High-grade serous carcinoma at risk-reducing salpingo-oophorectomy in asymptomatic carriers of BRCA1/2 pathogenic variants: prevalence and clinical factors

Stroot, I.A.S.; Brouwer, J.; Bart, J.; Hollema, H.; Stommel-Jenner, D.J.; Wagner, M.M.; ... ; HEBON Investigators

original reports

High-Grade Serous Carcinoma at Risk-Reducing Salpingo-Oophorectomy in Asymptomatic Carriers of *BRCA1/2* Pathogenic Variants: Prevalence and Clinical Factors

Iris A.S. Stroot, BSc[1,2]; Jan Brouwer, BSc[1]; Joost Bart, MD, PhD[3]; Harry Hollema, MD, PhD[3]; Denise J. Stommel-Jenner, MSc[4]; Marise M. Wagner, MD, PhD[1]; Helena C. van Doorn, MD, PhD[5]; Joanne A. de Hullu, MD, PhD[6]; Katja N. Gaarenstroom, MD, PhD[7]; Marc Beurden, MD, PhD[8]; Luc R.C.W. van Lonkhuijzen, MD, PhD[9]; Brigitte F.M. Slangen, MD, PhD[10]; Ronald P. Zweemer, MD, PhD[11]; Encarna B. Gómez Garcia, MD, PhD[12]; Margreet G.E.M. Ausems, MD, PhD[13]; Ingrid A. Boere, MD, PhD[14]; Klaartje van Engelen, MD, PhD[15]; Christi J. van Asperen, MD, PhD[16]; Marjanka K. Schmidt, PhD[4,16,17]; Marijke R. Wevers, MD, PhD[18]; Geertruida H. de Bock, PhD[2]; and Marian J.E. Mourits, MD, PhD[1,19]; on behalf of the HEBON Investigators

abstract

PURPOSE To investigate the prevalence of and clinical factors associated with high-grade serous carcinoma (HGSC) at risk-reducing salpingo-oophorectomy (RRSO) in asymptomatic *BRCA1/2*-pathogenic variant (PV) carriers.

PATIENTS AND METHODS We included *BRCA1/2*-PV carriers who underwent RRSO between 1995 and 2018 from the Hereditary Breast and Ovarian cancer in the Netherlands study. All pathology reports were screened, and histopathology reviews were performed for RRSO specimens with epithelial abnormalities or where HGSC developed after normal RRSO. We then compared clinical characteristics, including parity and oral contraceptive pill (OCP) use, for women with and without HGSC at RRSO.

RESULTS Of the 2,557 included women, 1,624 had *BRCA1*, 930 had *BRCA2*, and three had both *BRCA1/2*-PV. The median age at RRSO was 43.0 years (range: 25.3-73.8) for *BRCA1*-PV and 46.8 years (27.6-77.9) for *BRCA2*-PV carriers. Histopathologic review confirmed 28 of 29 HGSCs and two further HGSCs from among 20 apparently normal RRSO specimens. Thus, 24 (1.5%) *BRCA1*-PV and 6 (0.6%) *BRCA2*-PV carriers had HGSC at RRSO, with the fallopian tube identified as the primary site in 73%. The prevalence of HGSC in women who underwent RRSO at the recommended age was 0.4%. Among *BRCA1/2*-PV carriers, older age at RRSO increased the risk of HGSC and long-term OCP use was protective.

CONCLUSION We detected HGSC in 1.5% (*BRCA1*-PV) and 0.6% (*BRCA2*-PV) of RRSO specimens from asymptomatic *BRCA1/2*-PV carriers. Consistent with the fallopian tube hypothesis, we found most lesions in the fallopian tube. Our results highlight the importance of timely RRSO with total removal and assessment of the fallopian tubes and show the protective effects of long-term OCP.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Carriers of *BRCA1* and *BRCA2* pathogenic variants (PVs) (ie, *BRCA1/2*-PV carriers) have an increased lifetime risk of developing ovarian cancer, which describes any cancer that begins in the cells of the ovaries or fallopian tubes. Indeed, estimates suggest cumulative risks of 40%–44% for *BRCA1*-PV carriers and 17%–18% for *BRCA2*-PV carriers.[1,2] The most diagnosed subtype in both wild-type and *BRCA1/2*-PV carriers, high-grade serous carcinoma (HGSC),[3] has a poor 5-year survival rate of just 30%–40%.[4] The fallopian tubes have only recently emerged as the primary site of HGSC,[5-7] with evidence that serous intraepithelial carcinoma (STIC) is a likely precursor.[8,9] Screening has proven to be ineffective for both early detection and improving survival, leading to the recommendation that *BRCA1/2*-PV carriers should undergo risk-reducing salpingo-oophorectomy (RRSO) before the risk of HGSC rises.[10,11] RRSO can reduce the risk of HGSC by up to 96% when performed at age 35-40 years for *BRCA1*-PV and age 40-45 years for *BRCA2*-PV carriers.[11,12]

Nevertheless, studies indicate that 0.6%-27% of RRSO specimens may already contain HGSC (Data Supplement, online only).[5,13-16] This broad range may result from differences in the age at RRSO, the exclusion of women with preoperative signs and symptoms, and the comprehensiveness of histopathologic analysis.[17-19] Research also

CONTEXT

Key Objective

What is the prevalence of high-grade serous carcinoma at risk-reducing salpingo-oophorectomy (RRSO) in asymptomatic *BRCA1/2* pathogenic variant (PV) carriers and what clinical factors are associated with this diagnosis?

Knowledge Generated

In total, 24 (1.5%) *BRCA1* and 6 (0.6%) *BRCA2* PV carriers had high-grade serous carcinoma at RRSO, with 73% of all tumors originating from the fallopian tube. Older age at RRSO was associated with an increased risk, whereas long-term oral contraceptive pill use was protective.

