Exploring the role of homologous recombination deficiency and BRCA1/2 mutations in endometrial cancer

Jonge, M.M. de

Chapter 5

Endometrial cancer risk in women with germline *BRCA1* or *BRCA2* mutations: multicenter cohort study

Marthe M. de Jonge, Cornelis D. de Kroon, Denise J. Jenner, Jan Oosting, Joanne A. de Hullu, Marian J.E. Mourits, Encarna B. Gómez Garcia, Margreet G.E.M. Ausems, J. Margriet Collée, Klaartje van Engelen, Irma van de Beek, the HEBON group, Vincent T.H.B.M. Smit, Matti. A. Rookus, Geertruida H. de Bock, Flora E. van Leeuwen, Tjalling Bosse, Olaf M. Dekkers*, Christi J. van Asperen*

*** Contributed equally**

Journal of the National Cancer Institute 2021 Mar 12:djab036

Abstract

Background

Endometrial cancer (EC) risk in BReast CAncer gene 1/2 (*BRCA1/2)* mutation carriers is uncertain, therefore we assessed this in a large Dutch nationwide cohort study.

Methods

5,980 *BRCA1/2* (3,788 *BRCA1,* 2,151 *BRCA2,* 41 both *BRCA1/BRCA2)* and 8,451 non-*BRCA1/2* mutation carriers were selected from the HEBON-cohort. Follow-up started at date of nationwide PALGA coverage (January 1, 1989) or at the age of 25 years (whichever came last), and ended at date of EC diagnosis, last follow-up or death (whichever came first). EC risk in *BRCA1/2* mutation carriers was compared to: 1) general population, estimating standardized incidence ratios (SIRs) based on Dutch population-based incidence rates; and 2) non-*BRCA1/2* mutation carriers, using Cox-regression analyses, expressed as hazard ratio (HR). Statistical tests were two-sided.

Results

Fifty-eight *BRCA1/2* and 33 non-*BRCA1/2* mutation carriers developed EC over 119,296 and 160,841 person-years, respectively (SIR = 2.83, 95% confidence interval (CI) = 2.18-3.65; and HR = 2.37, 95% CI = 1.53-3.69, respectively). *BRCA1* mutation carriers showed increased risks for EC overall (SIR = 3.51, 95% CI = 2.61-4.72; HR = 2.91, 95% CI = 1.83-4.66), serous-like EC (SIR: 12.64, 95% CI = 7.62-20.96; HR = 10.48, 95% CI = 2.95-37.20), endometrioid EC (SIR = 2.63, 95% CI = 1.80-3.83; HR = 2.01, 95% CI = 1.18-3.45) and *TP53*-mutated EC (HR = 15.71, 95% CI = 4.62-53.40). For *BRCA2* mutation carriers, overall (SIR = 1.70, 95% CI = 1.01-2.87), and serous-like EC risks (SIR = 5.11, 95% CI = 1.92-13.63) were increased when compared to the general population. Absolute risks by 75 years remained low (overall EC = 3.0%; serous-like EC = 1.1%).

Conclusions

BRCA1/2 mutation carriers have a 2- to 3-fold increased risk for EC, with highest risk observed for the rare subgroups of serous-like and p53-abnormal EC in *BRCA1* mutation carriers.

Introduction

Women with a pathogenic germline mutation in the BReast CAncer genes (*BRCA1* and *BRCA2*) have strongly increased breast carcinoma (BC) and tubo-ovarian carcinoma (OC) risks. Penetrance studies of *BRCA1/*2 mutations report cumulative BC risks at age of 70 years of 50-59% for female *BRCA1* mutation carriers and 42-51% for female *BRCA2* mutation carriers, together with OC risks of 34-45% and 13-21%, respectively.[1]

Whether *BRCA1/2* mutations also confer elevated life-time risk for endometrial cancer (including uterine sarcomas; EC) is unclear. Studies have reported an increased EC risk in *BRCA1/2* mutation carriers compared to country-specific incidence rates (standardized incidence ratios (SIRs), range = 1.9 to 5.3),[2-4] but others found no clearly increased EC risk,[5-7] or found that increased risk was restricted to a rare but aggressive subgroup of EC, ECs with serous-like histology (e.g. uterine serous carcinomas, carcinosarcomas; SIR range = 14.8 to 32.2; **Supplementary Table 1**).[8-12] Furthermore, it has been suggested that the apparent increase in EC risk is not related to the *BRCA1/2* mutation, but to previous BC related tamoxifen-treatment.[2, 3] These conflicting data in previous cohort studies can be attributed to a limited number of ECs (*n*=2-17) as a result of small cohort sizes (315-4,456), low mean/median age at enrolment with limited follow-up periods, or absence of outcome validation (*n*=5*)*.[2-9, 13]

More recently, studies have suggested that in addition to EC of serous-like histology, a larger group of p53-abnormal ECs (one of the four molecularly-defined subgroups),[10, 14, 15] are more common in *BRCA1/2* mutation carriers. EC risks for this molecular subgroup have not yet been determined.

Accurate estimation of EC risk in *BRCA1/2* mutation carriers is important to counselling and clinical management. Therefore, the aim of this study was to confirm and quantify the risk of EC in a large cohort of *BRCA1/2* mutation carriers compared to both the general Dutch population and to non-*BRCA1/2* mutation carriers.

Methods

Study population

BRCA1/2 mutation carriers (*n*=6,072) were selected from the "HEreditary Breast and Ovarian cancer study, the Netherlands (HEBON cohort study)", an ongoing nationwide cohort study of hereditary breast and ovarian cancer (HBOC) families in the Netherlands (for details see[16, 17] and **Supplementary methods**). The HEBON cohort study has been approved by medical

ethical committees of all participating centers. The current study was approved by the Institutional Review Board of the Netherlands Cancer Institute.

BRCA1/2 mutation carriers

Women with a class 5/pathogenic or class 4/likely pathogenic *BRCA1* or *BRCA2* mutation were eligible.[18] The initial cohort consisted of 6,072 *BRCA1/2* mutation carriers, of whom 3,716 provided written informed consent allowing connection to disease registries, 876 who died before they could be invited to join the HEBON cohort, and 1,480 whose connection to disease registries (see below) was approved by the medical ethical committee because they did not respond to a request to participate and did not actively deny the request after three invitations to do so (**Figure 1**).

Dutch population-based cancer incidence rates (comparison group 1)

Age, calendar year- and country-specific EC incidence rates (crude rates/100,000 person-years, stratified by age and calendar time) were obtained from the Netherlands Cancer Registry (NCR) for the calendar years 1989-2015 (May 2020). All tumors with an *International Classification of Diseases for Oncology, Third edition, First revision (ICD-O-3.1;* http://codes.iarc.fr/*)* topographical code of either C54 (Corpus Uteri) and C55 (Uterus, NOS) were included.

In addition, age, calendar year and country-specific EC incidence rates were obtained from the NCR for the following five histologic subgroups based on the morphological ICD-0-3.1 codes: 1) Endometrioid (including mucinous), 2) Serous-like (e.g. uterine serous carcinoma, carcinosarcoma, mixed carcinomas), 3) Clear Cell Carcinoma, 4) Sarcoma and 5) Other (e.g. neuroendocrine carcinoma), see **Supplementary Table 2**.

Non-*BRCA1/2* mutation carriers (comparison group 2)

Non-*BRCA1/2* mutation carriers (*n*=8,575, within-cohort comparison group) were also selected from the HEBON cohort (**Figure 1**). Women were eligible if they: 1) were a member of a family with a proven likely pathogenic or pathogenic *BRCA1* or *BRCA2* mutation (not including variants of unknown significance), and 2) tested negative for this likely pathogenic or pathogenic *BRCA1/2* mutation.

Pathology review and assessment of histologic- and molecular subgroup

To confirm endometrial origin and define histologic and molecular subgroups, pathology reports, H&E-slides and FFPE tumor tissue blocks of ECs of both *BRCA1/2* and non-*BRCA1/2*-mutation carriers were collected via PALGA and centrally revised by at least one expert gynaecopathologist. If pathology review was not possible, histologic subtype and grade were extracted from pathology reports or based on the morphological ICD-0-3.1 code. Although some cases of rare uterine

sarcoma's were included in the study, for simplicity the term ' endometrial cancer' (EC) is used throughout the manuscript.

After review, ECs were classified into the same five histologic subgroups as described for comparison group 1, and were molecular classified similarly to as what has been previously described; p53-abnormal or "other" (including *POLE*-mutant, mismatch repair (MMR)-deficient and no surrogate marker profile group (NSMP)).[10, 14] For cases that were not available for review, assignment to molecular groups was based on histology (see the **Supplementary Methods**).

Data collection and data handling

Pseudonymized data were retrieved for *BRCA1/2* and non-*BRCA1/2* mutation carriers from the central HEBON database. With regular input from the NCR, the Dutch Pathology Registry (PALGA)[19] and the municipal administration (BRP), the HEBON cohort study gathers data centrally, including cancer incidence, date of cancer diagnosis, RRSO, and date of death. In the case of BC, these data also include hormone treatment (HT, type and duration not specified). PALGA is a nationwide archive containing excerpts of all histo- and cytopathology reports in the Netherlands since 1991.[19] For details see the **Supplementary Methods**.

Statistical analysis

Period at risk for EC. Both *BRCA1/2* and non-*BRCA1/2* mutation carriers were assigned a starting date for follow-up based on either nationwide PALGA coverage (Jan 1, 1989) or the date at which women are considered to be at risk for EC (≥25 years of age), whichever was later. Follow-up ended on the date of EC diagnosis (ICD-0-3 topographical code C54/C55), date of death, or date of end of follow-up (January 1, 2016 for *BRCA1/2* mutation carriers who provided informed consent; January 1, 2012 for all others), whichever was earlier. Women were excluded from analyses if an EC occurred before Jan 1, 1989 or before the age of 25 (**Supplementary Figure 1**). We were not informed about the extent of OC surgery and RRSO (whether or not this included a hysterectomy), and therefore the date of OC/RRSO was not used as censoring event.

