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Long-term outcome of high-grade serous carcinoma established in risk-reducing salpingo-oophorectomy specimens in asymptomatic *BRCA1/2* germline pathogenic variant carriers

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HIGHLIGHTS

- Three-quarters of the asymptomatic *BRCA1/2* GPV carriers with HGSC at RRSO had early stage disease.
- The ten-year disease-free survival was 68%, ten-year disease-specific survival was 88% and ten-year overall-survival was 82%.
- After a median follow-up of 13.5 years, recurrence rate was 32% with median time to recurrence of 6.9 years (range 0.8–9.2).
- Timely RRSO remains the only reliable method of reducing mortality of HGSC in *BRCA1/2* GPV carriers.

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ABSTRACT

Objective. The aim of this study was to describe the long-term outcome of asymptomatic *BRCA1/2* germline pathogenic variant (GPV) carriers with high-grade serous carcinoma (HGSC) in their risk-reducing salpingo-oophorectomy (RRSO) specimen.

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Methods. In a previously described cohort of asymptomatic *BRCA1/2* GPV carriers derived from the Hereditary Breast and Ovarian cancer in the Netherlands (HEBON) study, women with HGSC at RRSO were identified. Main outcome was ten-year disease-free survival (DFS). Secondary outcomes were time to recurrence, ten-year disease-specific survival (DSS), ten-year overall survival (OS). Patient, disease and treatment characteristics associated with recurrence were described.

Results. The 28 included women with HGSC at RRSO were diagnosed at a median age of 55.3 years (range: 33.5–74.3). After staging, eighteen women had (FIGO) stage I, three stage II and five had stage III disease. Two women did not undergo surgical staging and were classified as unknown stage. After a median follow-up of 13.5 years (range: 9.1–24.7), six women with stage I (33%), one woman with stage II (33%), two women with stage III (40%) and none of the women with unknown stage developed a recurrence. Median time to recurrence was 6.9 years (range: 0.8–9.2 years). Ten-year DFS was 68%, ten-year DSS was 88% and ten-year OS was 82%.

Conclusion. Most asymptomatic *BRCA1/2* GPV carriers with HGSC at RRSO were diagnosed at an early stage. Nevertheless, after a median follow-up of 13.5 years, nine of the 28 women with HGSC at RRSO developed a recurrence after a median of 6.9 years.

1. Introduction

Women carrying a germline pathogenic variant (GPV) in one of the *BRCA1/2* genes (i.e. *BRCA1/2* GPV carriers) have an increased risk of developing high-grade serous carcinoma (HGSC). The origin of the disease is thought to be the distal fallopian tube, with serous tubal intraepithelial carcinoma (STIC) as its most probable precursor. HGSC generally remains asymptomatic until it is disseminated intra-abdominally [1] and therefore 80% of all HGSC patients are diagnosed at an advanced stage with a poor five-year survival of less than 40% [2]. The cumulative risk of developing HGSC before the age of 70 is 40–44% for *BRCA1* GPV carriers and 17–18% for *BRCA2* GPV carriers [3]. Annual gynecological screening proved ineffective in detecting early stage HGSCs and is therefore no longer offered [4]. To effectively reduce mortality of HGSC, *BRCA1/2* GPV carriers are advised to undergo risk-reducing salpingo-oophorectomy (RRSO) before the age at which the risk of developing HGSC starts to rise (i.e. 35–40 years for *BRCA1* GPV and 40–45 years for *BRCA2* GPV) [3,5].

In a small proportion of women undergoing RRSO, however, HGSC is found during histological examination of the removed tissue. In our recent study, we reported asymptomatic HGSC at RRSO in 24 (1.5%) of the 1627 asymptomatic *BRCA1* GPV carriers and six (0.6%) of the 930 *BRCA2* GPV carriers [6]. Previous studies on the outcome of HGSC at RRSO showed that these tumors, when found in asymptomatic women, are more often in an early stage, indicative of a good prognosis [7–10]. Still, in two observational studies, in more than half of women with HGSC at RRSO, the disease recurred within three years despite being diagnosed at an early stage [11,12]. As disease recurrence is one of the most important predictors of HGSC-related death [13], this suggests that the prognosis for women with HGSC at RRSO may be less favorable than expected. To help guide clinical management and provide patients with more accurate information on prognosis, we aimed to describe long-term outcome in asymptomatic *BRCA1/2* GPV carriers in whom HGSC was diagnosed in the RRSO specimen.