Relevance *(G. Fleming)*

To minimize ovarian cancer risk, RRSO should be performed at the recommended ages: Between 35 and 40 years for *BRCA1* PV carriers and generally between 40 and 45 years for *BRCA2* PV carriers unless age at diagnosis in other family members warrants surgery at a younger age.*

*Relevance section written by *JCO* Associate Editor Gini Fleming, MD.

suggests an increased risk of occult HGSC at RRSO among *BRCA1*-PV carriers and those with a prior diagnosis of breast cancer.[17,18,20] However, no research has thoroughly investigated the factors known to protect against ovarian cancer,[21] such as oral contraceptive pill (OCP) use and parity, in relation to the occurrence of HGSC at RRSO in *BRCA1/2*-PV carriers.

In this study, we aimed to assess the prevalence of HGSC in asymptomatic *BRCA1/2*-PV carriers undergoing RRSO and to evaluate the reproductive and clinical factors associated with HGSC at RRSO.

PATIENTS AND METHODS

Study Cohort

This study included women from the database of the prospective Hereditary Breast and Ovarian cancer in the Netherlands (HEBON) cohort study, which follows women at high risk of breast and/or ovarian cancer (Data Supplement).[22] The HEBON database benefits from regular linkage with the Pathological Anatomical National Automated Archive (PALGA), which since 1981, has covered 99% of all histopathology and cytopathology reports in the Netherlands.[23] The medical ethical committees of all participating centers approved the HEBON study, and the Institutional Review Board of the Netherlands Cancer Institute approved the present study.

For the current study, we identified *BRCA1/2*-PV carriers in the HEBON database who underwent RRSO between 1995 and 2018, only including women who gave informed consent for linkage with PALGA. The RRSO pathology files for adnexal surgery in PALGA were then requested and screened to confirm the prophylactic nature and completeness of surgery (ie, removal of both ovaries and fallopian tubes). We excluded women if they had no linkable pathology file, if the complete pathology file was missing, clinical symptoms of ovarian cancer before RRSO on the basis of the clinical information in the pathology report, elevated CA125 or abnormal transvaginal ultrasound results before RRSO, or if the salpingo-oophorectomy was incomplete. Dutch guidelines required the RRSO to be performed laparoscopically where possible.[24]

Histopathologic Review

RRSO specimens have increasingly been embedded according to the Sectioning and Extensively Examining the Fimbriated end of the fallopian tube protocol since its introduction in 2006.[25] One of two experienced gynecopathologists performed histopathologic review on the hematoxylin and eosin slides available from initial assessment. We reviewed RRSO specimens if they contained atypia or dysplasia without additional Ki-67 and p53 immunohistochemistry, if they contained invasive or in situ carcinoma (Data Supplement), and if the RRSO specimen was issued as normal and the woman later developed HGSC. To select these women, we reviewed all cases of peritoneal cancer after RRSO suspected for HGSC to identify the origin and histologic subtype of the cancer, applying immunohistochemistry with p53 and WT-1 when possible and not originally performed (Data Supplement). We did not review RRSO specimens when there were no abnormalities in the pathology report or no HGSC in the follow-up after RRSO.

As detailed in the Data Supplement, the reviews focused on the morphology on hematoxylin and eosin slides and additional immunohistochemistry markers to help detect HGSC or STIC. We defined HGSC according to the 2014 WHO classification as an invasive high-grade serous cancer of the ovary and/or fallopian tube with consistent morphology and immunohistochemistry (the majority showing a mutant staining pattern of p53, PAX-8, and WT-1 positivity, combined with Ber-Ep4 and p16 positivity).[26] STIC was defined as an intraepithelial lesion with consistent morphological

features, a mutant staining pattern of p53, and > 10% Ki-67 expression.[27,28]

Data Collection

We retrieved data on PV type, date of birth, breast cancer history, and the use of chemotherapy for breast cancer from the HEBON database. The self-reported HEBON questionnaire included family history of breast and/or ovarian cancer, ever use of OCP (≥ 1 year), length of OCP use, parity, history of breastfeeding (≥ 1 month), age at menarche, and menopausal status at RRSO. The questionnaire was administered retrospectively for women included before 2012 and prospectively for women included after 2012 (Data Supplement). Information was also collected from pathology reports, including RRSO date, past adnexal surgery, RRSO completeness, and total embedding of the RRSO specimen. If prior adnexal surgery had been performed, the date of the last surgery resulting in complete resection was used as the RRSO date.

Statistical Analysis

To assess the clinical and histopathologic characteristics of the study population, we stratified women by *BRCA1/2*-PV carriage and included those with both *BRCA1* and *BRCA2*-PVs in the *BRCA1*-PV group. Categorical data are presented as frequencies and percentages, and continuous data are presented as medians and ranges. To assess the impact of missing data for variables with > 20% missing data (ie, family history, OCP use, age at menarche, breastfeeding, parity, and menopausal status at RRSO), the known characteristics were compared between groups with complete and missing data. Furthermore, we assessed whether bias was introduced by excluding women with missing data in a complete case analysis. The prevalence of HGSC at RRSO was calculated with 95% CIs stratified by PV type and whether RRSO was performed within or after age recommendations (ie, age 35-40 years for *BRCA1*-PV and age 40-45 years for *BRCA2*-PV). The clinical characteristics of women with HGSC and normal findings at RRSO, again stratified by PV type, were compared by Mann–Whitney *U* tests, *t* tests, or chi-squared tests, as appropriate. For *BRCA1*-PV carriers, logistic regression analyses were applied to estimate the odds ratios (ORs) and 95% CIs for factors associated with HGSC diagnosis at RRSO. Variables were included in the multivariable analysis if the *P* value was ≤ .1 in the univariate analysis. We performed all data analyses in IBM SPSS version 23.0 for Windows (IBM Corp, Armonk, NY) and considered two-sided *P* values < .05 significant.