Comparison 1: BRCA1/2 mutation carriers versus Dutch country-specific incidence rates. For the *BRCA1/2* mutation carrier cohort, expected EC incidence was estimated based on calculated person-time at risk, stratified by age, and calendar-time. SIRs were calculated by dividing observed ECs by expected ECs, and 95% confidence intervals (CIs) and 2-sided *p* values were estimated assuming a Poisson distribution. SIRs were also stratified for histologic subgroup after pathology review, mutation type (*BRCA1/BRCA2),* and attained age.

Comparison 2: BRCA1/2 mutation carriers versus non-BRCA1/2 mutation carriers. Differences in EC occurrence between *BRCA1/2* and non-*BRCA1/2* mutation carriers were analysed using

Cox regression and expressed as Hazard Ratio (HR), with accompanying 95% CI adjusted for age. HRs were also calculated after stratification for mutation type and for histologic and molecular subgroup following pathology review. Women carrying both a *BRCA1*- and *BRCA2* mutation (*n*=41, no ECs) were analysed in both the *BRCA1*- and *BRCA2*-mutation carrier group.

The following sensitivity analyses were performed. First, to exclude potential confounding by tamoxifen use for BC, two separate sensitivity analyses were performed; for the first, patients were censored at date of (first) BC diagnosis that led to HT (type and duration not specified), and for the second, patients were censored at date of (first) BC diagnosis (both analyses included cases with DCIS). Second, to exclude testing bias (testing *BRCA1/2* mutation because of EC diagnosis), person-years at risk began on the date of the *BRCA1/2* DNA test. Third, to minimize potential bias due to unequal observation periods, the end date for follow-up was set to January 1, 2012 for all *BRCA1/2* and non-*BRCA1/2* mutation carriers.

Baseline characteristics between *BRCA1/2* and non-*BRCA1/2* mutation carriers were compared using the Chi-square test (categorical variables) and the Mann-Whitney U-test (numerical variables). Median follow-up time was estimated using the Reverse Kaplan-Meier Method. The cumulative risk of developing EC, and EC of serous-like and endometrioid histology up to age of 75 years was estimated using competing risk analyses.

A *p* value of <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS version 23.0 and STATA Statistical Software version 14.1 (College Station, TX: StataCorp LP).

Results

Cohort characteristics

A total of 5,980 *BRCA1/2* and 8,451 non-*BRCA1/2* mutation carriers were included (**Figure 1**). Cohort characteristics and follow-up details are described in **Table 1**. The total number of person-years at risk and events (overall and stratified by histologic subgroup) per 5-year age category are shown in **Supplementary Table 3**. Details on EC characteristics and pathology review are described in **Supplementary Table 4-6**.

EC Risk in *BRCA1/2* mutation carriers compared to the Dutch country-specific incidence rates

Overall EC risk in *BRCA1/2* mutation carriers was increased 2.83-fold (95% CI = 2.18-3.65) compared to Dutch EC incidence rates (*BRCA1,* SIR = 3.51, 95% CI = 2.61-4.72; *BRCA2,* SIR = 1.70, 95% CI =1.01-2.87), **Table 2**.

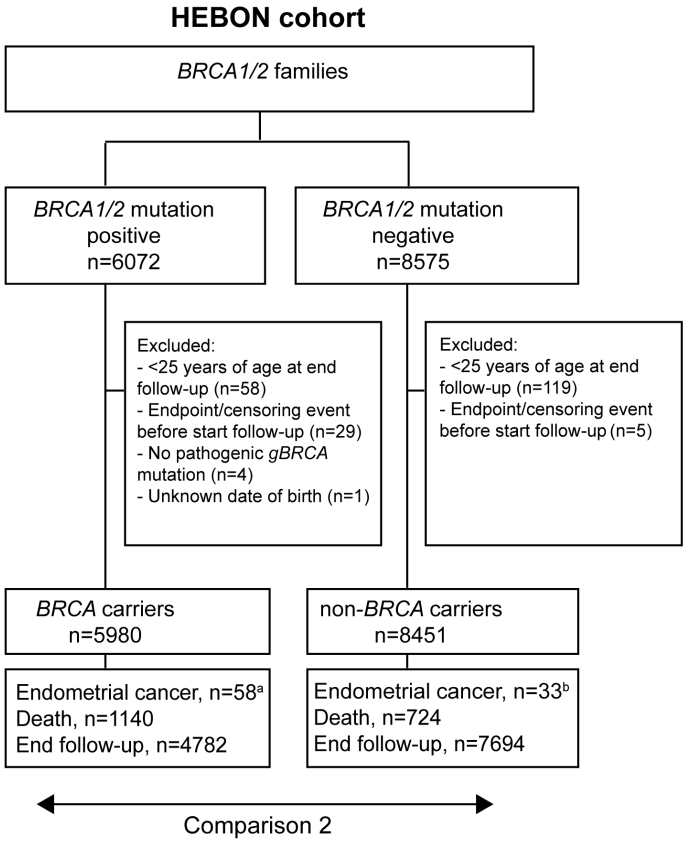


Figure 1. Schematic overview of the *BRCA1/2* mutation carrier cohort and the non-*BRCA1/2* mutation carrier cohort. a. Four events were excluded as they occurred outside of the observation period: two before the start of follow-up (January 1, 1989) and two after the end of follow-up (once on January 1, 2012 and once on January 1, 2016). **b.** Seven events were excluded: five events occurred after the observation period ended (January 1, 2012) and two events were excluded because the tumors were considered of non-endometrial origin after pathology review.

When ECs were stratified by histologic subgroup, *BRCA1/2* mutation carriers were at increased risk for endometrioid EC (SIR = 2.08, 95% CI = 1.49-2.89) and for EC of serous-like histology (SIR = 9.77, 95% CI = 6.23-15.31), **Table 2**. *BRCA1* mutation carriers displayed greater risk for endometrioid EC (SIR = 2.63, 95% CI = 1.80-3.83), and especially for EC of serous-like histology (SIR = 12.64, 95% CI = 7.62-20.96). Risk for EC of serous-like histology in *BRCA2* mutation carriers was lower (SIR = 5.11, 95% CI 1.92-13.63).

Overall EC risks were highest in the youngest age category of 25-40 years (SIR = 9.84, 95% CI = 2.68-25.20), although confidence intervals were broad and the majority of events occurred in older age categories, **Table 3**. For EC of serous-like histology, the highest risks were observed in the age category 60-80 years (SIR = 11.27, 95% CI = 5.99-19.27).

Table 1. Demographic characteristics of *BRCA1/2* mutation carriers and non-*BRCA1/2* mutation carriers

Demographic characteristics	*BRCA1/2* carriers	non-*BRCA1/2* carriers
Total, No. (%)	5980 (100)	8451 (100)[a]
BRCA1 mutation, No. (%)	3788 (63.3)	0 (0)
BRCA2 mutation, No. (%)	2151 (36.0)	0 (0)
BRCA1 and *BRCA2* mutation, No. (%)	41 (0.7)	0 (0)
Median age at start of follow-up (years, IQR)	27.4 (25.0-37.8)	28.0 (25.0-38.2)
<40 years, No. (%)	4737 (79.2)	6657 (78.8)
40-49 years, No. (%)	775 (13.0)	1197 (14.2)
50-59 years, No. (%)	321 (5.4)	395 (4.7)
≥60 years, No. (%)	147 (2.5)	202 (2.4)
Median age at end of follow-up (years, IQR)	51.9 (42.5-61.6)	50.7 (42.1-60.7)
Median observation period (years, IQR)	22.5 (15.2-27.0)	23.0 (16.4-23.0)
Total person-years at Risk (SD)	119296 (7.1)	160841 (5.8)
Of which post *BRCA* DNA test (SD)[b]	56579 (6.3)	48044 (5.1)
Ovarian Cancer History, No. (%)[c]	716 (12.0)	267 (3.2)
Before start observation period, No. (%)	34 (0.6)	19 (0.2)
During observation period, No. (%)	682 (11.4)	248 (2.9)
Endometrial Cancer and simultaneous/history of Ovarian Cancer[d]	5 (0.08)	5 (0.06)
Breast Cancer History, No. (%)[e,f]	2762 (46.2)	2788 (33.0)
Before start observation period, No. (%)	291 (4.9)	140 (1.7)
During observation period, No. (%)	2471 (41.3)	2648 (31.3)
Hormone Treatment		
HT-BC, No. (%)	755 (12.6)	1155 (13.7)
Before start follow-up, No. (%)	14 (0.2)	4 (0.0)
During follow-up, No. (%)	741 (12.4)	1151 (13.6)
HT-BC unknown, No. (%)[f]	209 (3.5)	127 (1.5)
Before start follow-up, No. (%)	72 (1.2)	39 (0.5)
During follow-up, No. (%)	137 (2.3)	88 (1.0)
RRSO History, No. (%)[g]	3619 (60.5)	695 (8.2)
Before start follow-up, No. (%)	19 (0.3)	25 (0.3)
During follow-up, No. (%)	3600 (60.2)	670 (7.9)
History RRSO unknown, No. (%)	119 (2.0)	4324 (51.2)

[a]Includes 96 women with a *BRCA* variant of unknown significance, of whom two developed a endometrial carcinoma (none carried the (likely) pathogenic familial variant). Abbreviations: BC: Breast Cancer, HT: Hormone Treatment, RRSO: Risk-Reducing Salpingo-oophorectomy

[b]Post *BRCA* DNA test; Person-years from date *BRCA1/2*-DNA test until end of follow-up. The date of *BRCA1/2*-mutation test was missing for 1,682 (28.1%) carriers and 1,214 (14.4%) non-carriers. For these women, the date of *BRCA1/2* DNA test was considered to be January 1, 1995. *BRCA1/2* DNA tests were performed from 1995 until 2012 (median year 2007).

[c]Date of OC diagnosis unknown for two non-*BRCA* mutation carriers.

[d]For details, see **Supplementary Table 5 and 6**.

[e]DCIS was considered as BC. Considered the first BC if women had a history of more than one BC.

[f]Date of diagnosis unknown for one BC in the *BRCA* mutation carrier group.

[g]Includes adnexextirpation for reasons other than RRSO, e.g. during hysterectomy or for OC.

