		General study characteristics				*BRCA1/2* PVs in total and per histological subtype of OC[b]							
Ref	Author, year	Country	Included OC patients	Test[a]	MGP	Total (n/N)	HGS (n/N)	E (n/N)	CC (n/N)	LGS (n/N)	M (n/N)	CS (n/N)	Other (n/N)
[25]	Ataseven, 2020	Germany	All	G	Yes	127/545	125/435	1/29	0/23	0/33	0/16	1/1	0/8
[26]	Bu, 2019	China	All	G	No	117/506	97/398	1/17	7/23	6/33	2/13	–	4/22
[27]	Choi, 2015	Korea	All	G	No	18/70	18/44	0/6	0/9	–	0/9	–	0/2
[28]	Enomoto, 2019	Japan	All	G	No	93/634	78/274	8/120	4/187	1/5	0/19	–	2/29
[29]	Flaum, 2020	UK	Non-mucinous	G	No	89/481	86/427	2/21	0/14	0/8	–	1/11	–
[30]	George, 2016	UK	Non-mucinous, partial age < 65	G	No	33/207	32/173	1/22	0/2	0/6	–	–	0/4
[23,24]	Hauke, 2019 & Harter, 2017	Germany	All	B	Yes	g: 95/473 s: 29/473	g: 86/373 s: 23/373	g: 4/29 s: 5/29	g: 0/6 s: 0/6	g: 1/16 s: 0/16	g: 0/6 s: 0/6	–	g: 2/18 s: 0/18
[31]	Hirasawa, 2017	Japan	All	G	Yes	27/230	22/74	2/58	2/71	0/3	0/18	–	1/6
[32]	Kim, 2020	Korea	All	B	No	g: 13/56 s: 3/56	g: 13/51 s: 3/51	g: 0/1 s: 0/1	g: 0/3 s: 0/3	g: 0/1 s: 0/1	–	–	–
[33]	Kowalik, 2019	Poland	All	S*	No	g: 35/193 s: 6/193	g: 28/116 s: 5/116	g: 1/21 s: 1/21	g: 1/9 s: 0/9	g: 5/32 s: 0/32	g: 0/6 s: 0/6	–	g: 0/9 s: 0/9
[34]	Lertkhachonsuk, 2020	Thailand	HGS, HGE, clear cell	S*	No	g: 14/138 s: 9/138	g: 13/76 s: 7/76	g: 0/4 s: 0/4	g: 1/55 s: 2/55	–	–	–	g: 0/3 s: 0/3
[35]	Lhotova, 2020	Czech Republic	All, incl. Borderline	G	Yes	288/1120	152/478	18/90	1/15	12/85	5/43	–	4/90
[36]	Li, 2019	China	All	B	Yes	g: 14/62 s: 4/62	g: 13/48 s: 4/48	g: 0/3 s: 0/3	g: 0/5 s: 0/5	g: 0/1 s: 0/1	g: 0/1 s: 0/1	–	g: 0/4 s: 0/4
[37]	Manchana, 2019	Thailand	Non-mucinous	G	Yes	20/112	19/49	0/28	1/24	0/6	–	–	0/4
[38]	Morgan, 2019	UK	Non Jewish	G	No	103/557	90/475	5/29	2/18	0/10	0/4	1/6	0/2
[1]	Norquist, 2016	USA	All, partial selection on FIGO stage	G	Yes	280/1915	240/1498	7/77	4/58	4/70	0/16	1/22	1/9
[39]	Peixoto, 2020	Portugal	Non-mucinous	S	No	g: 18/135 s: 8/135	g: 17/95 s: 5/95	g: 0/9 s: 2/9	g: 0/10 s: 0/10	g: 0/14 s: 0/14	–	g: 1/4 s: 1/4	g: 0/3 s: 0/3
[40]	Plaskocinska, 2016	UK	HGS, HGE	G	No	18/323	17/192	0/20	–	–	–	–	0/5
[41]	Rahman, 2019	UK	Non-mucinous, high grade	G	No	18/122	17/100	0/9	0/5	–	–	1/5	0/3
[42]	Rivera, 2020	Italy	Non-mucinous	B	No	g: 12/66 s: 7/66	g: 12/59 s: 6/59	g: 0/1 s: 1/1	g: 0/3 s: 0/3	g: 0/1 s: 0/1	–	–	g: 0/2 s: 0/2
[43]	Rumford, 2020	UK	Non-mucinous	G	No	34/255	34/197	0/25	0/14	–	–	0/8	0/11
[44]	Rust, 2018	Scotland	Non-mucinous, partial selection on family	G	Yes *RAD51*	114/599	102/519	–	0/9	0/14	0/5	0/7	0/1
[45]	Sakamoto, 2016	Japan	All	G	No	12/95	12/57	0/6	0/10	0/17	–	–	0/5
[46]	Seo, 2019	Korea	All	G	No	88/310	84/254	0/6	0/15	2/20	1/10	–	1/5
[47]	Shi, 2017	China	All	G	No	153/916	114/613	9/49	1/51	0/6	0/38	–	1/11
[48]	Sugino, 2019	Japan	Non- neoadjuvant chemotherapy	B	Yes	g: 13/207 s: 13/207	g: 10/50 s: 6/50	g: 1/39 s: 2/39	g: 1/99 s: 5/99	g: 0/6 s: 0/6	g: 1/13 s: 0/13	–	–
[6]	Vos, 2020	The Netherlands	All	S*	No	g: 25/298 s: 19/298	g: 21/188 s: 12/188	g: 0/15 s: 3/15	g: 1/19 s: 0/19	g: 0/17 s: 1/17	g: 0/17 s: 1/17	g:1/10 s:0/10	g: 2/12 s: 1/12
[49]	Wu, 2017	China	All	G	No	235/823	186/601	7/30	3/37	3/18	2/10	2/3	1/4