2. Methods

2.1. Context of the study

For a detailed analysis of the prevalence of HGSC at RRSO in asymptomatic *BRCA1/2* GPV carriers, we have constructed a cohort of female Dutch *BRCA1/2* GPV carriers who were registered in the Hereditary Breast and Ovarian cancer in the Netherlands (HEBON) study, and who had a RRSO between 1995 and 2018 while being asymptomatic [14]. We previously described the selection process for this cohort of asymptomatic *BRCA1/2* GPV carriers who underwent RRSO, the characteristics of this cohort and how women with HGSC at RRSO were identified within this group [6]. In short, we ensured that all 2557 included women had a complete RRSO (i.e. both fallopian tubes and both ovaries were removed). Then, we assessed whether the RRSO was prophylactic (i.e. absence of pre-operative signs and symptoms of ovarian cancer). This was done by retrieval of information from HEBON study and by retrieval of all pathology reports of the RRSOs by linkage with the Dutch Nationwide Pathology Databank (PALGA) [15]. Based on this information, women were excluded if RRSO was incomplete, if no pathology report could be retrieved, if symptoms related to ovarian cancer were present pre-operatively or if pre-operative screening with CA125 and/or transvaginal ultrasound was abnormal. The HEBON study was approved by all ethical committees of particpating centers. All women gave informed consent for the use of their data.

2.2. Study population

In this study, we aimed to describe the long-term outcome of asymptomatic *BRCA1/2* GPV carriers with HGSC at RRSO. To achieve this, we performed a follow-up analysis of the asymptomatic *BRCA1/2* GPV carriers with HGSC at RRSO identified in the aforementioned study [6]. Two women were diagnosed retrospectively only by histopathological revision of the RRSO specimen in study setting [6]. Therefore, they did not meet the inclusion criterion and were excluded for the current study. In Supplementary methods 1, the immunohistochemistry protocol that was used in the histopathological review procedure is described. HGSC was defined as an invasive cancer that met the morphological and immunohistochemical profile as defined in the 2014 WHO classification [16].

2.3. Data collection

For the previous study [6], data on *BRCA* GPV type, date of birth, date of RRSO and diagnosis of invasive carcinoma at RRSO were collected from the HEBON cohort and pathology reports. For the current study, we additionally collected data from medical records including: results of CA125 and/or transvaginal ultrasound before RRSO, staging procedures, International Federation of Gynecology and Obstetrics (FIGO) stage, (completeness of) surgical staging, (completeness of) cytoreductive procedures, chemotherapy and date of recurrence. Complete surgical staging was defined as: collection of peritoneal fluid for cytology, an infracolic omentectomy, sampling of para-aortal, parailiac and obturator lymph nodes and biopsies of peritoneum of bladder, Douglas pouch, paracolic recesses (bilateral) and diaphragm (bilateral). Cytoreductive surgery was considered complete if all macroscopic tumor was removed. Furthermore, vital status and date of death was retrieved from the Dutch personal records database (last retrieval on

October 18, 2022). Last date of follow-up from medical records was July 7, 2022.

2.4. Study outcomes

Main outcome was ten-year disease-free survival (DFS). DFS was calculated as time from RRSO to date of first recurrence (defined as radiologic or histologic confirmation of disease progression in peritoneal cavity) with censoring at the last date of follow-up from medical records or at date of death. Secondary outcomes were time to recurrence (calculated as the time from date of RRSO to date of first recurrence), ten-year disease-specific survival (DSS) (calculated as time from RRSO to date of death from HGSC, with censoring at date of death of another cause than HGSC or at last date of known vital status) and ten-year overall survival (OS) (calculated as time from RRSO to date of death, with censoring at last date of known vital status). Lastly, we assessed patient, disease and treatment factors associated with an unfavorable prognosis. For this assessment, unfavorable outcome was defined as the development of a recurrence.