Table 2. Observed and expected endometrial cancer rates in *BRCA1/2* mutation carriers, compared to the Dutch country-specific incidence rates

	***BRCA1/2* carriers**	**Dutch population**		
EC subgroups	**Observed**	**Expected**	**SIR (95% CI)**	***P*[a]**
All endometrial cancers	58	20.53	2.83 (2.18-3.65)	<0.001
BRCA1	44	12.53	3.51 (2.61-4.72)	<0.001
BRCA2	14	8.23	1.70 (1.01-2.87)	0.04
Endometrioid	35	16.85	2.08 (1.49-2.89)	<0.001
BRCA1	27	10.27	2.63 (1.80-3.83)	<0.001
BRCA2	8	6.77	1.18 (0.59-2.36)	0.37
Serous-like	19	1.95	9.77 (6.23-15.31)	<0.001
BRCA1	15	1.19	12.64 (7.62-20.96)	<0.001
BRCA2	4	0.78	5.11 (1.92-13.63)	0.01
Sarcoma	3	1.3	2.30 (0.74-7.14)	0.14
BRCA1	1	0.81	1.24 (0.17-8.78)	0.55
BRCA2	2	0.51	3.95 (0.99-15.81)	0.09
Clear cell	1	0.29	3.40 (0.48-24.11)	0.25
BRCA1	1	0.18	5.58 (0.79-39.65)	0.16
BRCA2	0	0.12	NA	NA

[a]*p* values were estimated assuming a Poisson distribution. Abbreviations: SIR: Standardized Incidence Ratio, CI: Confidence Interval NA: not applicable

EC Risk *BRCA1/2* mutation carriers compared to non-*BRCA1/2* mutation carriers

In total, 58 *BRCA1/2* mutation carriers developed ECs compared to 33 non-*BRCA1/2* mutation carriers, over 119,296 and 160,841 at risk person-years, respectively (HR = 2.37, 95% CI = 1.53-3.69), **Table 4**. *BRCA1* mutation carriers displayed higher relative EC risk (HR = 2.91, 95% CI = 1.83-4.66) compared to *BRCA2* mutation carriers (HR = 1.45, 95% CI = 0.75-2.81)**.**

Combined *BRCA1/2* histologic subgroup analysis showed strongly increased risks for EC with serous-like histology (HR = 8.08, 95% CI = 2.34-27.94), with *BRCA1* showing higher relative risk (HR = 10.48, 95% CI = 2.95-37.20) than *BRCA2* mutation carriers (HR = 4.13, 95% CI = 0.83-20.50), **Table 4**. The highest HR was observed for p53-abnormal EC in *BRCA1* mutation carriers (HR = 15.71, 95% CI = 4.62-53.40). The risk for endometrioid EC in *BRCA1* mutation carriers was increased two-fold (HR = 2.01, 95% CI = 1.18-3.45), unlike *BRCA2* (HR = 0.93, 95% CI = 0.41-2.11).

Table 3. Observed and expected endometrial cancer rates in *BRCA1/2* mutation carriers compared to the Dutch country-specific incidence rates, according to attained age

	***BRCA1/2* carriers**	**Dutch population**	
EC subgroup, age categories	**Observed**	**Expected**	**SIR (95% CI)**
All endometrial cancers	58[a]	20.53	2.83 (2.18-3.65)
25-40 years	4	0.41	9.84 (2.68-25.20)
40-60 years	25	10.0	2.50 (1.62-3.69)
60-80 years	28	9.56	2.93 (1.95-4.24)
Serous-like	19	1.95	9.77 (6.23-15.31)
25-40 years	0	0.02	0.00 (0.00-149.82)
40-60 years	6	0.69	8.68 (3.19-18.90)
60-80 years	13	1.15	11.27 (5.99-19.27)

[a]One endometrial cancer occurred after 80 years of age. Given the low number of person-years after 80 years of age, this age category is not presented in the table. Abbreviations: SIR: Standardized Incidence Ratio, CI: Confidence Interval.

When only follow-up after the date of *BRCA1/2* DNA test is considered, EC risk among mutation carriers remained increased, with higher HRs compared to the main analyses, though with broader confidence intervals, **Table 4**. When excluding cases for which the *BRCA1/2* DNA test date was unknown, HRs remained roughly similar, **Supplementary Table 7**.

To eliminate potential confounding by tamoxifen, a sensitivity analyses was performed by additionally censoring at the time of (first) HT-treated BC. This yielded HRs that were similar to the main analyses, both regarding overall EC risk and stratified for mutation-type/histologic/molecular subgroup, **Table 4**. For additional sensitivity analyses, see **Supplementary Table 7**.

When overall EC risk and EC risk stratified by histologic subgroup were compared between non-*BRCA1/2* carriers and Dutch country-specific incidence rates, no statistically significant differences were observed (**Supplementary Table 8**).

At the age of 75 years, the estimated cumulative risk ('life-time risk') for *BRCA1/2* mutation carriers to develop EC was 3.0% (95% CI = 2.20%-3.91%; *BRCA1*: 3.4%, 95% CI = 2.46%-4.81%; *BRCA2*: 2.0%, 95% CI = 1.09%-3.30%), for the subgroup of EC with serous-like histology, this was 1.1% (95% CI = 0.69%-1.80%; *BRCA1*: 1.4%, 95% CI = 0.79%-2.37%; *BRCA2:* 0.6%, 95% CI = 0.21%-1.60%), see **Supplementary Table 9**.

Table 4. Endometrial cancer risks *BRCA1/2* mutation carriers versus non-*BRCA1/2* mutation carriers

	BRCA1/2 carriers			non-*BRCA1/2* carriers				
Subgroup	**Total, No.**	**Event, No.**	**Person-years at risk**	**Total, No.**	**Events, No.**	**Person-years at risk**	**Hazard Ratio (95% CI)[a]**	***P*[b]**
Main analysis								
All	5980	58	119296	8451	33	160841	2.37 (1.53-3.69)	<0.001
BRCA1[c]	3829	44	75366	8451	33	160841	2.91 (1.83-4.66)	<0.001
BRCA2[c]	2192	14	44809	8451	33	160841	1.45 (0.75-2.81)	0.27
Histologic groups								
Endometrioid	5980	35	119296	8451	30	160841	1.61 (0.97-2.66)	0.06
BRCA1[c]	3829	27	75366	8451	30	160841	2.01 (1.18-3.45)	0.01
BRCA2[c]	2192	8	44809	8451	30	160841	0.93 (0.41-2.11)	0.86
Serous-like	5980	19	119296	8451	3	160841	8.08 (2.34-27.94)	0.001
BRCA1[c]	3829	15	75366	8451	3	160841	10.48 (2.95-37.20)	<0.001
BRCA2[c]	2192	4	44809	8451	3	160841	4.13 (0.83-20.50)	0.08
Molecular group								
p53-abnormal[d]	5980	27	119296	8451	3	160841	11.31 (3.37-37.95)	<0.001
BRCA1[c]	3829	23	75366	8451	3	160841	15.71 (4.62-53.40)	<0.001
BRCA2[c]	2192	4	44809	8451	3	160841	4.11 (0.83-20.39)	0.08
Sensitivity analyses								
Start follow-up from date of *BRCA1/2* DNA test[d]								
All histotypes	5771	37	56579	8098	11	48044	3.26 (1.65-6.44)	0.001
Endometrioid	5771	22	56579	8098	10	48044	2.76 (1.26-6.02)	0.01
Serous-like	5771	14	56579	8098	1	48044	18.28 (2.33-143.34)	0.01

Continue

Continued

Subgroup	*BRCA1/2* carriers			non-*BRCA1/2* carriers				
	Total, No.	Event, No.	Person-years at risk	Total, No.	Events, No.	Person-years at risk	Hazard Ratio (95% CI)[a]	*P*[b]
p53-abnormal[d]	5771	21	56579	8098	1	48044	26.64 (3.51-202.32)	0.01
BRCA1, all histotypes[c]	3700	29	37984	8098	11	48044	5.57 (2.69-11.54)	<0.001
BRCA2, all histotypes[c]	2108	8	18971	8098	11	48044	2.18 (0.80-5.91)	0.13
Additional censoring HT-BC[f]								
All	5966	50	113033	8447	30	155002	2.30 (1.44-3.66)	<0.001
Endometrioid	5966	32	113033	8447	28	155002	1.56 (0.93-2.64)	0.09
Serous-like	5966	14	113033	8447	2	155002	8.78 (1.94-39.65)	0.01
p53-abnormal[d]	5966	22	113033	8447	2	155002	13.62 (3.15-59.00)	<0.001
BRCA1, all histotypes[c]	3821	37	72423	8447	30	155002	2.61 (1.58-4.31)	<0.001
BRCA2, all histotypes[c]	2186	13	41461	8447	30	155002	1.60 (0.82-3.12)	0.17

Abbreviations and explanations: BC: Breast Cancer, HT: Hormone Treatment

[a]All hazard ratios were adjusted for age.

[b] The P values assessing the null hypothesis of HR=1.00.

[c]Women with both a *BRCA1* and a *BRCA2* mutation were included in both analyses stratified for *BRCA1/2* mutation status.

[d]Includes cases for which p53-status was unknown (no FFPE tumor block available) and for whom p53-status was based on most common p53-status for the histotype as described in the material and methods. When excluding cases for which p53-status was based on histotype, the number of events remained the same for *BRCA1/2* carriers, but only two events occurred in the non-*BRCA1/2* mutation carriers (HR: 17.07, 95%-CI: 4.0-72.8, p<0.001).

[e]If the date of *BRCA1/2*-DNA test was unknown, this date was considered to be January 1, 1995.

[f]DCIS was considered as BC. If a woman developed a BC/DCIS for which hormone treatment status was unknown, the date of diagnoses was not considered as censoring event.

Discussion

We presented data from a large cohort study that assessed EC risk among *BRCA1/2* mutation carriers (n=5,980). Strengths of the study compared to earlier studies are, high number of events (n=58), long follow-up (median = 22.5 years) and pathology review to validate the outcome. We found that *BRCA1* and *BRCA2* mutation carriers show a 2-3 fold increased EC risk, with highest increased risks found for the subgroups EC of serous-like histology (8-10 fold) and p53-abnormal EC (11-12 fold). We also showed that increased risk cannot be fully explained by previous HT use and is therefore most likely causally associated with *BRCA1/2* mutations.