RESULTS

Characteristics of the Study Population

We included 2,557 of 2,780 women who underwent RRSO between 1995 and 2018 (Fig 1). Of these, 1,624 had a *BRCA1*-PV, 930 had a *BRCA2*-PV, and three had both (Table 1). At RRSO, the median age of *BRCA1*-PV and *BRCA2*-PV carriers was 43.0 years (range: 25.3-73.8) and 46.8 years (range: 27.6-77.9), respectively. Of note, 68.8% of *BRCA1*-PV carriers and 58.8% of *BRCA2*-PV carriers underwent RRSO when older than the recommended age, whereas 58.4% of *BRCA1*-PV carriers and 68.6% of *BRCA2*-PV carriers had ever used OCP. Women with missing data underwent RRSO more often in earlier years (Data Supplement), and those with missing family history or breastfeeding data had a lower risk of HGSC at RRSO (Data Supplement). In the earlier years, women undergoing RRSO were older and more often carried a *BRCA1*-PV, but otherwise, the groups were broadly comparable (Data Supplement).

Results of the Histopathologic Review

Figure 2 shows the results of the histopathologic review. Of the 29 RRSO specimens reported to have invasive carcinoma, one showed apparent Walthard cell rests, and we confirmed HGSC in 28 cases. None of the RRSO specimens with in situ carcinoma (n = 9) or with atypia or dysplasia (n = 63) showed HGSC. In total, 20 of the 30 reviewed peritoneal cancers were confirmed to be HGSC. Pathology review found a missed HGSC in two cases (two of 2,528; error rate, 0.08%). These peritoneal HGSCs can therefore be considered a recurrence of the missed HGSC in the RRSO specimen.

Prevalence of HGSC at RRSO

Histopathologic review confirmed that 30 of 2,557 asymptomatic *BRCA1/2*-PV carriers had HGSC at RRSO, corresponding to a prevalence of 1.2% (95% CI, 0.7 to 1.6) (Table 2). HGSC was present in 24 of the 1,627 *BRCA1*-PV carriers (1.5%; 95% CI, 0.9 to 2.1) and six of the 930 *BRCA2*-PV carriers (0.6%; 95% CI, 0.1 to 1.1). The prevalence of HGSC was 0.4% (95% CI, 0.1 to 0.8) for the 891 women who underwent RRSO at the recommended age: three of 508 *BRCA1*-PV carriers (0.6%; 95% CI, 0.0 to 1.3) and one of 382 *BRCA2*-PV carriers (0.3%; 95% CI, 0.0 to 0.7). The prevalence of HGSC was 1.5% (95% CI, 0.9 to 2.1) for the 1,667 women who underwent RRSO after the recommended age: 21 of 1,119 *BRCA1*-PV carriers (1.8%; 95% CI, 1.0 to 2.6) and five of 548 *BRCA2*-PV carriers (0.9%; 95% CI, 0.1 to 1.7).

The fallopian tubes were the primary location of HGSC in 22 of the 30 asymptomatic *BRCA1/2*-PV carriers (73.3%): 17 in the fallopian tubes only and five in both the ovaries and fallopian tubes. HGSC lesions predominantly appeared in the distal fallopian tubes or fimbriae and were detected exclusively in the ovaries of eight women (all underwent RRSO after the recommended age; median 54.7 years). The pathology reports of three of these women revealed inadequate sampling of the fallopian tubes.

Sixteen women had concurrent STIC and HGSC in the fallopian tubes. However, concurrent STIC was not found in the samples of women with HGSC limited to the ovaries. No women had evidence of ovarian intraepithelial lesion (Table 2).

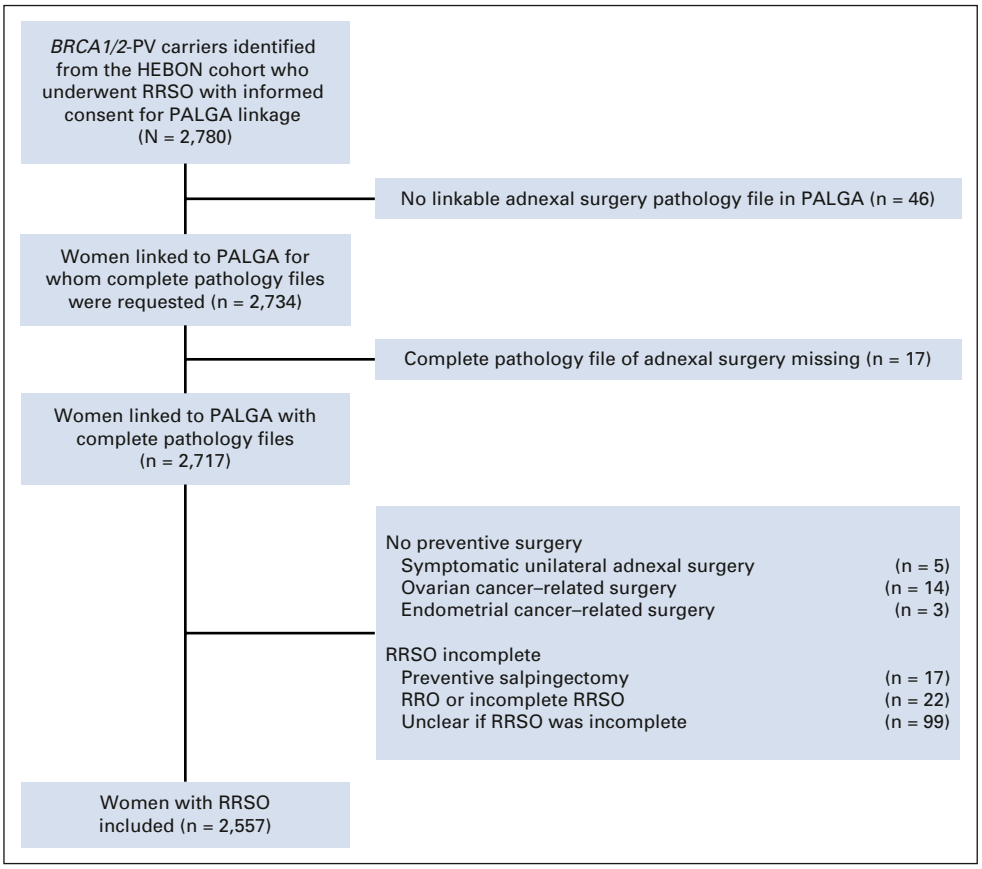

FIG 1. Inclusion of asymptomatic *BRCA1/2*-PV carriers who underwent RRSO. *BRCA*, breast cancer susceptibility gene; HEBON, Hereditary Breast and Ovarian cancer in the Netherlands study; PALGA, Pathological Anatomical National Automated Archive (the Dutch Pathology Registry); PV, pathogenic variant; RRO, risk-reducing oophorectomy; RRSO, risk-reducing salpingo-oophorectomy.