2.5. Statistical analysis

Patient characteristics at baseline were described with frequencies and percentages for categorical data, and with median and range for continuous data. Ten-year DFS, DSS and OS were calculated using the Kaplan-Meier method. To evaluate factors associated with the development of a recurrence, Kaplan-Meier curves of DFS were created and stratified for age at RRSO, FIGO stage, treatment after RRSO and *BRCA* GPV type. Women with FIGO stage I and FIGO stage II are classified as early stage, women with FIGO stage III as advanced stage. Due to the small number of cases, only descriptive data analysis could be used and no statistical testing was applied. Data analyses were performed using IBM SPSS statistics version 28.0 for Windows (IBM corp., Armonk, NY, USA).

3. Results

3.1. Patient characteristics

After exclusion of two women in whom HGSC was diagnosed in hindsight at pathology review [6], a total of 28 asymptomatic *BRCA1/2* GPV carriers with HGSC at RRSO could be included in this study (Fig. 1). In total, 22 women carried a *BRCA1* GPV and six a *BRCA2* GPV. Of the 28 women, 24 (86%) underwent their RRSO after the advised age. The median age at RRSO of women was 55.3 years (range: 33.5–74.3 years): *BRCA1* GPV carriers had a median age of 51.7 years (range: 33.5–70.6 years), *BRCA2* GPV carriers had a median age of 63.2 years (range: 44.6–74.3 years) (Table 1).

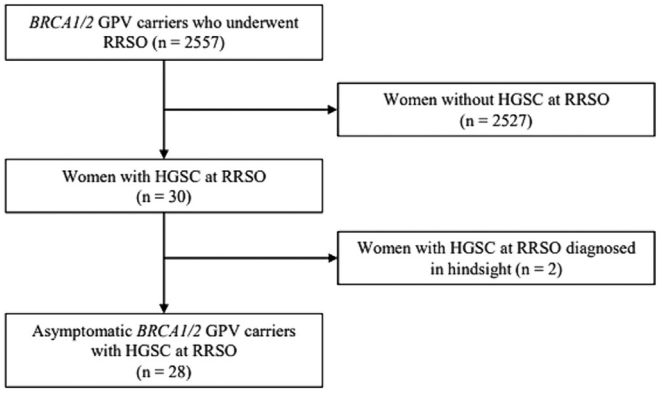

Fig. 1. Flow diagram of patient selection.
Abbreviations: *BRCA* = breast cancer susceptibility gene; GPV = germline pathogenic variant; RRSO = risk-reducing salpingo-oophorectomy; HGSC = high-grade serous carcinoma.

Of the identified 28 patients, 26 women underwent additional surgical staging after RRSO, resulting in diagnosis of FIGO stage I in eighteen patients, FIGO stage II in three patients and FIGO stage III in five patients. The FIGO stage of the other two patients was classified as unknown because these women did not undergo surgical staging, but received six cycles of chemotherapy with carboplatin and paclitaxel. In total, sixteen patients received chemotherapy: seven with FIGO stage I, all with FIGO stage II and III and two with unknown stage. Of the seven women with FIGO stage I who received chemotherapy, three had FIGO stage IA, one had FIGO stage IB and three had FIGO stage IC. Of the twelve women who did not receive chemotherapy, ten had FIGO stage IA and two had FIGO stage IC. For a detailed description of patient and treatment characteristics of all 28 cases with HGSC at RRSO, see Supplementary table 2.

3.2. Follow-up and survival

Follow-up and survival of the 28 women with HGSC at RRSO are shown in Table 2. Median follow-up was 13.5 years (range: 9.1–24.7 years): 13.3 years (range: 9.3–24.7 years) for *BRCA1* GPV carriers and 14.2 years (range: 9.1–21.3 years) for *BRCA2* GPV carriers. At the end of follow-up, nine of the 28 patients (32%) had developed a recurrence. Median time to recurrence was 6.9 years (range: 0.8–9.2 years). In total, six of the eighteen women (33%) with FIGO stage I, one of the three women (33%) with FIGO stage II, two of the five women (40%) with FIGO stage III and none of the women with unknown stage developed a recurrence. In total, nine women died, including six women who died due to HGSC. Ten-year DFS was 68% (95% CI:

Table 1
Patient, disease and treatment characteristics of 28 asymptomatic *BRCA1/2* GPV carriers diagnosed with HGSC at RRSO.

	n / median	% / range
Median age at time of RRSO, years	55.3	33.5–74.3
GPV type		
BRCA1 GPV	22	79
BRCA2 GPV	6	21
FIGO stage		
I	18	64
II	3	11
III	5	18
Unknown[1]	2	7
Surgery after RRSO		
Staging surgery	22	79
Incomplete[2]	2	9
Complete	20	91
Cytoreductive surgery	4	14
Incomplete (tumor residual)	0	–
Complete (no tumor residual)	4	100
No surgery	2	7
Chemotherapy		
No	12	43
Yes	16	57
Adjuvant chemotherapy	13	81
Neoadjuvant chemotherapy[3]	1	5
Chemotherapy as only treatment	2	13

Abbreviations: *BRCA* = breast cancer susceptibility gene; GPV = germline pathogenic variant; HGSC = high-grade serous carcinoma; RRSO = risk-reducing salpingo-oophorectomy; FIGO = International Federation of Gynecology and Obstetrics.
[1] Two women did not undergo surgical staging but received chemotherapy as primary treatment.
[2] Reason for incomplete surgical staging: no biopsies of peritoneum ($n = 1$), no lymphadenectomy (n = 1). Four women underwent a complete surgical staging procedure without hysterectomy; this was nevertheless classified as complete surgical staging.
[3] Because of a simultaneously diagnosed metastatic recurrence of breast cancer, this patient first underwent four cycles of chemotherapy, before undergoing an interval cytoreductive surgery. After this debulking surgery, she received another two cycles of chemotherapy.

Table 2
Follow-up of 28 asymptomatic *BRCA1/2* GPV carriers diagnosed with HGSC at RRSO.

Follow-up	
Median, years (range)	13.5 (9.1–24.7)
Recurrence	
Yes, n	9
FIGO stage I, n (%)	6 (33)
FIGO stage II, n (%)	1 (33)
FIGO stage III, n (%)	2 (40)
No, n	19
FIGO stage I, n (%)	12 (67)
FIGO stage II, n (%)	2 (67)
FIGO stage III, n (%)	3 (60)
Unknown, n (%)	2 (100)
Time to recurrence	
Median time to recurrence, years (range)	6.9 (0.8–9.2)
Patient status at last moment of follow-up,n	
Alive	19
NED	17
AWD	2
Deceased	9
Death of disease	6
Death of other malignancy	2
Death, cause unknown	1
10-year DFS, % (95% CI)	68 (51–85)
10-year DSS, % (95% CI)	89 (77–100)
10-year OS, % (95% CI)	82 (69–95)

Abbreviations: RRSO = risk-reducing salpingo-oophorectomy; *BRCA* = breast cancer susceptibility gene; GPV = germline pathogenic variant; HGSC = high-grade serous carcinoma; NED = no evidence of disease; AWD = alive with disease; DFS = disease-free survival; DSS = disease-specific survival; OS = overall survival; CI = confidence interval.

51–85%), ten-year DSS was 88% (95% CI: 77–100%) and ten-year OS was 82% (95% CI: 69–95%). DFS curves stratified by patient, clinical and treatment characteristics are presented in Fig. 2.

4. Discussion

The aim of this study was to describe the long-term outcome of asymptomatic *BRCA1/2* GPV carriers diagnosed with HGSC at RRSO. In this series of 28 asymptomatic *BRCA1/2* GPV carriers with HGSC in the RRSO specimen, the majority of the tumors were found at an early stage and most women had a favorable survival with a 10-year OS of 82%. However, after a median follow-up time of 13.5 years, nine of the 28 women had developed a recurrence. Median time to recurrence was 6.9 years with a wide range of time to recurrence from 0.8 to 9.2 years.