Conflicting data from earlier cohort studies, most likely due to lack of power, has resulted in uncertainty regarding increased EC risk in *BRCA1/2* mutation carriers (**Supplementary Table 1**),[2-9] as only three of eight reported statistically significantly increased overall EC risk (SIR range = 1.9-5.3). Those figures broadly agree with results from this study (2-3 fold increase).[2-4] A striking observation reported in three of the seven studies that stratified for histotype[2, 4-9] was the statistically significantly increased risk (SIR range = 14.3-32.2) for EC of serous-like histology, which seemed to be restricted to *BRCA1* mutation carriers.[4, 8, 9] Our study confirms that finding, with the highest risk indeed observed for *BRCA1* mutation carriers (10-13 fold), but with *BRCA2* mutation carriers also showing 5-fold increased risk compared to the general population. By contrast, endometrioid EC risk was only increased for *BRCA1*-mutation carriers (2-3 fold). That *BRCA* mutations contribute to the development of EC is further supported by the recent study of Hughley and colleagues,[20] in which they present the 'etiological index': a case-only measure of *BRCA1/2* mutation associated cancer risks based on the fraction of tumors harboring biallelic *BRCA1/2* inactivation. While the *BRCA1/2* etiological index for nonestablished *BRCA1/2*-associated cancers was 1.6, the respective *BRCA1* etiological index of endometrial cancer was 4.0, supporting an etiological role in cancer causation.

A history of tamoxifen use is considered an important confounder when assessing EC risk.[21, 22] These patients also seem to develop less favourable histologic subtypes such as carcinosarcomas, sarcomas and p53-abnormal tumors.[21, 23] As we were not informed about the type of HT (tamoxifen, aromatase inhibitor) women received for their BC, a potential effect was eliminated by censoring for all HT-BC in a sensitivity analysis. We nonetheless found persistent increased risk for EC overall, EC of serous-like histology and p53-abnormal EC, and can therefore conclude that increased EC risk in *BRCA1/2* mutation carriers can, at best, be only partly explained by previous HT/tamoxifen use.

Highest increased EC risks were found for EC with serous-like histology, and more specifically p53-abnormal EC. We have previously shown that ECs in *BRCA1/2* mutation carriers are noticeably enriched for tumors of the p53-abnormal molecular subgroup, that these tumors

demonstrate LOH of *BRCA* wildtype allele,[16] and that ECs of this subgroup are frequently homologous recombination deficient (HRD) or show genomic scars associated with HRD.[15, 24] The molecular alterations in these tumors are similar to those found in high-grade serous OC and basal-like BC, tumor subtypes particularly associated with the *BRCA1/2*-associated HBOC syndrome.[10, 25-27] Due to the above observations, we would argue that ECs with serous-like histology and especially ECs of the p53-abnormal molecular subgroup should be regarded as part of the *BRCA1/2*-associated HBOC syndrome.

A limitation of this study was the possibility of a cancer-related testing bias. EC is not an indication for *BRCA1/2* DNA testing, therefore, although person-time before *BRCA* DNA testing was included in the main analysis, it is unlikely that this influenced the results. Only including person-time after *BRCA1/2* DNA testing resulted in higher HRs (though with broader confidence intervals) compared to the main analysis. This might be due to the older age of the post-*BRCA1/2* DNA testing cohort, as higher SIRs were observed for older age categories (**Table 3**). Another potential limitation is the presence of left censoring, as the possible occurrence of EC in the period before the NCR and PALGA databases achieved nationwide coverage has naturally not been recorded but cannot be entirely excluded. However, since the majority of women were young at start of follow-up and the majority of ECs are recorded >40 years of age (54 of 58 *BRCA1/2* and 31 of 33 non-*BRCA1/2* mutation carriers) any influence is likely minor. Data on previous hysterectomies was unavailable, but as a *BRCA1/2* mutation is not an indication for hysterectomy in the Netherlands this is unlikely to have affected our results. Pathology review could not be performed for all ECs, nor for the Dutch population controls, therefore, a subset of ECs might have been misclassified. This is especially relevant for high-grade EC (review resulted in histologic subgroup changes for 22% of EC in *BRCA1/2* mutation carriers) which are more difficult to classify and more common in *BRCA1/2* mutation carriers.[13, 16] We were not informed about body weight and the use of hormone replacement therapy (HRT) for the majority of cases. Especially obesity, but not modern combined HRT, is a well-known risk factor for endometrial cancer (both endometrioid and non-endometrioid subtypes).[28-31] However, there is no reason to believe that *BRCA1/2* mutation carriers are more frequently obese.

Our results provide important additional information with regard to EC risks, that is essential for adequate genetic counselling of *BRCA1/*2 mutation carriers. Despite the observed increased overall EC risks in *BRCA1/2* mutation carriers, the cumulative overall EC risk (3.0%) and risk for EC of serous-like histology (1.1%) by 75 years remains low (**Supplementary Table 9**), as the life-time risk of developing EC is low in the general population (approximately 1%-1.4%, with ECs of serous-like histology being even less common: 10% of all ECs).[8, 32, 33] Therefore we should not recommend a concurrent risk-reducing hysterectomy at the time of RRSO routinely, especially since this will increase the complication risk of the procedure. Nevertheless, risk-reducing hysterectomy should be considered especially in the presence

of other EC risk factors or when a hysterectomy is considered for other (benign) uterine pathology. Taken together, given the observed relative and absolute risks, the potential hazards and possible benefits of risk-reducing hysterectomy need to be carefully weighed, and shared decision making is crucial in order to conclude about an individually-tailored treatment advice with regard to risk-reducing surgery *BRCA1/2* mutation carriers.

Secondly, ECs that harbor *BRCA1/2* mutations (germline and somatic) will likely benefit from PARP-inhibitor treatment. PARP inhibitors are proven effective maintenance treatment for *BRCA*-associated platinum-sensitive OC,[34] and trials are currently testing efficacy in EC.

Thirdly, although previous studies have reported low incidences of *BRCA1/2* mutations when screening EC patients with a history of BC (3.8%, not selected for histotype)[35] or an unselected cohort of patients with uterine serous carcinomas (2%)[36], *BRCA1/2* mutation incidences in women with p53-abnormal EC, especially with a history of BC, should be studied to determine the potential value of *BRCA1/2* screening in this patient population.

In summary, *BRCA1/2* mutation carriers do have an important increased risk of EC. This is especially the case for the EC subgroups with unfavourable clinical outcome: serous-like EC and p53-abnormal EC. The observed increase in risk cannot be explained by previous BC-related hormone treatment. Importantly, life-time EC risk through 75 years remains low. This report adds critical evidence to the ongoing discussion whether or not EC is a *BRCA1/2*-associated disease, and further supports the mounting evidence that at least serous-like and p53-abnormal EC should be considered to be an integral part of the *BRCA1/2*-associated HBOC syndrome.

Funding

The HEBON study is supported by the Dutch Cancer Society grants NKI1998-1854, NKI2004-3088, NKI2007-3756, the Netherlands Organisation of Scientific Research grant NWO 91109024, the Pink Ribbon grants 110005 and 2014-187.WO76, the BBMRI grant NWO 184.021.007/CP46 and the Transcan grant JTC 2012 Cancer 12-054.

Notes

Role of the funders: The funders had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

Disclosures: The authors have no conflicts of interest to disclose.

Prior presentations: The study has been presented at the Joint Meeting of HEBON-IMPAHC-VKGN 2019 d.d. November 7, 2019

Author contributions: Conception and design: MMJ, CDK, VTHBMS, MAR, GHB, FEL, TB, OD, CJA, Administrative support: MMJ, DJJ, JO, TB, OD, Collection and assembly of data: MMJ, DJJ, JO, JAH, MJEM, EBGG, MGEMA, MC, KE, IB, VTHBMS, MAR, GHB, FEL, TB, CJA, Data analysis and interpretation: MMJ, CDK, VTHBMS, TB, MJEM, JAH, MAR, OD, CJA, FEL, Manuscript writing: MMJ, CDK, VTHBMS, TB, MJEM, JAH, OD, FEL, CJA,

Acknowledgements: The Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON) consists of the following Collaborating Centers: Netherlands Cancer Institute (coordinating center), Amsterdam, NL: M.A. Rookus, F.B.L. Hogervorst, F.E. van Leeuwen, M.A. Adank, M.K. Schmidt, D.J. Jenner; Erasmus Medical Center, Rotterdam, NL: J.M. Collée, A.M.W. van den Ouweland, M.J. Hooning, I.A. Boere; Leiden University Medical Center, NL: C.J. van Asperen, P. Devilee, R.B. van der Luijt, T.C.T.E.F. van Cronenburg; Radboud University Nijmegen Medical Center, NL: M.R. Wevers, A.R. Mensenkamp; University Medical Center Utrecht, NL: M.G.E.M. Ausems, M.J. Koudijs; Amsterdam Medical Center, NL: T.A.M. van Os, I. van de Beek; VU University Medical Center, Amsterdam, NL: K. van Engelen, J.J.P. Gille; Maastricht University Medical Center, NL: E.B. Gómez García, M.J. Blok, M. de Boer; University of Groningen, NL: 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; The nationwide network and registry of histo- and cytopathology in The Netherlands (PALGA): E.C. van den Broek. HEBON thanks the study participants and the registration teams of IKNL and PALGA for contributing to data collection. The authors would like to thank Michael Schaapveld for his help with the SIR to attained age analyses. The authors would like to thank all pathology departments at the hospitals that have send pathology material for study purposes, including the NKI-AVL Biobank. The authors thank the registration team at the Netherlands Comprehensive Cancer Organisation (IKNL) for the collection of data for the Netherlands Cancer Registry. The authors would like to thank J.J.R. Barkey Wolf for his help with writing part of the R-script.

Data availability

The data underlying this article were collected with informed consent in the national collaborative HEBON cohort study. The HEBON steering group provided permission to share the data for this purpose with the study team, including the corresponding author (HOP2016006).