Risk Factors for HGSC at RRSO

Women with HGSC at RRSO were significantly older than those without, for both *BRCA1*-PV (52.6 *v* 43.2 years, $P < .001$; OR, 1.09 per year; 95% CI, 1.04 to 1.14) and *BRCA2*-PV (63.2 *v* 47.3 years, $P < .01$) (Tables 3 and 4). In the *BRCA1*-PV group, significantly more women with HGSC at RRSO reported never using OCPs (16.7% *v* 4.4%, $P = .02$; OR, 0.27; 95% CI, 0.09 to 0.84). Compared with *BRCA1/2*-PV carriers without HGSC at RRSO, those with HGSC had used OCPs for significantly shorter median times (*BRCA1*-PV: 8 *v* 12 years, $P = .001$; OR, 0.89 per year; 95% CI, 0.82 to 0.96; *BRCA2*-PV: 5 *v* 12 years, $P = .04$). No other factors reached statistical significance (Tables 3 and 4).

Concerning the risk of HGSC at RRSO, the inclusion of age, length of OCP use, and embedding of RRSO specimens in a multivariable model revealed that the risk of HGSC increased significantly as age increased (OR, 1.07 per year; 95% CI, 1.02 to 1.12) and risk fell significantly as the length of OCP use increased (OR, 0.91 per year; 95% CI, 0.84 to 0.99). When including age, the risk of HGSC was independently associated neither with ever use of OCP nor with the way in which the RRSO specimens were embedded.

DISCUSSION

In this large series of asymptomatic *BRCA1/2*-PV carriers, the prevalence of HGSC at RRSO was 1.5% among *BRCA1*-PV carriers and 0.6% among *BRCA2*-PV carriers. Most HGSCs (n = 22; 73.3%) originated in the fallopian tubes, with the remainder presenting exclusively in the ovaries (n = 8; 26.7%) although the fallopian tubes were inadequately sampled in three cases. For both *BRCA1*-PV and *BRCA2*-PV carriers, higher age at RRSO was associated with an increased risk of HGSC at RRSO, whereas long-term OCP use seemed to be protective.

Compared with previously published studies,[15-17,20,29] we report a low prevalence of HGSC at RRSO. However, one prospective study performed in a similar population of asymptomatic *BRCA1/2*-PV carriers did reveal a comparable prevalence of 1.1% for occult cancer at RRSO.[5] Both the lower median age at RRSO and the exclusion of women with abnormal preoperative screening results and symptoms of ovarian cancer can explain the low prevalence in

TABLE 1. Clinical Characteristics of Asymptomatic *BRCA1/2*-PV Carriers Who Underwent RRSO (n = 2,557)

		***BRCA1*-PV[a] (n = 1,627)**		***BRCA2*-PV (n = 930)**
Characteristic	**Median, No.**	**Range, %**	**Median, No.**	**Range, %**
Median age at time of RRSO, years	43.0	25.3-73.8	46.8	27.6-77.9
RRSO after advised age[b]	1,119	68.8	547	58.8
Year of RRSO				
1995-2000	207	12.7	45	4.8
2001-2010	986	60.6	617	66.4
2011-2018	434	26.7	268	28.8
Breast cancer before RRSO				
No	894	55.0	550	59.1
Yes	732	45.0	379	40.8
Not treated with chemotherapy	208	28.4	129	34.0
Treated with chemotherapy	524	71.6	250	66.0
Family history				
No family history of breast or ovarian cancer	193	11.9	138	14.8
Only breast cancer	501	30.8	392	42.2
Only ovarian cancer	104	6.4	50	5.4
Both breast and ovarian cancers	261	16.0	142	15.3
Missing	568	34.9	208	22.4
Age at menarche, years				
≤ 11	131	8.1	114	12.3
12-14	697	42.8	462	49.7
≥ 15	201	12.4	135	14.5
Missing	598	36.8	219	23.5
Parity				
0	180	11.1	107	11.5
1	195	12.0	118	12.7
2	424	26.1	318	34.2
≥ 3	241	14.8	167	18.0
Missing	587	36.1	219	23.5
Breastfeeding				
No	444	27.3	266	37.5
Yes	596	36.6	444	47.7
< 6 months	243	40.8	173	39.0
≥ 6 months	353	59.2	271	61.0
Missing	587	36.1	220	23.7
OCP use before RRSO				
Never	74	4.5	70	7.5
Ever	950	58.4	638	68.6
≤ 5 years	127	13.4	173	27.1
6-10 years	258	27.2	121	19.0
≥ 11 years	565	59.5	344	53.9
Missing	587	36.1	220	23.7
Menopause before RRSO				

(continued on following page)

TABLE 1. Clinical Characteristics of Asymptomatic *BRCA1/2*-PV Carriers Who Underwent RRSO (n = 2,557) (continued)

	BRCA1-PV[a] (n = 1,627)		*BRCA2*-PV (n = 930)	
Characteristic	**Median, No.**	**Range, %**	**Median, No.**	**Range, %**
No	397	24.4	220	23.7
Yes	643	39.5	492	52.9
Missing	587	36.1	218	23.4
Previous adnexal surgery				
No	1,555	95.6	891	95.8
Yes	72	4.4	39	4.2
Prior RRO	21	29.2	4	10.3
Prior RRS	3	4.2	1	2.6
Incomplete RRSO	48	66.7	34	87.2

Abbreviations: BRCA, breast cancer susceptibility gene; OCP, oral contraceptive pill; PV, pathogenic variant; RRO, risk-reducing oophorectomy; RRS, risk-reducing salpingectomy; RRSO, risk-reducing salpingo-oophorectomy.