Abbreviations: UK: United Kingdom, USA: United States of America, OC: ovarian carcinoma, MGP: multi-gene panel, MA: meta-analysis, PV: pathogenic variant, g: germline, s: somatic, HGS: high-grade serous, (HG)E: (high-grade) endometrioid, CC: clear cell, LGS: low-grade serous, M: mucinous, CS: carcinosarcoma.

[a] Test: only germline testing (G), germline and tumor testing (B), or tumor testing and subsequent germline testing when test was positive (S). *marks germline testing not performed for all patients with positive tumor test, these patients were excluded from our analysis.

[b] Number of patients with *BRCA* PVs in total population and per histological subtype: HGS, E, CC, LGS, M, CS, other. Number of patients with *BRCA* PVs (n) per number of tumors tested (N). 'other' is combined group from: seromucinous, transitional cell, undifferentiated, mixed and other. — indicates histological subtype is not present in this cohort. Excluded from this table are: (ovarian) carcinoma not specified, serous not specified and borderline tumors.

patients was 6.0% (95% CI 5.0 to 7.3), as illustrated in Fig. 2B. Heterogeneity does not seem to play a role here ($I^2 = 0\%$), indicating no major differences among studies. Proportions of somatic *BRCA1* and *BRCA2* PVs were more or less similar; 3.5% (95% CI 2.7 to 4.5, $I^2 = 21\%$) and 2.7% (95% CI 2.0 to 3.6, $I^2 = 0\%$), respectively. Fig. 3C presents a pie-chart of the histological subtypes of tumors with a somatic *BRCA1/2* PV. Tumors with a somatic *BRCA1/2* PV are predominantly HGS and endometrioid carcinomas, and rarely clear cell, mucinous, carcinosarcoma and other carcinomas, more or less similar to the general OC population in our study.