References

1. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 2007;25(11):1329–33.
2. Beiner ME, Finch A, Rosen B, et al. The risk of endometrial cancer in women with BRCA1 and BRCA2 mutations. A prospective study. Gynecol Oncol 2007;104(1):7–10.
3. Segev Y, Iqbal J, Lubinski J, et al. The incidence of endometrial cancer in women with BRCA1 and BRCA2 mutations: an international prospective cohort study. Gynecol Oncol. 2013;130(1):127–31.
4. Laitman Y, Michaelson-Cohen R, Levi E, et al. Uterine cancer in Jewish Israeli BRCA1/BRCA2 mutation carriers. Cancer 2019;125(5):698–703.
5. Lee YC, Milne RL, Lheureux S, et al. Risk of uterine cancer for BRCA1 and BRCA2 mutation carriers. Eur J Cancer 2017;84:114–20.
6. Reitsma W, Mourits MJ, de Bock GH, Hollema H. Endometrium is not the primary site of origin of pelvic high-grade serous carcinoma in BRCA1 or BRCA2 mutation carriers. Mod Pathol 2013;26(4):572–8.
7. Kitson SJ, Bafligil C, Ryan NAJ, et al. BRCA1 and BRCA2 pathogenic variant carriers and endometrial cancer risk: A cohort study. Eur J Cancer 2020;136:169-75.
8. Shu CA, Pike MC, Jotwani AR, et al. Uterine Cancer After Risk-Reducing Salpingo-oophorectomy Without Hysterectomy in Women With BRCA Mutations. JAMA Oncol 2017;3(3):417–418.
9. Saule C, Mouret-Fourme E, Briaux A, et al. Risk of Serous Endometrial Carcinoma in Women With Pathogenic BRCA1/2 Variant After Risk-Reducing Salpingo-Oophorectomy. J Natl Cancer Inst 2018;110(2).
10. Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. Nature 2013;497(7447):67–73.
11. Hamilton CA, Cheung MK, Osann K, et al. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. Br J Cancer 2006;94(5):642–6.
12. McGunigal M, Liu J, Kalir T, Chadha M, Gupta V. Survival Differences Among Uterine Papillary Serous, Clear Cell and Grade 3 Endometrioid Adenocarcinoma Endometrial Cancers: A National Cancer Database Analysis. Int J Gynecol Cancer 2017;27(1):85–92.
13. Thomas S, Hussein Y, Bandyopadhyay S, et al. Interobserver Variability in the Diagnosis of Uterine High-Grade Endometrioid Carcinoma. Arch Pathol Lab Med. 2016;140(8):836–43.
14. León-Castillo A, de Boer SM, Powell ME et al. Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy. J Clin Oncol. 2020;38(29):3388-97.
15. de Jonge MM, Auguste A, van Wijk LM, et al. Frequent homologous recombination deficiency in high-grade endometrial carcinomas. Clin Cancer Res 2019;25(3):1087–1097.
16. de Jonge MM, Ritterhouse LL, de Kroon CD, et al. Germline BRCA-associated Endometrial Carcinoma is a Distinct Clinicopathologic Entity. Clin Cancer Res 2019;25(24):7517–7526.
17. Heemskerk-Gerritsen BA, Seynaeve C, van Asperen CJ, et al. Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk reduction. J Natl Cancer Inst 2015;107(5).

18. Plon SE, Eccles DM, Easton D, et al. Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. Hum Mutat 2008;29(11):1282–91.
19. Casparie M, Tiebosch AT, Burger G, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. Cell Oncol 2007;29(1):19–24.
20. Hughley R, Karlic R, Joshi H, Turnbull C, Foulkes WD, Polak P. Etiologic Index–A Case-Only Measure of BRCA1/2-Associated Cancer Risk. N Engl J Med 2020;16;383(3):286-288.
21. Bergman L, Beelen ML, Gallee MP, Hollema H, Benraadt J, van Leeuwen FE. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of Liver and Endometrial cancer Risk following Tamoxifen. Lancet 2000;356(9233):881–7.
22. Swerdlow AJ, Jones ME. Tamoxifen treatment for breast cancer and risk of endometrial cancer: a case-control study. J Natl Cancer Inst 2005;97(5):375–84.
23. Jones ME, van Leeuwen FE, Hoogendoorn WE, et al. Endometrial cancer survival after breast cancer in relation to tamoxifen treatment: pooled results from three countries. Breast Cancer Res 2012;14(3):R91.
24. Ashley CW, Da Cruz Paula A, Kumar R, et al. Analysis of mutational signatures in primary and metastatic endometrial cancer reveals distinct patterns of DNA repair defects and shifts during tumor progression. Gynecol Oncol 2019;152(1):11–19.
25. Cancer Genome Atlas Research Network. Comprehensive molecular portraits of human breast tumors. Nature 2012;490(7418):61–70.
26. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature 2011;474(7353):609–15.
27. Lord CJ, Ashworth A. BRCAness revisited. Nat Rev Cancer 2016;16(2):110–20.
28. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 2008;371(9612):569-78.
29. McCullough ML, Patel AV, Patel R et al. Body mass and endometrial cancer risk by hormone replacement therapy and cancer subtype. Cancer Epidemiol Biomarkers Prev 2008;17(1):73-9.
30. Renehan AG, MacKintosh ML, Crosbie EJ. Obesity and endometrial cancer: unanswered epidemiological questions. BJOG 2016;123(2):175-8.
31. Medicines & Healthcare products Regulatory Agency. https://assets.publishing.service.gov.uk/media/5d680384ed915d53b8ebdba7/table2.pdf. Date accessed: October 2020
32. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. Lancet 2016;387(10023):1094–108.
33. Integraal Kankercentrum Nederland. www.iknl.nl/nkr-cijfers. Date accessed: January 2019
34. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol 2014;15(8):852–61.

35. Fulk K, Milam MR, Li S, et al. Women with breast and uterine cancer are more likely to harbor germline mutations than women with breast or uterine cancer alone: A case for expanded gene testing. Gynecol Oncol 2019;152(3):612–617.
36. Pennington KP, Walsh T, Lee M, et al. BRCA1, TP53, and CHEK2 germline mutations in uterine serous carcinoma. Cancer 2013;119(2):332–8.

Supplementary methods

HEBON cohort study

Women are eligible for inclusion in the "HEreditary Breast and Ovarian cancer study, the Netherlands (HEBON cohort study)[1, 2] if they have undergone genetic testing for *BRCA1/2* and *CHEK2* in one of the participating centres (all Dutch academic medical centres and the Netherlands Cancer Institute). The HEBON cohort study collects data from participants via questionnaires and input from the Netherlands Cancer Registry (NCR), the Dutch Pathology Registry (PALGA)[3] and the municipal administration (BRP). The HEBON cohort study is performed in accordance with the declaration of Helsinki.

Data collection

Data entry into the central HEBON database is exclusively performed by trained data managers. Data on the type of mutation (*BRCA1, BRCA2*) and the date of the *BRCA1/2* DNA test were retrieved from the hospitals where screening took place. Data on personal cancer history (based on topographical and morphological codes; ICD-0-3 codes; http://codes.iarc.fr/), date/age/year of cancer diagnosis and treatment history (latter only available for breast cancer (BC) and tubo-ovarian cancer (OC)) were retrieved from the NCR, which registers all cancer diagnoses in the Netherlands and includes other variables such as treatment history. If additional data were found in pathology reports obtained via PALGA (e.g. on treatment history), these were added to the previously mentioned variables. Data on risk-reducing salpingo-oophorectomies (RRSO) and date of RRSO was obtained via PALGA. Data on deaths and date of deaths were obtained via the BRP, supplemented with data from the NCR, pathology reports and information obtained from family members.

For *BRCA1/2* mutation carriers who provided informed consent the most recent data input from the NCR and PALGA was in June and December 2017 (tumour registration/data complete up to January 2016). For all other women (*BRCA1/2* and non-*BRCA1/2* mutation carriers), the most recent NCR and PALGA input dates to April and June 2015, respectively (tumour registration/data complete up to January 2012). The most recent data from the BRP were received in December 2016 for *BRCA1/2* mutation carriers with informed consent, and June 2012 for all other women.

Data handling and missing variables

Four women (*BRCA1/2* mutation carriers, *n*=3/5,980 (0.05%); non-*BRCA1/2* mutation carriers, *n*=1/8,451 (0.1%)) were registered as deceased in the HEBON database while the date/age/year of death was unknown. In these cases, the date of death was considered to be between the last live contact and the end of follow-up.

For 2,896 women (*BRCA1/2* mutation carriers, *n*=1,682/5,980 (28.1%); non-*BRCA1/2* mutation carriers, *n*=1,214/5,980 (14.4%)), the date of the *BRCA1/2* DNA test was unknown. In these cases the date of a *BRCA1/2* DNA test was considered to be 01-01-1995 (date from which *BRCA1/2* DNA testing became regularly available).

The date/age/year of BC diagnosis was unknown for one *BRCA2* mutation carrier. In the subanalyses where BC was added as censoring event, the first occurring censoring event other than date of BC was used for censoring. For the description of baseline characteristics, BC was considered to have occurred during the observation period.

The date/age/year of OC diagnoses was unknown for two non-*BRCA1/2* mutation carriers. For the description of baseline characteristics, OC diagnoses were considered to have occurred during the observation period.

Data on a history of RRSO were manually curated for all women who developed endometrial cancer (including uterine sarcomas; EC) during follow-up, using the pathology reports (if available) retrieved from PALGA.

Data on whether or not women received hormone treatment (HT) for a specific BC was retrieved by the NCR from medical files, and centrally collected by HEBON. This variable was available for the majority of BCs, but the type and duration of HT was not specified. If a women had both a history of HT-treated BC and a tumour with an unknown HT status (*BRCA1/2* mutation carriers *n*=17, non-*BRCA1/2* mutation carriers *n*=8), the date of HT-treated BC was used for all analyses that included HT-status.

Pathology review and histologic and molecular subgrouping

Pathology reports, hematoxylin and eosin (H&E) stained slides and formalin-fixed paraffin-embedded (FFPE) tumour tissue blocks for ECs of HEBON cohort *BRCA1/2* and non-*BRCA1/2* mutation carriers were collected via PALGA and centrally reviewed by at least one expert gynaecopathologist to confirm histotype and endometrial origin. All specimens were handled in compliance with the Code of Conduct for dealing responsibly with human tissue in the context of health research (2011) drawn up by the Federation of Dutch Medical Scientific Societies.