[a]Three women with a *BRCA1*-PV and *BRCA2*-PV are included in the *BRCA1*-PV group.

[b]The advised age is 40 years for *BRCA1*-PV and 45 years for *BRCA2*-PV.

our study. Still, only 31.2% of *BRCA1*-PV carriers and 41.2% of *BRCA2*-PV carriers underwent RRSO before the recommended age, probably because of delayed DNA testing for *BRCA1/2*-PV carriership.

Our results support the hypothesis that the fallopian tubes represents a major origin site for HGSC. Consistent with earlier reports, 73.3% (22 women) with HGSC at RRSO had a focus in the fallopian tubes.[5,14,17,20,30] Most also had concurrent STIC, adding to the evidence that this is the most likely precursor of HGSC.[6,7,9] However, in eight women (26.7%) with HGSC at RRSO, we only detected a tumor in the ovaries. Given that three women had inadequately sampled fallopian tubes, it can be hypothesized that a HGSC or STIC of the fallopian tube has been missed. As expected, none of the eight women had an ovarian intraepithelial lesion.[31] Another explanation is that concurrently bulky tumors in an ovary might have overgrown smaller tumors in the fallopian tubes, on the basis of evidence that the ovaries are the preferred site of growth rather than origin.[32] Finally, these ovarian HGSCs might have developed from metaplastic tubal cells implanted in ovarian inclusion cysts or deposited on the ovarian surface (precursor escape).[8,33,34]

Salpingectomy with delayed oophorectomy has recently gained increasing attention as a preventive option for *BRCA1/2*-PV carriers. This method minimizes the effects of an acute surgical menopause, but it does leave a residual chance of developing ovarian HGSC after salpingectomy.[35] The delayed oophorectomy is advised at 45 years for *BRCA1*-PV and 50 years for *BRCA2*-PV carriers.[36] Six of the ovarian HGSCs we found in this study were diagnosed in women who underwent RRSO at older age. Therefore, our results indicate that delayed oophorectomy may be acceptable if performed within the recommended age range and after a thorough histopathologic examination of the fallopian tubes.

Older *BRCA1*-PV and *BRCA2*-PV carriers had an increased risk of HGSC at RRSO in this study, comparable with those previously reported.[18,20,29,30] Despite the low prevalence of HGSC at RRSO among women who underwent RRSO at the recommended age (0.6% in *BRCA1*-PV carriers and 0.3% in *BRCA2*-PV carriers), three *BRCA1*-PV carriers and one *BRCA2*-PV carrier developed a HGSC before RRSO. Other studies have occasionally reported cases of HGSC at RRSOs performed within the advised age ranges.[30,37,38] Nonetheless, we contend that the prevalence of HGSC at RRSO will further decrease as more *BRCA1/2*-PV carriers opt for earlier prophylactic isolated salpingectomy and delayed oophorectomy.

To our knowledge, this is the first study showing an association between long-term OCP use and a reduced risk of HGSC at RRSO in asymptomatic *BRCA1/2*-PV carriers. However, a protective effect of OCP use on symptomatic ovarian cancer has been shown for *BRCA1/2*-PV carriers. In a prospective study of more than 6,400 *BRCA1/2*-PV carriers, OCP use for $>$ 10 years compared with $<$ 5 years was associated with a 63% risk reduction for ovarian cancer.[39] This lasted for $>$ 15 years, suggesting that prolonged OCP use offered long-term protection. Another two other studies investigating the effect of OCP on the occurrence of occult cancer at RRSO found that OCP use offered no protection.[19,29] Although numerous studies have shown the protective benefits of OCP use against HGSC, we still do not fully understand the causal mechanism. One plausible explanation concerns the carcinogenic effect of follicular fluid on the distal fallopian tube epithelium with each ovulation.[40,41] As such, the protective effect may result from the simple fact that prolonged OCP use substantially reduces the number of ovulations over time. Moreover, although long-term OCP use may increase the risk of breast cancer,[39] a recent analysis concluded that its benefits for