3.5. Proportion and histology of germline variants in other ovarian carcinoma risk genes

Our systematic review included nine studies that investigated the prevalence of germline PVs in other OC risk genes (*BRIP1*, *RAD51C*, *RAD51D*, *PALB2*, *ATM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*). Individual study results are presented in supplement S5. Rough estimates of the prevalence of germline PVs in these genes are: *BRIP1* 0.9% (42/4658), *RAD51C* 0.8% (44/5257), *RAD51D* 0.7% (34/5195), *PALB2* 0.6% (27/4658), *ATM* 0.3% (14/4658), *MSH6* 0.3% (14/4658), *PMS2* 0.2% (7/3538), *MLH1* 0.2% (7/4658), *MSH2* 0.2% (7/4658) (as presented in supplement S6). In total, the combined probability of detecting a germline PV in *BRIP1*, *RAD51C*, *RAD51D*, *PALB2*, or *ATM* is around 3.3% in OC patients. The probability of detecting a germline PV in a mismatch repair gene (*MLH1*, *MSH2*, *MSH6* or *PMS2*) was <1% in total.

Fig. 3D and E present pie-charts that illustrate the OC histological subtypes of patients with a germline PV in the genes *BRIP1*, *RAD51C*, *RAD51D*, *PALB2*, *ATM* and the mismatch repair (MMR) genes, respectively. HGS was the predominant histological subtype for both groups of genes. Furthermore, germline PVs in the genes *BRIP1*, *RAD51C*, *RAD51D*, *PALB2* and *ATM* were detected in all histological subtypes, whereas germline PVs in MMR genes were predominantly detected in HGS and endometrioid OCs.