Several studies have analyzed the survival of *BRCA1/2* GPV carriers diagnosed with 'ovarian cancer' at RRSO. Cowan et al. reported a five-year DFS of 72% and a five-year DSS of 96% in 26 asymptomatic *BRCA1/2* GPV carriers with 'incidentally detected' HGSC at RRSO after a median follow-up of 5.6 years [9]. In their study, all 26 patients underwent complete surgical staging. Kotsopolous et al. reported a ten-year OS of 74% for 52 *BRCA1/2* GPV carriers with cancer at RRSO after a mean follow-up period of 6.8 years [10]. However, detailed information regarding tumor histology, pre-operative screening, surgical staging, disease stage, and recurrences was not presented in their study. In another study by Powell et al. [17], a recurrence rate of 47% after a median follow-up of 7.3 years was reported for 15 *BRCA1/2* GPV carriers with 'unsuspected invasive neoplasia' at RRSO. However, women with symptoms were not explicitly excluded. Therefore, their study is not entirely comparable to our study. Overall, a direct comparison between our results and those of previous studies is difficult to make due to the considerably shorter follow-up time and the lack of detailed information in those studies. Yet, our results regarding survival are more or less comparable to the studies by Cowan et al. and Kotsopolous et al. [9,10]. We hypothesize that the relatively favorable survival observed in the majority of the women included in our study is the result of the high number of women with correctly staged early stage disease combined with the careful selection of asymptomatic *BRCA1/2* GPV carriers. In addition, the improvement in the treatment of HGSC over time with the introduction of PARP inhibitors in the last decade, especially in *BRCA* mutant patients [18], could provide another explanation.

Nevertheless, nine of the 28 women included in our study developed a recurrence, in some women many years after the initial diagnosis. Our recurrence rate of 32% in women with early stage HGSC is similar to what other studies observed in women with incident, early stage HGSC [19,20]. Our results indicate that even women with early stage disease are at risk of developing a recurrence. Especially the late recurrences in women with early stage HGSC strongly suggests that tumor cells may have exfoliated and disseminated throughout the abdominal cavity at an early stage of the disease, even if the tumor seems to be confined to the fallopian tube. Although it is difficult to determine the origin of such cells, it can be assumed that these exfoliated HGSC tumor cells remained in the abdominal cavity, after surgery. These cells could eventually give rise to a recurrence in the abdominal cavity, as has been suggested for carcinogenesis of HGSC after a diagnosis of isolated STIC [21].

Furthermore, we observed that the recurrence rate in our study did not vary between women with early or advanced stage HGSC, respectively 33% and 40%. In comparison, Cowan et al. [9] described a considerably lower recurrence rate of 11% in a total of eighteen women with early stage HGSC, whereas the recurrence rate in the eight women with advanced stage disease was 75%. This difference in recurrence rate for women with early stage HGSC between the study of Cowan et al. [9] and our study could possibly be explained by the small sample size of both studies, which can cause quite a variation in outcomes. Another explanation could lie in the fact that, compared with the study by Cowan et al., in our study a lower percentage of women with early stage disease received chemotherapy (47% as compared to 89%) [9]. According to the Dutch guidelines, adjuvant chemotherapy is indicated from completely staged FIGO stage IIb and onwards [22], as there is no strong evidence for improved survival after adjuvant chemotherapy in FIGO stage I after complete surgical staging [19,20]. Furthermore, the considerably shorter follow-up time in the study by Cowan et al. [9] may explain the difference in recurrence rate. Since we demonstrated that women with HGSC at RRSO can develop a recurrence many years after the initial diagnosis, it can be hypothesized that the follow-up time of Cowan et al. was too short to detect all recurrences in their study population. We additionally observed that carrying a *BRCA2* GPV was associated with a higher risk to develop a recurrence, but this is most likely the result of the small number of *BRCA2* GPV carriers included in this study.

Of the 28 women who had HGSC at RRSO, 86% underwent the RRSO after the recommended age. This emphasizes that timely RRSO is crucial in preventing HGSC in *BRCA1/2* GPV carriers. This is closely related to timely DNA testing, the importance of which we also emphasize. In the recent years, many efforts have been made to improve testing for *BRCA1/2* GPVs, such as offering testing to all women with ovarian cancer and implementing tumor testing for somatic *BRCA1/2* PVs [23]. In addition, barriers in genetic *BRCA1/2* testing have been identified [24], but more action is needed to further improve early detection of BRCA1/2 GPVs to take timely preventive measures.