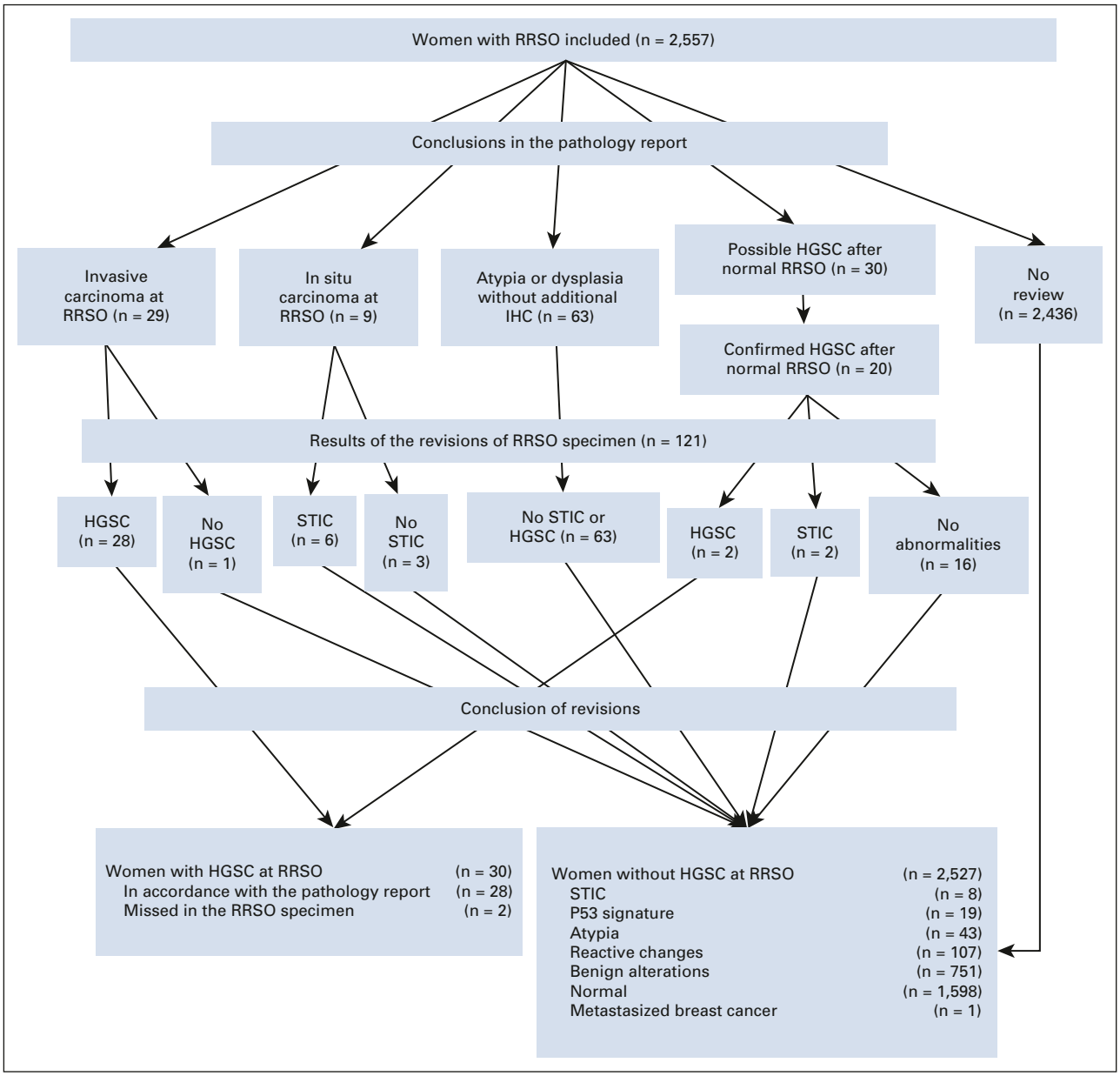

FIG 2. Flowchart of the histopathologic review and pathologic findings. We assessed 2,557 pathology reports and 120 RRSO specimens. HGSC, high-grade serous carcinoma; IHC, immunohistochemistry; RRSO, risk-reducing salpingo-oophorectomy; STIC, serous tubal intraepithelial carcinoma.

ovarian cancer risk might outweigh the risk of OCP-associated breast cancer in *BRCA1/2*-PV carriers.[42] It should be noted that timely RRSO reduces this positive net benefit as this procedure remains the most effective option for preventing ovarian cancer in *BRCA1/2*-PV carriers.

This study benefited from the use of a nationwide series of asymptomatic *BRCA1/2*-PV carriers undergoing RRSO, access to histopathology reviews to confirm each case of HGSC, and the availability of detailed prospectively collected data from the HEBON database and questionnaires. Furthermore, case selection for histopathologic review was thorough and efficient, reducing the likelihood that we missed a case of HGSC. This included a review of all RRSO specimens for women who developed HGSC after RRSO with a mean follow-up (11.1 years) that was longer than the median time to HGSC diagnosis after RRSO (7.2 years).

However, several limitations must also be considered. First, both the multicenter approach and the 20-year study period meant that a uniform histopathologic protocol could not be applied. This resulted in heterogeneity of tissue handling, potentially leading to smaller lesions being missed because not all RRSO specimens were analyzed thoroughly (Data Supplement).[17,20] Second, the prevalence of HGSC at RRSO was low despite the large sample size; therefore, few cases were available, especially for *BRCA2*-PV carriers. This might

TABLE 2. Patient and Tumor Characteristics Related to HGSCs Found in RRSO Specimens of Asymptomatic *BRCA1/2*-PV Carriers

Characteristic	Age at RRSO, Years	Location in Fallopian Tube	HGSC in One or Both Ovaries	STIC Present?	FIGO Stage	Year of Diagnosis
BRCA1-PV						
Fallopian tube	33.5	Fimbriae	—	No	Ia	1998
	37.7	Fimbriae	—	No	Ia	2013
	45.2	Fimbriae	—	No	Ia	2000
	47.0	Fimbriae	—	Yes	Ia	2004
	50.9	Fimbriae	—	Yes	Ia	2008
	51.3	Unknown	—	No	Ic	2000
	53.2	Fimbriae	—	Yes	Ia	2011
	53.2[a]	Unknown	—	Yes	Ia	2010
	60.5	Fimbriae	—	Yes	IIb	2008
	60.9	Fimbriae	—	Yes	Ic	2005
	64.2	Medial tube	—	Yes	IIIb	2007
	65.3[a]	Fimbriae	—	Yes	Ia	2008
	69.4	Fimbriae	—	Yes	Ic	2012
	70.6	Fimbriae		Yes	Ia	2010
Ovary	40.5	—	1 ovary	No	IIIc	2010
	42.9	—	1 ovary	No	Ia	2010
	49.4	—	1 ovary	No	Ia	2006
	52.0	—	Both ovaries	No	IIIa	2007
	57.4	—	1 ovary	No	Ic	2005
	62.3	—	1 ovary	No	Ia	2003
Fallopian tube + ovary	38.1	Fimbriae	Both ovaries	Yes	IIb	2010
	49.6	Distal tube	Both ovaries	Yes	Ib	2007
	63.2	Fimbriae	1 ovary	Yes	IIa	2009
	57.9	Unknown	Both ovaries	No	IIIc	2009
BRCA2-PV						
Fallopian tube	44.6	Unknown	—	No	Ia	2003
	63.0	Fimbriae	—	Yes	Ia	2008
	63.3	Fimbriae	—	Yes	Ia	2007
Ovary	58.2	—	1 ovary	No	Ia	2009
	64.5		1 ovary	No	IIIa	2001
Fallopian tube + ovary	74.3	Fimbriae	1 ovary	Yes	Ic	2009

Abbreviations: BRCA, breast cancer susceptibility gene; FIGO, International Federation of Gynecology and Obstetrics; HGSC, high-grade serous carcinoma; PV, pathogenic variant; RRSO, risk-reducing salpingo-oophorectomy; STIC, serous intraepithelial carcinoma.