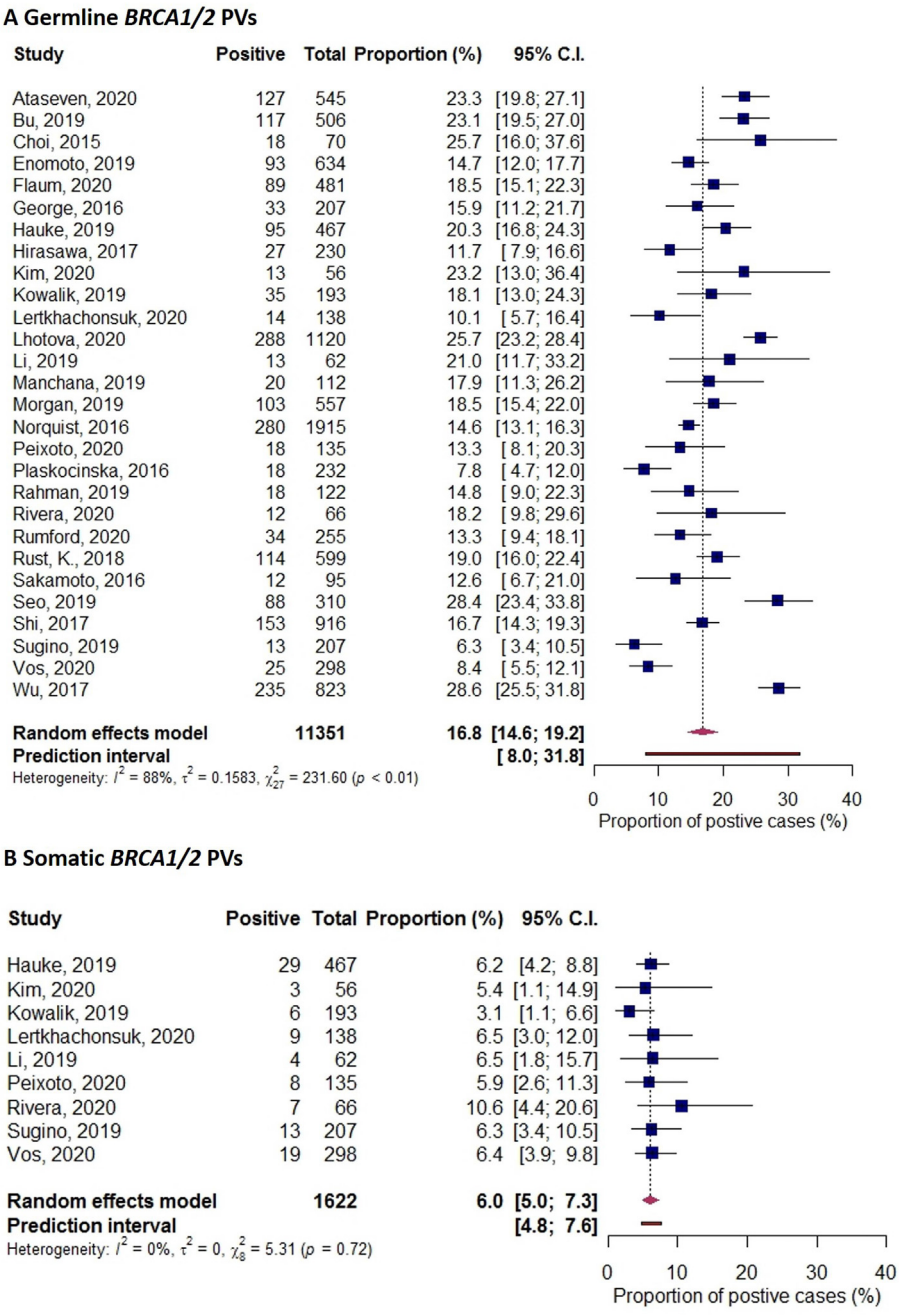

Fig. 2. Forest plots presenting meta-analyses of proportions of germline (A) and somatic (B) *BRCA1/2* PVs in all histological subtypes of ovarian carcinoma combined. Somatic *BRCA1/2* PVs are defined as those that are present in tumor DNA but absent in normal tissue or blood.

4. Discussion

In this systematic review and meta-analysis, we have shown that germline *BRCA1/2* PVs were detected in 16.8% (95% CI 14.8 to 19.2) of the patients with OC. The probability of detecting a germline *BRCA1/2* PV varied widely among the various histological subtypes of OC; ranging from 22.2% (95% CI 19.6 to 25.0) in patients with HGSOC to 3.0% (95% CI 1.6 to 5.6) in patients with clear cell OC and 2.5% (95% CI 0.6 to 9.6) in patients with mucinous OC. Unlike the generally accepted assumption that *BRCA1/2* PVs are exclusively related to HGS histology [50,51], our meta-analysis indicated that *BRCA1/2* PVs are also found in all other histological subtypes of OC (endometrioid, clear cell, LGS, mucinous, carcinosarcoma and 'other'). Therefore, limiting genetic predisposition testing to HGSOC patients will likely be insufficient to identify all patients with an underlying germline pathogenic variant.

The overall estimated probability of finding a germline *BRCA1/2* PV in OC patients (16.8%, 95% CI 14.8 to 19.2) seemed somewhat higher than reported in a previous systematic review (12.7%, 95% CI 9.5 to 15.9) [6]. Importantly, proportions of germline *BRCA1/2* PVs differed substantially among included studies. The differences could not be explained by ethnicity, since subgroup analysis revealed no difference between Asian (predominantly Asian ethnicity) and European/American countries (predominantly Caucasian ethnicity). This suggests differences are caused by more specific characteristics of the included populations. Outliers were screened and we identified potential explanations: variation in the presence of founder mutations [40] (e.g.