The main strength of our study is the long follow-up period, which is to our knowledge the longest to date for asymptomatic *BRCA1/2* GPV carriers diagnosed with HGSC at RRSO. Another strength of our study is the complete and detailed description of clinical data of one of the largest series of *BRCA1/2* GPV carriers with HGSC at RRSO.

Our study also had some limitations. The sample size restricted us to descriptive data analysis and no definite conclusions could be drawn. The low sample size is explained by the low prevalence of HGSC at RRSO in the large cohort of asymptomatic *BRCA1/2* GPV, resulting in identification of a relatively small number of women with asymptomatic HGSC at RRSO. Furthermore, the retrospective nature of our study could have influenced our results. Additionally, the relatively favorable survival observed in this study could be the result of lead-time bias, when comparing our results to survival data of women with incident

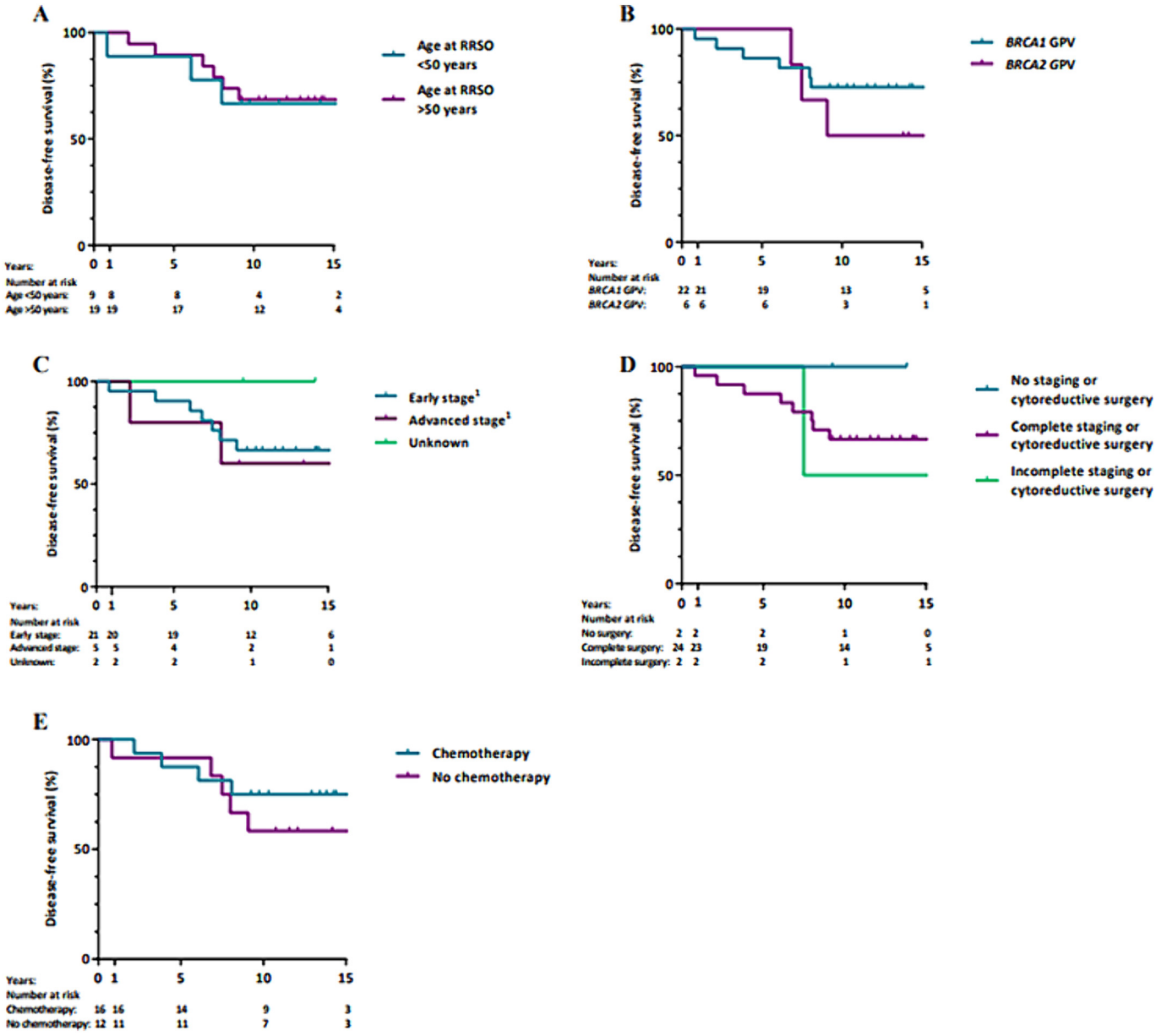

Fig. 2. Disease-free survival curves stratified for patient, disease and treatment characteristics.
[1] Early stage = FIGO stage I and FIGO stage II; Advanced stage = FIGO stage III.
Abbreviations: *BRCA* = breast cancer susceptibility gene; GPV = germline pathogenic variant; RRSO = risk-reducing salpingo-oophorectomy; FIGO = International Federation of Gynecological Oncology.

HGSC. Lastly, the date of the DNA test was unknown for three of the 28 women included. For them, it could not be determined with certainty whether the RRSO was performed before or after DNA testing for carrier status of a *BRCA1/2* GPV for these women. Because this might imply that they were symptomatic prior the RRSO, we collected clinical data on pre-operative symptoms from the medical records and were able to verify that all three were asymptomatic prior to the RRSO. The same was true for the other 25 women in whom the DNA test was performed prior to RRSO. Therefore, we assume that all RRSO were indeed prophylactic and that the unknown date of the DNA test in three women did not affect our results.