Assignment of histologic subgroups

Histologic subtype diagnosis for cases that were available for pathology review were based on The World Health Organization (2014) criteria. Pathology review was primarily based on morphology (H&E slides without immunohistochemical stains), with the exception of high-grade EC without defining features (ambiguous EC). All cases with high-grade histology without defining features/for which histotype was difficult to establish (“ambiguous”) were reviewed

by at least two gynaecopathologists. When both agreed that the case was "ambiguous", *TP53*-mutation status/P53-IHC expression was used for further differentiation. *TP53*-wildtype/p53-wildtype ambiguous carcinomas were considered to be of the "endometrioid" histologic subgroup, and *TP53*-mutant/p53-abnormal ambiguous carcinomas were considered to be of the "serous-like" histologic subgroup. For cases that were not available for revision, histologic subtype and grade were extracted from pathology reports or, if unavailable, from the morphological ICD-0-3.1 code.

After pathology review, ECs were divided in the same histologic subgroups as the comparison group 1: (1) endometrioid (including *TP53*-wildtype/p53-wildtype ambiguous carcinomas), (2) serous-like (including *TP53*-mutant/p53-abnormal ambiguous carcinomas), (3) clear cell carcinoma, (4) sarcoma and (5) other.

Histologic, molecular and clinical characteristics of a subset of ECs in *BRCA1/2* mutation carriers were comprehensively described previously (case-ID; 1-41).[2]

Assignment of molecular subgroups

In the case of the *BRCA1/2* mutation carriers included in the study by de Jonge and colleagues,[2] the UCM-OncoPlus Assay[4] on FFPE-isolated tumour DNA was used for *TP53* mutation analyses. For the ECs in *BRCA1/2* mutation carriers included in this study, but for which mutation analysis failed/was not available (*n=3),* and for the ECs of both *BRCA1/2* mutation carriers (CaseID 42-62) and non-*BRCA1/2* mutation carriers (CaseID 101-140) that were not included in the study by de Jonge and collegues,[2] p53 immunohistochemistry was used as a surrogate marker to determine *TP53* mutation status. This was either performed manually (clone DO-7, 1:2000, DAKO) as described previously[2] or using the Dako Omnis autostainer (Agilent, Santa Clara, CA). For the Dako Omnis autostainer, slides were deparaffinized and antigen retrieval was achieved on board using EnVision FLEX High pH Target Retrieval Solution for 30 minutes at 97 °C. Slides were then incubated on board at 32 °C with the following primary antibodies: p53, clone DO-7, Ready-To-Use (Dako) for 25 minutes; PMS2, clone EP51.2, ready-to-use for (Dako) for 25 minutes and MSH6 1:400; clone EPR3945 (Abcam) for 20 minutes. For PMS2, this was followed by incubation with a secondary antibody (EnVision FLEX+ rabbit LINKER) for 10 minutes. EnVision FLEX DAB+ was used as chromogen for 5 minutes, followed by counterstaining of the slides for 6 minutes using Mayer's hematoxylin.

Focal, weak and heterogeneous (not subclonal) nuclear p53 staining was considered as p53 "wild-type". Diffuse and strong nuclear staining >90% or completely absent nuclear staining "null pattern" (with positive internal control) was considered as p53-abnormal/mutant. In cases where p53 IHC was inconclusive, molecular analysis using next-generation sequencing was performed to determine final *TP53* mutation status (*n*=1). If a EC showed abnormal p53 expression or a *TP53* mutation, additional staining for MMR proteins (PMS2, MSH6) was

performed. Expression of MMR proteins was scored in three categories (retained, loss and subclonal/regional loss of protein expression) as described previously reported by Stelloo and colleagues.[5] Tumours in which at least one of the mismatch repair proteins showed loss of expression were considered MMR-deficient (MMRd).

Using these surrogate markers, tumours were subsequently classified in one of the molecular subgroups as previously described:[6-8] (1) p53-abnormal or (2) other (including *POLE*-mutant: only analysed for cases included in the study by de Jonge and colleagues;[2] mismatch repair (MMR)-deficient and no surrogate marker profile group (NSMP)). In case both a *TP53* mutation/abnormal p53 expression and a MMRd phenotype were present (not considering subclonal/regional loss of MMRd), cases were assigned to the "other" group.[6, 9]

For cases in which no FFPE block was available for p53 analysis, p53 status was based upon histologic subtype and grade. These were used for classification in the molecular subgroups and subsequent analyses: EEC grade1/2, adenocarcinoma NOS grade 1/2, EEC/adenocarcinoma NOS grade not specified and clear cell carcinomas were assigned to the *TP53*-wildtype group.[6, 10, 11] EEC grade 3 and adenocarcinoma NOS grade 3 were considered 50% *TP53* wildtype, 50% *TP53* mutant.[6, 12] Uterine serous carcinomas and carcinosarcomas were considered *TP53* mutant.[6, 13]

Supplementary references

1. Heemskerk-Gerritsen BA, Seynaeve C, van Asperen CJ, et al. Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk reduction. J Natl Cancer Inst 2015;107(5).
2. de Jonge MM, Ritterhouse LL, de Kroon CD, et al. Germline BRCA-associated Endometrial Carcinoma is a Distinct Clinicopathologic Entity. Clin Cancer Res 2019;25(24):7517–7526.
3. Casparie M, Tiebosch AT, Burger G, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. Cell Oncol 2007;29(1):19–24.
4. Kadri S, Long BC, Mujacic I, et al. Clinical Validation of a Next-Generation Sequencing Genomic Oncology Panel via Cross-Platform Benchmarking against Established Amplicon Sequencing Assays. J Mol Diagn 2017;19(1):43–56.
5. Stelloo E, Jansen AML, Osse EM, et al. Practical guidance for mismatch repair-deficiency testing in endometrial cancer. Ann Oncol 2017;28(1):96–102.
6. Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67–73.
7. Talhouk A, McConechy MK, Leung S, et al. A clinically applicable molecular-based classification for endometrial cancers. Br J Cancer 2015;113(2):299–310.
8. Stelloo E, Bosse T, Nout RA, et al. Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; a TransPORTEC initiative. Mod Pathol 2015;28(6):836–44.
9. León-Castillo A, de Boer SM, Powell ME et al. Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy. J Clin Oncol 2020;38(29):3388-97.
10. DeLair DF, Burke KA, Selenica P, et al. The genetic landscape of endometrial clear cell carcinomas. J Pathol 2017;243(2):230–241.
11. Stelloo E, Nout RA, Osse EM, et al. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts. Clin Cancer Res 2016;22(16):4215–24.
12. Bosse T, Nout RA, McAlpine JN, et al. Molecular Classification of Grade 3 Endometrioid Endometrial Cancers Identifies Distinct Prognostic Subgroups. Am J Surg Pathol 2018;42(5):561–8.
13. Cherniack AD, Shen H, Walter V, et al. Integrated Molecular Characterization of Uterine Carcinosarcoma. Cancer cell 2017;31(3):411–23.

Supplementary Table 1. Previously published cohort studies on endometrial cancer risk in *BRCA1/2* mutation carriers

Study	Cohort size	Total years at risk	Mean/median age at enrolment	Mean/ median follow-up years	Path review	Observed (of which tamoxifen exposed)	Expected	SIR (95% CI, *p*-value)	EC distribution by *BRCA*-mutation	Countrie(s) from which the study population was retrieved
Beiner et al., 2007	All: 857 *BRCA1;* 619 *BRCA2;* 236 both; 2	2787	54.4 (range: 45-70)	3.3 (range: 0.01-9.6)	No	6 (4) EC *6 (4) endometrioid*	1.13 n.a	5.3 (n.a, *p*=0.0011)[a]	4x *BRCA1* 2x *BRCA2*	North America, Europe, and Israel
Segev et al., 2013	All: 4456 *BRCA1;* 3536 *BRCA2;* 920	25322	42.7 (range: n.a.)	5.7 (range: n.a.)	No	17 (8) EC	9.06	1.87 (1.13-2.94, *p*=0.01)[b]	13x *BRCA1* 4x *BRCA2*	Canada, Italy, USA, Austria, Poland, Norway
Reitsma et al., 2013	All: 315 *BRCA1;* 201 *BRCA2;* 114	2062	43 (range: 30–71)	6 (range: 0-27)	No	2 (0) EC *2 (0) endometrioid*	0.94 *n.a*	2.13 (0.24-7.69, *p*=0.27)	1x *BRCA1* 1x *BRCA2*	The Netherlands
Shu et al., 2016	All: 1083 *BRCA1;* 627 *BRCA2;* 453 both; 3	6377	45.6 (IQR: 40.9-52.5)	5.1 (IQR: 3.0-8.4)	Partly	8 (5) EC *2 (2) endometrioid* *5 (3) serous(-like)* *1 (0) sarcoma*	4.30 3.62 0.34 0.14	1.9 (0.8-3.7, *p*=0.09) *0.6 (0.1-2.0, p=0.88)* *14.8 (4.8-34.6, p<0.001)*[c] *7.1 (0.2-39.4, p=0.13)*	5x *BRCA1* 3x *BRCA2*	USA and United Kingdom
Lee et al., 2017	All: 828 *BRCA1;* 438 *BRCA2;* 390	*n.a.*	43 (IQR: 34-52)	9 (IQR: n.a.)	No	5 (3) EC *5 (3) endometrioid*	2.04 *n.a*	2.45 (0.80-5.72, *p*=0.11)	3x *BRCA1* 2x *BRCA2*	Australia and New Zealand
Saule et al., 2018	All: 369 *BRCA1;* 238 *BRCA2;* 131	1779	*BRCA1:*47.22 (IQ: 1.29) *BRCA2:* 52.75 (IQ: 6.83)	*n.a.*[d] *n.a.*[d]	Yes	2 (0) EC *2 (0) serous*	0.62 0.062	"not increased", *p*=0.26 *32.2 (11.5-116.4, p<0.001)*	2x *BRCA1* 0x *BRCA2*	France