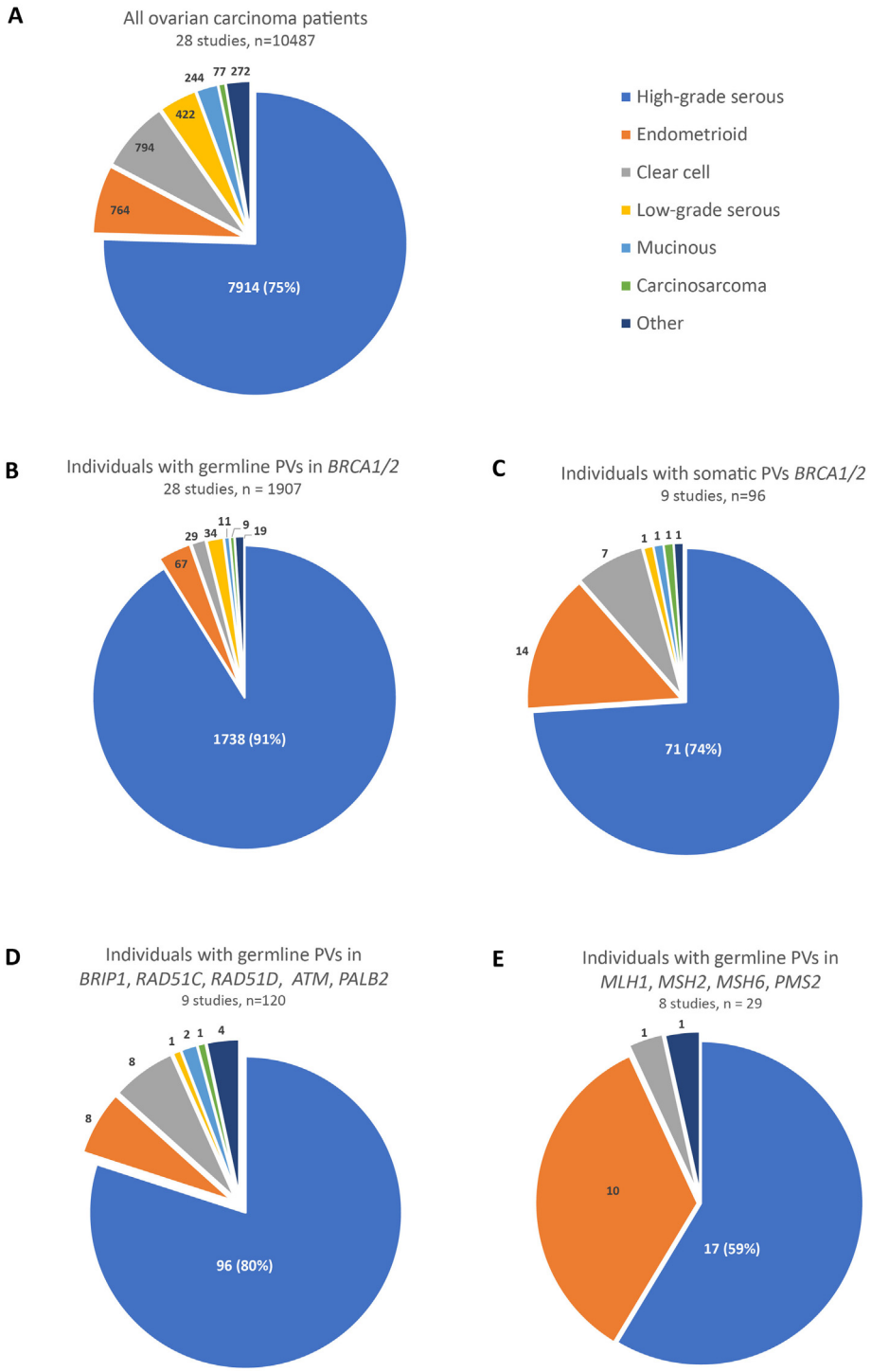

Fig. 3. Pie-charts representing the presence of histological subtypes in all ovarian carcinoma patients (A), patients with germline *BRCA1/2* PV (B), patients with somatic *BRCA1/2* PV (C), patients with germline PV in *BRIP1, RAD51C, RAD51D, PALB2* and *ATM* (D) and patients with germline PV in *MLH1, MSH2, MSH6, PMS2* (E). This excludes the presence of the following histological subtypes: ovarian carcinoma not specified, adenocarcinoma not specified, serous not specified, borderline & unknown (excluded: A $n = 864$, B $n = 198$, C $n = 2$, D $n = 41$, E $n = 6$).

presence of Ashkenazi Jews in population), variation in histological subtypes included and classification criteria used [46,48], and variation in the testing and prevention program (i.e. risk reducing surgeries) of various countries [6,26,49]. Unfortunately, as there were no non-European/American/Asian studies identified during our search, we are uncertain if our results apply to other populations. Furthermore, germline *BRCA1* PVs were more frequently observed than germline *BRCA2* PVs, probably related to the overall lifetime risk of developing OC that is more than twice as high for women with a *BRCA1* PV than for those with a *BRCA2* PV [52,53]. Somatic (non-germline) *BRCA1* and *BRCA2* PVs were present in comparable proportions, detected with a total estimate proportion of approximately 6% in all histological subtypes.