[a]HGSC found during histopathologic revisions.

TABLE 3. Factors Associated With Invasive HGSC at RRSO in Asymptomatic *BRCA1/2*-PV Carriers

	BRCA1-PV (n = 1,627)					*BRCA2*-PV (n = 930)				
	HGSC at RRSO (n = 24)		Normal RRSO (n = 1,603)			HGSC at RRSO (n = 6)		Normal RRSO (n = 924)		
Characteristic	No.	%, ± or range	No.	%, ± or range	*P*	No.	%, ± or range	No.	%, ± or range	*P*
Median age at RRSO, years	52.6	33.5-70.6	43.2	25.3-75.6	< .001	63.2	44.6-74.3	47.3	25.6-78.3	.004
RRSO after the advised age[a]	21	87.5	1,098	68.5	.046	5	83.3	542	58.7	.221
BC before RRSO					.364					.645
No	11	45.8	883	55.1		3	50.0	547	59.2	
Yes	13	54.2	719	44.9		3	50.0	376	40.7	
Chemotherapy for BC before RRSO					.320					.569
No	14	58.3	1,087	67.8		5	83.3	673	72.8	
Yes	10	41.7	514	32.1		1	16.7	249	26.9	
Family history of BC or OC					.075					.971
No family history	6	25.0	187	11.7		1	16.7	137	14.8	
Only BC	8	33.3	493	30.8		3	50.0	389	42.1	
Only OC	1	4.2	103	6.4		0	—	50	5.4	
Both BC and OC	6	25.0	255	15.9		1	16.7	141	15.3	
Mean age at first menarche, years	13.3	1.5	13.2	1.5	.705	16.0	8.2	13.1	1.6	.471
Median parity	2	0-4	2	0-5	.343	2	1-2	2	0-12	.866
Breast-feeding					.988					.418
No	9	37.5	435	27.1		1	16.7	265	28.7	
Yes	12	50.0	584	36.4		4	66.7	440	47.6	
Median length of breast-feeding in months	3	0-23	2	0-80	.746	1	0-14	3	0-105	.811
Ever use of OCP					.019					.447
No	4	16.7	70	4.4		1	16.7	69	7.5	
Yes	15	62.5	935	58.3		4	66.7	634	68.6	
Median length of OCP use in years[b]	8	1-27	12	1-35	.001	5	3-8	12	1-36	.039
Menopause before RRSO					.645					.133
No	7	29.2	390	24.3		0	—	220	23.8	
Yes	14	58.3	629	39.2		5	83.3	487	52.7	
Previous adnexal surgery					.508					.967
No	23	95.8	1,532	95.6		6	100	885	95.8	
Prior RRO	1	4.2	20	1.2		0	—	4	0.4	
Prior RRS	0	—	3	0.2		0	—	1	0.1	
Incomplete RRSO	0	—	48	3.0		0	—	34	3.7	

NOTE. Numbers might not add up to the total number given because of missing values.

Abbreviations: BC, breast cancer; BRCA, breast cancer susceptibility gene; HGSC, high-grade serous carcinoma; OC, ovarian cancer; OCP, oral contraceptive pill; PV, pathogenic variant; RRO, risk-reducing oophorectomy; RRS, risk-reducing salpingectomy; RRSO, risk-reducing salpingo-oophorectomy.

[a]The recommended age is 40 years for *BRCA1*-PV and 45 years for *BRCA2*-PV.

[b]Cases without ever use of OCP were filtered out.

TABLE 4. Univariate and Multivariable Logistic Regression of Factors Associated With Invasive HGSC at RRSO in Asymptomatic *BRCA1*-PV Carriers (n = 996)

	Univariate		Multivariable	
Patient Characteristic	**OR**	**95% CI**	**OR**	**95% CI**
Age at RRSO	1.088*	1.038 to 1.140	1.070**	1.021 to 1.122
RRSO after the advised age				
No	1			
Yes	3.523	0.805 to 15.418		
BC before RRSO				
No	1			
Yes	1.578	0.543 to 4.585		
Chemotherapy for BC before RRSO				
No	1			
Yes	1.166	0.448 to 3.034		
Family history of BC or OC				
No family history	1			
Only BC	0.617	0.178 to 2.136		
Only OC	0.406	0.045 to 3.683		
Both BC and OC	0.992	0.276 to 3.569		
Age at first menarche, years				
≤ 11	1			
12-14	1.229	0.274 to 5.512		
≥ 15	0.969	0.276 to 5.880		
Parity	1.035	0.677 to 1.583		
Breast-feeding				
No	1			
Yes	0.862	0.337 to 2.203		
Length of breast feeding	0.993	0.935 to 1.054		
Ever use of OCP				
No	1			
Yes	0.270***	0.087 to 0.842		
Length of use of OCP	0.886**	0.818 to 0.959	0.912***	0.844 to 0.986
Menopause before RRSO				
No	1			
Yes	1.178	0.432 to 3.211		
Embedding of the RRSO specimen				
Not totally embedded	1		1	
Totally embedded	0.324	0.093 to 1.127	0.299	0.085 to 1.049

Abbreviations: BC, breast cancer; BRCA, breast cancer susceptibility gene; HGSC, high-grade serous carcinoma; OC, ovarian cancer; OCP, oral contraceptive pill; OR, odds ratio; PV, pathogenic variant; RRSO, risk-reducing salpingo-oophorectomy.

*$P < .001$; **$P < .01$; ***$P < .05$.

have influenced the accuracy of the risk factor estimates for HGSC at RRSO and prevents us from drawing conclusions about the factors associated with HGSC at RRSO for *BRCA2*-PV carriers. Third, some variables had large percentages of missing data, because of questionnaire mailing. Consequently, women included before 2012 had substantially more missing data than women included after 2012. This further reduced the accuracy of our estimates. Fourth, we could not include women who died before receiving an invitation to the HEBON study because of a lack of informed consent, possibly introducing selection bias. Finally, the retrospective study design meant that we could not always clearly distinguish between prophylactic and therapeutic adnexal surgery on the basis of available clinical information. This might have introduced further selection bias.