Continue

Continued

Study	Cohort size	Total years at risk	Mean/median age at enrolment	Mean/ median follow-up years	Path review	Observed (of which tamoxifen exposed)	Expected	SIR (95% CI, *p*-value)	EC distribution by *BRCA*-mutation	Countrie(s) from which the study population was retrieved
Laitman et al., 2019	All: 2627	32774	*n.a.*	*n.a.*	No	14 (2[e]) EC	3.52	3.98 (2.174-6.673, *p<0.001*)	10x *BRCA1*	Israel, mainly includes founder mutations; (*BRCA1*; 185delAG & 5382insC, *BRCA2*; 6174delT)
	BRCA1; 1463					*5 ([e]) endometrioid*	*n.a*	*n.a.*	*4x BRCA2*	
	BRCA2; 1154					*5 (1) serous(-like)*	0.35	*14.29 (4.639-33.34, p<0.001)*		
	both; 10					*4 (1) sarcoma*	0.106	*37.74 (10.28-96.62, p<0.001)*		
Kitson et al., 2020	All: 2609	59199	20.0 (IQR: 20.0-31.6)	23.8 (IQR: n.a.)	Partly	14 (3[f]) EC	8.22	1.70 (0.74-3.33, *p=n.a.*)	7x *BRCA1*	United Kingdom
	BRCA1; 1350					*7 (2[f]) endometrioid*	*n.a.*	*n.a.*	7x *BRCA2*	
	BRCA2; 1259					*3 (1[f]) serous-like*	0.82	*3.66 (0.01-23.41, p=n.a.)*		
						4 (0[f]) unknown	*n.a.*	*n.a.*		
de Jonge et al., current study	**All: 5980**	119296	27.4 (IQR: 25.0-37.8)	22.5 (IQR: 15.2-27.0)	Partly	58 (8[g]) EC	20.53	2.83 (2.2-3.7), p<0.001[h]	44x *BRCA1*	The Netherlands
	BRCA1; 3788					*35 (3[g]) endometrioid*	16.85	*2.07 (1.5-2.9), p<0.001*[h]	14x *BRCA2*	
	BRCA2; 2151					*19 (5[g]) serous(-like)*	1.95	*9.77 (6.2-15.3), p<0.001*[h]		
	both; 41					*3 (0) sarcoma*	1.3	*2.30 (0.7-7.1), p=0.14*		
						1 (0) clear cell	0.29	*3.40 (0.5-24.1), p=0.25*		

[a]SIR only including non-tamoxifen exposed women; 2.7 (95% CI: n.a., *p*=0.17). [b]SIR only including non-tamoxifen exposed women; 1.67 (95% CI: 0.81-3.07, p=0.1). [c]SIR (serous-like) only including non-tamoxifen exposed women; 11.3 (95% CI: 1.4-40.8, *p*=0.01). [d]Age at end follow-up was given instead of follow-up years; *BRCA1*: 52.75 (IQR: 6.83), *BRCA2*: 56.51 (IQR: 0.8). [e]For 2/5 endometrioid EC, tamoxifen-exposure status was unknown, [f]History of tamoxifen-use was unknown for 4 cases; 1 with endometrioid histology, 2 with serous-like histology and 1 with unknown histology [g]Type and duration of hormone treatment not available. [h]For hazard ratios when additionally censoring for hormone-treated breast cancer, see Table 4.

Supplementary Table 2. Description of morphological ICD-0-3.1 codes assigned to the different histologic subgroups

Endometrioid (includes mucinous)	ICD-0 code	Serous/serous-like	ICD-0 code	Clear cell	ICD-0 code	Sarcoma	ICD-0 code	Other	ICD-0 code
Endometrioid adenocarcinoma, NOS	8380	Serous cystadenocarcinoma, NOS	8441	Clear cell adenocarcinoma, NOS	8310	Endometrial stromal sarcoma, NOS	8930	Neoplasm, malignant	8000
Endometrioid adenocarcinoma, secretory variant	8382	Papillary adenocarcinoma, NOS	8260			Endometrial stromal sarcoma, low grade	8931	Tumour cells, malignant	8001
Endometrioid adenocarcinoma, ciliated cell variant	8383	Serous surface papillary carcinoma	8461			Leiomyosarcoma, NOS	8890	Carcinoma, undifferentiated, NOS	8020
Adenocarcinoma with squamous metaplasia	8570	Papillary serous cystadenocarcinoma	8460			Epithelioid leiomyosarcoma	8891	Large cell carcinoma, NOS	8012
Adenosquamous carcinoma	8560	Cystadenocarcinoma	8440			Myxoid leiomyosarcoma	8896	Large cell neuroendocrine carcinoma	8013
Adenocarcinoma with spindle cell metaplasia	8572	Mesodermal mixed tumour	8951			Rhabdomyosarcoma, NOS	8900	Large cell carcinoma with rhabdoid phenotype	8014
Adenocarcinoma with apocrine metaplasia	8573	Carcinosarcoma, NOS	8980			Myosarcoma	8895	Glassy cell carcinoma	8015
Mucin-producing adenocarcinoma	8481	Mullerian mixed tumour	8950			Pleomorphic rhabdomyosarcoma, adult type	8901	Giant cell carcinoma	8031
Villous adenocarcinoma	8262	Metaplastic carcinoma, NOS	8575			Mixed type rhabdomyosarcoma	8902	Pseudosarcomatous carcinoma	8033
Adenocarcinoma, NOS	8140	Carcinofibroma	8934			Embryonal rhabdomyosarcoma, NOS	8910	Small cell carcinoma, NOS	8041
Carcinoma, NOS	8010	Adenocarcinoma with mixed subtypes	8255			Alveolar rhabdomyosarcoma	8920	Combined small cell carcinoma	8045
Solid carcinoma, NOS	8230	Mixed cell adenocarcinoma	8323			Sarcoma, NOS	8800	Non-small cell carcinoma	8046
Adenocarcinoma in adenomatous polyp	8210					Spindle cell sarcoma	8801	Squamous cell carcinoma, NOS	8070
Adenocarcinoma in villous adenoma	8261					Giant cell sarcoma (except of bone M-9250/3)	8802	Squamous cell carcinoma, keratinizing, NOS	8071
Adenocarcinoma in tubolovillous adenoma	8263					Small cell sarcoma	8803	Squamous cell carcinoma, large cell, nonkeratinizing, NOS	8072
Endometrioid adenofibroma, malignant	8381					Undifferentiated sarcoma	8805	Squamous cell carcinoma, spindle cell	8074

Continue

Continued

Endometrioid (includes mucinous)	ICD-0 code	Serous/serous-like	ICD-0 code	Clear cell	ICD-0 code	Sarcoma	ICD-0 code	Other	ICD-0 code
Mucinous adenocarcinoma	8480					Fibrosarcoma, NOS	8810	Basaloid squamous cell carcinoma	8083
						Malignant fibrous histiocytoma	8830	Squamous cell carcinoma, clear cell type	8084
						Malignant perivascular epitheliod cell tumour	8714	Transitional cell carcinoma	8120
						Adenosarcoma	8933	Scirrhous adenocarcinoma	8141
						Stromal sarcoma, NOS	8935	Superficial spreading adenocarcinoma	8143
						Mesenchymoma, malignant	8990	Adenoid cystic carcinoma	8200
						Synovial sarcoma, NOS	9040	Cribriform carcinoma, NOS	8201
						Haemangiosarcoma	9120	Tubular adenocarcinoma	8211
						Chondrosarcoma, NOS	9220	Carcinoid tumour, NOS	8240
						Ewing sarcoma	9260	Mixed adenoneuroendocrine carcinoma	8244
								Neuroendocrine carcinoma, NOS	8246
								Acidophil carcinoma	8280
								Clear cell adenocarcinofibroma	8313
								Granular cell carcinoma	8320
								Follicular adenocarcinoma, NOS (C73.9)	8330
								Adenocarcinoma, endocervical type	8384
								Papillary cystadenocarcinoma, NOS	8450
								Papillary mucinous cystadenocarcinoma	8471
								Mucinous adenocarcinoma, endocervical type	8482

Continue

Continued

Endometrioid (includes mucinous)	ICD-0 code	Serous/serous-like	ICD-0 code	Clear cell	ICD-0 code	Sarcoma	ICD-0 code	Other	ICD-0 code
								Signet ring cell carcinoma	8490
								Adenocarcinoma with neuroendocrine differentiation	8574
								Mesonephroma, malignant	9110
								Peripheral neuroectodermal tumour	9364
								Malignant peripheral nerve sheath tumour	9540
								No microscopic confirmation	9990

Supplementary Table 3. Number of person-years at risk and number of events per 5-year age category for *BRCA1/2* mutation carriers and non-*BRCA1/2* mutation carriers

	BRCA1/2 carriers					non-*BRCA1/2* carriers			
Age category	**Person-years at risk, No. (%)**	**All ECs[a], No (%)**	**Endometrioid, No. (%)**	**Serous-like, No. (%)**	**Sarcoma, No. (%)**	**Person-years at risk, No. (%)**	**All ECs[b], No. (%)**	**Endometrioid, No. (%)**	**Serous-like No. (%)**
25-29	14643 (12.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	19663 (12.2)	1 (3.0)	1 (3.3)	0 (0.0)
30-34	17091 (14.3)	2 (3.4)	1 (2.9)	0 (0.0)	1 (33.3)	23376 (14.5)	0 (0.0)	0 (0.0)	0 (0.0)
35-39	17990 (15.1)	2 (3.4)	2 (5.7)	0 (0.0)	0 (0.0)	24984 (15.5)	1 (3.0)	1 (3.3)	0 (0.0)
40-44	17408 (14.6)	2 (3.4)	2 (5.7)	0 (0.0)	0 (0.0)	24303 (15.1)	0 (0.0)	0 (0.0)	0 (0.0)
45-49	15435 (12.9)	7 (12.1)	4 (11.4)	3 (15.8)	0 (0.0)	21314 (13.3)	4 (12.1)	4 (1.3)	0 (0.0)
50-54	12578 (10.5)	7 (12.1)	5 (14.2)	0 (0.0)	2 (66.7)	16704 (10.4)	9 (27.3)	8 (26.7)	1 (33.3)
55-59	9306 (7.8)	9 (15.5)	5 (14.2)	3 (15.8)	0 (0.0)	12133 (7.5)	5 (15.2)	5 (16.7)	0 (0.0)
60-64	6377 (5.3)	11 (19.0)	6 (14.2)	5 (26.3)	0 (0.0)	8124 (5.1)	6 (18.2)	6 (0.2)	0 (0.0)
65-69	4052 (3.4)	14 (24.1)	7 (20.0)	7 (36.8)	0 (0.0)	4580 (2.8)	3 (9.1)	3 (10.0)	0 (0.0)
70-74	2355 (2.0)	3 (5.2)	2 (5.7)	1 (5.3)	0 (0.0)	2709 (1.7)	3 (9.1)	2 (6.7)	1 (33.)
75-79	1225 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1593 (1.0)	1 (3.0)	0 (0.0)	1 (33.3)
80-84	558 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	826 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
85-89	219 (0.2)	1 (1.7)	1 (2.9)	0 (0.0)	0 (0.0)	382 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
90-94	42 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	121 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
95+	16 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	27 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a]One clear cell carcinoma occurred at age 59 years, this tumour is not separately mentioned in the columns. [b]None of the non-*BRCA1/2* mutation carriers developed a sarcoma or clear cell carcinoma during follow-up. Abbreviations; EC: Endometrial Cancer