Our result that *BRCA1/2* PVs were detected in patients having endometrioid OC, clear cell OC, LGSOC, or mucinous OCs does not fit

Table 2
Meta-analyses of proportion germline *BRCA1/2* PVs per histological subtype of OC.

Histology	Number of studies	Positive	Total	Pooled proportion (%)	95% CI (%)	Prediction Interval (%)[a]	Hetero-geneity (I^2)	Numbers needed to test to find 1 PV (95% CI)
High-grade serous	28	1738	7914	22.2	19.6 to 25.0	11.6 to 38.2	88%	5 (4 to 6)
Carcinosarcoma	10	9	77	11.9	5.8 to 22.6	3.6 to 32.3	0%	9 (5 to 18)
Endometrioid	27	67	764	5.8	3.3 to 9.9	1.0 to 26.8	0%	18 (11 to 31)
Low-grade serous	23	34	422	5.2	2.3 to 11.3	0.8 to 27.0	0%	20 (9 to 44)
Clear cell	27	29	794	3.0	1.6 to 5.6	0.0 to 48.4	17%	34 (18 to 63)
Mucinous	17	11	244	2.5	0.6 to 9.6	0.1 to 31.4	0%	40 (11 to 167)
Other	25	19	272	7.0	4.5 to 10.7	4.4 to 10.9	0%	15 (10 to 23)

[a] Prediction interval reflects the range in which proportions are expected to be found in future research.

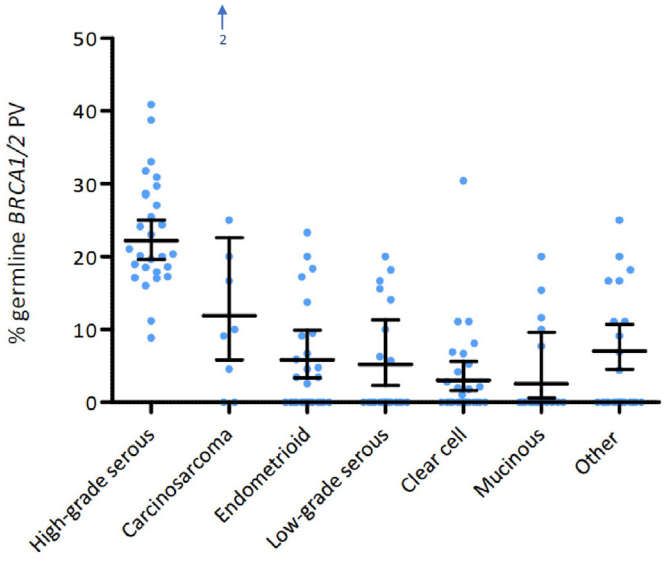

Fig. 4. Meta-analysis of pooled proportion of germline *BRCA1/2* PVs per histological subtype of ovarian carcinoma. The pooled proportion including 95%CI is presented, and individual study results.

within the classical hypothesis of the origin of these carcinomas. Endometrioid and clear cell OCs are thought to develop from endometriosis [54], whereas LGSOCs are thought to develop from cystadenomas or tubal lesions [55], and mucinous OCs are thought to develop from Brenner tumors or teratomas [56]. The development of non-HGSOC in women with *BRCA1/2* PV suggests another carcinogenic pathway, but precursor lesions of these histological subtypes are not known to be more frequently observed during prophylactic RRSO in women with *BRCA1/2* PV. In addition, the identification of germline *BRCA1/2* PVs in these patients does not necessarily indicate a causal relationship with tumor development. However because the incidence of *BRCA1/2* PV is higher than in the general population, the results of our meta-analysis challenge the hypothesis that germline *BRCA1/2* are exclusively related to HGSOC.