In conclusion, to our knowledge, this is the largest nationwide series reporting the prevalence of histologically proven HGSC at RRSO in asymptomatic women carrying a *BRCA1*-PV and/or *BRCA2*-PV (1.5% and 0.6%, respectively). Our findings highlight not only the importance of performing RRSO at the recommended age and ensuring total removal and careful examination of the fallopian tubes but also the protective effect of long-term OCP use.

AFFILIATIONS

[1]Department of Obstetrics and Gynecology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[2]Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[3]Department of Pathology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[4]Department of Epidemiology, Netherlands Cancer Institute, Amsterdam, the Netherlands
[5]Department of Gynecologic Oncology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands
[6]Department of Obstetrics and Gynecology, Radboud University Medical Center, Nijmegen, the Netherlands
[7]Department of Obstetrics and Gynecology, Leiden University Medical Center, Leiden, the Netherlands
[8]Department of Gynecology, Antoni van Leeuwenhoek, Amsterdam, the Netherlands
[9]Department of Gynecologic Oncology, Amsterdam University Medical Center-Center for Gynecological Oncology Amsterdam, Amsterdam, the Netherlands
[10]Department of Gynecology, Maastricht University Medical Center, Maastricht, the Netherlands
[11]Department of Gynecologic Oncology, University Medical Center Utrecht, Utrecht, the Netherlands
[12]Department of Clinical Genetics, University Medical Center Maastricht, Maastricht, the Netherlands
[13]Division Laboratories, Pharmacy and Biomedical Genetics, Department of Genetics, University Medical Center Utrecht, Utrecht, the Netherlands
[14]Department of Medical Oncology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands
[15]Department of Human Genetics, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands
[16]Department of Clinical Genetics, Leiden University Medical Center, Leiden, the Netherlands
[17]Division of Molecular Pathology, Netherlands Cancer Institute, Amsterdam, the Netherlands
[18]Department of Clinical Genetics, Radboud University Medical Center, Nijmegen, the Netherlands
[19]Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON), Coordinating Center: Netherlands Cancer Institute, Amsterdam, the Netherlands

CORRESPONDING AUTHOR

Marian J.E. Mourits, MD, PhD, Department of Obstetrics and Gynecology, University Medical Center Groningen, University of Groningen, PO Box 30 001, 9700 RB Groningen, the Netherlands; e-mail: m.j.e.mourits@umcg.nl.

EQUAL CONTRIBUTION

I.A.S.S. and J.B. contributed equally to this work.

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AUTHOR CONTRIBUTIONS

Conception and design: Jan Brouwer, Harry Hollema, Joanne A. de Hullu, Brigitte F.M. Slangen, Ronald P. Zweemer, Marjanka K. Schmidt, Geertruida H. de Bock, Marian J.E. Mourits
Financial support: Jan Brouwer, Marian J.E. Mourits
Administrative support: Joost Bart
Provision of study materials or patients: Joost Bart, Harry Hollema, Encarna B. Gómez Garcia, Margreet G.E.M. Ausems, Klaartje van Engelen, Christi J. van Asperen, Marian J.E. Mourits
Collection and assembly of data: Iris A.S. Stroot, Jan Brouwer, Joost Bart, Harry Hollema, Denise J. Stommel-Jenner, Katja N. Gaarenstroom, Luc R.C.W. van Lonkhuijzen, Brigitte F.M. Slangen, Encarna B. Gómez Garcia, Margreet G.E.M. Ausems, Klaartje van Engelen, Christi J. van Asperen, Marian J.E. Mourits
Data analysis and interpretation: Iris A.S. Stroot, Jan Brouwer, Joost Bart, Harry Hollema, Marise M. Wagner, Helena C. van Doorn, Brigitte F.M. Slangen, Ingrid A. Boere, Marijke R. Wevers, Geertruida H. de Bock, Marian J.E. Mourits
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

High-Grade Serous Carcinoma at Risk-Reducing Salpingo-Oophorectomy in Asymptomatic Carriers of *BRCA1/2* Pathogenic Variants: Prevalence and Clinical Factors

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Margreet G.E.M. Ausems
Honoraria: AstraZeneca
Consulting or Advisory Role: AstraZeneca, Astellas Pharma (Inst), Meridian HealthComms (Inst)
Research Funding: AstraZeneca (Inst), Pfizer (Inst)

Ingrid A. Boere
Consulting or Advisory Role: Tesaro/GSK (Inst), AstraZeneca (Inst)
Research Funding: GlaxoSmithKline (Inst)

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APPENDIX

The Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON) consists of the following Collaborating Centers: Netherlands Cancer Institute (coordinating center), Amsterdam, the Netherlands: M.A. Rookus, F.B.L. Hogervorst, F.E. van Leeuwen, M.A. Adank, M.K. Schmidt, D.J. Jenner; Erasmus Medical Center, Rotterdam, the Netherlands: J.M. Collée, A.M.W. van den Ouweland, M.J. Hooning, I.A. Boere; Leiden University Medical Center, the Netherlands: C.J. van Asperen, P. Devilee, R.B. van der Luijt, T.C.T.E.F. van Cronenburg; Radboud University Nijmegen Medical Center, the Netherlands: M.R. Wevers, A.R. Mensenkamp; University Medical Center Utrecht, the Netherlands: M.G.E.M. Ausems, M.J. Koudijs; Amsterdam Medical Center, the Netherlands: T.A.M. van Os, I. van de Beek; VU University Medical Center, Amsterdam, the Netherlands: K. van Engelen, J.J.P. Gille; Maastricht University Medical Center, the Netherlands: E.B. Gómez García, M.J. Blok, M. de Boer; University of Groningen, the Netherlands: L.P.V. Berger, A.H. van der Hout, M.J.E. Mourits, G.H. de Bock; the Netherlands Comprehensive Cancer Organisation (IKNL): S. Siesling, J. Verloop; Nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA): E.C. van den Broek.