To conclude, most asymptomatic *BRCA1/2* GPV carriers with HGSC at RRSO were diagnosed with early stage HGSC, resulting in a favorable long-term survival for the majority. However, nine of the 28 included women developed a recurrence, in some cases more than nine years after the initial diagnosis. Since more than 85% of the women underwent RRSO after the advised age, our results underscore the need for earlier detection of *BRCA1/2* GPVs to take timely preventive measures, as RRSO before the age of 35–40 years for *BRCA1* GPV carriers and 40–45 years for *BRCA2* GPV carriers remains the only reliable method of preventing mortality of HGSC in *BRCA1/2* GPV carriers.

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CRediT authorship contribution statement

Iris A.S. Stroot: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Joost Bart:** Writing – review & editing, Writing – original draft, Resources, Formal analysis, Data curation. **Harry Hollema:** Writing – review & editing, Resources, Data curation. **Mathilde Jalving:** Writing – review & editing. **Refika Yigit:** Writing – review & editing. **Helena C. van Doorn:** Writing – review & editing. **Joanne A. de Hullu:** Writing – review & editing, Conceptualization. **Katja N. Gaarenstroom:** Writing – review & editing. **Marc van Beurden:** Writing – review & editing. **Luc R.C.W. van Lonkhuijzen:** Writing – review & editing. **Brigitte F.M. Slangen:** Writing – review & editing. **Ronald P. Zweemer:** Writing – review & editing. **Encarna B. Gómez Garcia:** Writing – review & editing, Resources. **Margreet G.E.M. Ausems:** Writing – review & editing, Resources. **Ingrid A. Boere:** Writing – review & editing, Resources. **Liselotte P. van Hest:** Writing – review & editing, Resources. **Floor A.M. Duijkers:** Writing – review & editing, Resources. **Christi J. Van Asperen:** Writing – review & editing, Resources. **Marjanka K. Schmidt:** Writing – review & editing, Resources. **Marijke R. Wevers:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Marielle W.G. Ruijs:** Writing – review & editing, Resources. **Peter Devilee:** Writing – review & editing, Resources. **J. Margriet Collée:** Writing – review & editing, Resources. **Geertruida H. de Bock:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Marian J.E. Mourits:** Writing – review & editing, Writing – original draft, Supervision, Resources, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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

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