We should however take into account the potential risk of misclassification of histological subtypes and its influence on our results. Seven of our included studies had performed pathological revision, and in these specific studies *BRCA1/2* PVs were identified in non-HGS OC as well. However, it is impossible to reliably evaluate quality of pathological assessment in a literature review, as this measure is partly subjective depending on experience of pathologist and histological criteria used which are both seldomly reported. We included studies published after 2015 as the WHO2014 OC histological classification system is demonstrated to be more reproducible compared to previous systems [15], but patient inclusion and pathological assessment were sometimes performed before 2014. In addition, studies rarely indicated which classification system was used and whether immunohistochemistry was used to support histologic classification. Therefore, when interpreting our results, one should consider that these resemble evidence from most recent literature, but they do not represent the most recent diagnostic criteria. Prospectively investigating the effect of assessing histology by experienced gynecological pathologists on the probability of detecting *BRCA1/2* PVs in non-HGSOC would be essential in future research.

The presence of germline *BRCA1/2* PVs in patients having non-HGSOC clearly requires additional investigation to elucidate true presence (and potential carcinogenic pathway) or misclassification. The rarity of some non-HGS histological subtypes will likely complicate this investigation. Our meta-analysis was limited by the rarity of some non-HGSOC as well. We demonstrated that *BRCA1/2* PVs were detected the least frequent in mucinous OC. However, conclusions on this data should be interpreted with caution as several studies (8 out of 28) specifically excluded mucinous OC. Because of scarce data of some histological subtypes, we used a GLMM meta-analysis model to estimate all pooled proportions. This model has been recommended as good alternative for conventional two-step methods [20,57]. The sensitivity of our model was assessed by removing studies one-by-one, which demonstrated that the probability of detecting a germline *BRCA1/2* PV was more uncertain in patients having non-HGSOC (specifically carcinosarcoma OC, LGSOC and mucinous OC) compared to patients having HGSOC. This is also visible from the wide confidence intervals. Future research on the presence of germline *BRCA1/2* PVs in patients with non-HGSOC should consider their power and sample size to detect variants in these histological subtypes.

Additionally, as wider panels are expected to become increasingly common because of decreasing costs, assessment of the added clinical value of expanding the *BRCA1/2* test panel to include moderate risk genes for OC is important. In comparison to *BRCA1* and *BRCA2*, the detected proportions of germline PVs were considerably lower in *BRIP1* (0.9%), *RAD51C* (0.8%), *RAD51D* (0.7%), *PALB2* (0.6%), *ATM* (0.3%), *MLH1* (0.2%), *MSH2* (0.2%), *MSH6* (0.3%), and *PMS2* (0.2%). Noticeably, our systematic search did not focus on identification of these articles specifically. Previous studies have more elaborately investigated presence and cancer risks of germline PVs in these genes [4,58]. Besides testing for *BRCA1/2*, we encourage testing all patients with OC for germline PVs in *RAD51C*, *RAD51D, BRIP1* and *PALB2*, and where possible also *ATM.* However, testing all OC patients for *MLH1*, *MSH2*, *MSH6* and *PMS2* is debatable given the rare occurrences and the fact that testing for *MLH1*, *MSH2*, *MSH6* and *PMS2* can be restricted to those with additional reasons to do so, for example a family history with Lynch syndrome associated cancers [59,60], or endometrioid OC (which has been associated to mismatch repair deficiency and Lynch syndrome [61,62]).

In conclusion, germline *BRCA1/2* PVs are being detected in all histological subtypes of OC, and most frequently in HGSOC. Limiting genetic predisposition testing to HGSOC will likely be inadequate to identify all patients with an underlying germline pathogenic variant. Future research (e.g. focusing on cost-effectiveness) might shed new light on the issue. However, based on current literature, we strongly encourage

to test all OC patients for germline *BRCA1/2* PVs, irrespective of their histological subtype. These considerations will contribute to optimize recognition of heredity in ovarian carcinoma patients.

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Author contributions

All authors critically revised the manuscript and provided final approval of the version to be published. VW and MvB performed data collection and wrote the original draft of the manuscript. VW, MvB and JV were involved in analyzing the data. VW, MvB, ML, TB and NH contributed to the study design and data interpretation. NH supervised the study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.10.072.

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