Supplementary Table 4. Details on the included endometrial cancers in the cohort

	***BRCA* carriers**	**Non-*BRCA* carriers**	***p* value**[a]
Endometrial cancer, No. (%)	58 (100)	33 (100)	
Median age at diagnoses, yrs (range)	60.2 (33.1-85.4)	57.4 (29.7-79.8)	0.49
Histotype (after review)			
Endometrioid			
grade 1, No. (%)	18 (31.0)	14 (42.4)	
grade 2, No. (%)	3 (5.2)	2 (6.1)	
grade 3, No. (%)	6 (10.3)	1 (3.0)	
Mucinous, No. (%)	1 (1.7)	0 (0)	
Serous, No. (%)	9 (15.5)	1 (3.0)	
Carcinosarcoma, No. (%)	4 (6.9)	2 (6.1)	
Ambiguous, No. (%)	6 (10.3)	0 (0)	
Low grade endometrial stromal sarcoma, No. (%)	1 (1.7)	0 (0)	
Leiomyosarcoma, No. (%)	1 (1.7)	0 (0)	
Adenosarcoma, No. (%)	1 (1.7)	0 (0)	
Not reviewed, No. (%)	8 (13.8)	13 (39.4)	
Histologic groups			0.02
Endometrioid, No. (%)	35 (60.3)	30 (90.9)	
Serous/Serous-like[b], No. (%)	19 (32.8)	3 (9.1)	
Sarcoma, No. (%)	3 (5.2)	0 (0)	
Clear cell, No. (%)	1 (1.7)	0 (0)	
Other, No. (%)	0 (0)	0 (0)	
Occurrence EC			
After *BRCA1/2* DNA test, No. (%)	28 (48.3)	7 (21.2)	
Before *BRCA1/2* DNA test, No. (%)	20 (34.5)	22 (66.7)	
Date *BRCA1/2* DNA test unknown, No. (%)	10 (17.2)	4 (12.1)	
Pathology review			0.01
Available, No. (%)	50 (86.2)	20 (60.6)	
Not available, No. (%)	8 (13.8)	13 (39.4)	
Histologic group change after review			0.0102
Yes, No. (%)	11 (19.0)	0 (0.0)	
No, No. (%)	39 (67.2)	20 (60.6)	
Not reviewed, No. (%)	8 (13.8)	13 (39.4)	
p53-abnormal, including cases not available for review			<0.001
Yes, No. (%)	27 (46.6)	3 (9.1)	
No, No. (%)	31 (53.4)	30 (90.9)	
P53-abnormal, excluding cases not available for review			<0.001
Yes, No. (%)	27 (46.6)	2 (6.1)	
No, No. (%)	23 (39.7)	17 (51.5)	
Not available, No. (%)	8 (13.8)	14 (42.4)	
P53-status based on;			<0.001
Mutation analyses, No. (%)	37 (63.8)	0 (0.0)	
IHC, No. (%)	13 (22.4)	19 (57.6)	
Histotype, No. (%)	8 (13.8)	14 (42.4)	

Abbreviations: EC: Endometrial cancer, IHC: immunohistochemistry

[a]*p* values were calculated using the Chi-square test (categorical variables) and the Mann-Whitney U-test (numerical variables). [b]Includes six carcinomas of ambiguous morphology that were classified as serous-like based on p53-status.

Supplementary Table 5. Characteristics of endometrial cancers that occurred in the *BRCA1/2* mutation carrier cohort

Case ID[a]	Final histological subgroup[b]	BRCA mutation	Year	Age	Original diagnoses	Diagnoses after pathology review	P53-status[c]	Category change histologic subgroup after review	Molecular subgroup	RRSO, years in between RRSO-EC	Adnexal involvement/ (history of) ovarian malignancy	Adnexal specimens available for revision	Hysterectomy with/ without adnexae
Included as endometrial cancer in main analyses													
1	endometrioid	BRCA1	2011	63	EEC gr1	EEC gr1	wildtype[d]	No	Other	No	No	Yes	Hysterectomy, adnexae removed shortly before (RRSO with EC diagnoses in concurrently performed curettage)
2	endometrioid	BRCA1	2005	55	EEC gr2	EEC gr1	wildtype[d]	No	Other	Yes, 5.1	No	No	Hysterectomy without adnexae (history RRSO)
3	endometrioid	BRCA1	2013	70	EEC gr3	EEC gr3	mutant[d]	No	p53-abnormal	Yes, 15.6	No	Yes	Hysterectomy without adnexae (history RRSO)
11	endometrioid	BRCA1	2004	63	adenocarcinoma NOS, gr1	EEC gr1	wildtype[d]	No	Other	No	No	Yes	Hysterectomy with adnexae
13	endometrioid	BRCA1	2004	50	EEC gr1	EEC gr1	wildtype[d]	No	Other	No	No	Yes	Hysterectomy with adnexae
15	endometrioid	BRCA1	2009	74	EEC gr3	EEC gr3	mutant[d]	No	p53-abnormal	No	No	No, not removed	Hysterectomy without adnexae
17	endometrioid	BRCA1	2013	65	EEC gr3	EEC gr3	mutant[d]	No	p53-abnormal	Yes, 9.0	No	Yes	Hysterectomy without adnexae (history RRSO)
18	endometrioid	BRCA1	2005	59	EEC gr1	EEC gr1	wildtype[d]	No	Other	No	No	Yes	Hysterectomy with adnexae
19	endometrioid	BRCA1	1997	46	EEC gr2	EEC gr1	wildtype[d]	No	Other	No	No	Yes	Hysterectomy, adnexae removed shortly before
20	endometrioid	BRCA1	2011	49	EEC gr2	EEC gr3	mutant[d]	No	p53-abnormal	Yes, 9.5	No	Yes	Hysterectomy without adnexae (history RRSO)
21	endometrioid	BRCA1	2013	65	EEC gr2	EEC gr2	mutant[d]	No	p53-abnormal	Yes, 11.6	No	Yes	Hysterectomy without adnexae (history RRSO)
23	endometrioid	BRCA1	2011	53	mucinous	mucinous	wildtype[d]	No	Other	Yes, 6.1	No	Yes	Hysterectomy without adnexae (history RRSO)
28	endometrioid	BRCA1	2002	44	EEC gr1	EEC gr1	wildtype[d]	No	Other	Yes, 0.4	No	Yes	Hysterectomy without adnexae (history RRSO)
30	endometrioid	BRCA1	2012	39	EEC gr2	n.a.	n.a., considered *TP53* wildtype	n.a.	Other[e]	No	No	No, unknown if removed	Unknown
33	endometrioid	BRCA1	2000	49	EEC gr2	EEC gr1	wildtype[d]	No	Other	No	No	Yes	Hysterectomy with adnexae
34	endometrioid	BRCA1	2005	54	adenocarcinoma NOS, gr2	EEC gr2	mutant[d]	No	p53-abnormal	No[g]	No	Yes	Hysterectomy with fallopian tubes
35	endometrioid	BRCA1	2000	49	EEC gr1	EEC gr1	wildtype[d]	No	Other	No	No	Yes	Hysterectomy with adnexae

Continue

Continued

Case ID[a]	Final histological subgroup[b]	BRCA mutation	Year	Age	Original diagnoses	Diagnoses after pathology review	P53-status[c]	Category change histologic subgroup after review	Molecular subgroup	RRSO, years in between RRSO-EC	Adnexal involvement/ (history of) ovarian malignancy	Adnexal specimens available for revision	Hysterectomy with/ without adnexae
37	endometrioid	BRCA1	2014	33	EEC gr2-3	EEC gr2	mutant[d]	No	p53-abnormal	Yes, 5.1	No	Yes	Hysterectomy without adnexae (history RRSO)
38	endometrioid	BRCA1	2010	56	EEC gr1	EEC gr1	wildtype[d]	No	Other	Yes[h], 4.8	History ovarian clear cell carcinoma	Yes	Hysterectomy without adnexae (history ovariectomy)
41	endometrioid	BRCA1	2007	50	EEC gr2	EEC gr1	wildtype[d]	No	Other	Yes, 0.6	No	Yes	Hysterectomy without adnexae (history RRSO)
47	endometrioid	BRCA1	1999	58	adenocarci-noma NOS, gr1-2	EEC gr1	wildtype	No	Other	No	Simultaneous bilateral HGSOC	Yes	Hysterectomy with adnexae
50	endometrioid	BRCA1	2006	85	EEC gr3	EEC gr3	mutant[d]	No	p53-abnormal	No	No	No	Hysterectomy with adnexae
51	endometrioid	BRCA1	1996	69	EEC gr3	EEC gr3	mutant	No	p53-abnormal	No	No	Yes	Hysterectomy with adnexae
56	endometrioid	BRCA1	2007	63	EEC gr1	n.a.	n.a., considered *TP53* wildtype	n.a.	Other[e]	No	Simultaneous HGSOC left side, right side not reported	No	Hysterectomy with adnexae
60	endometrioid	BRCA1	1994	57	adenocarcino-ma NOS gr1	n.a.	n.a., considered *TP53* wildtype	n.a.	Other[e]	No	No	No, unknown if removed	Unknown
61	endometrioid	BRCA1	2006	68	EEC, gr not specified	n.a.	n.a., considered *TP53* wildtype	n.a.	Other[e]	No	Simultaneous HGSOC right side, left side not involved	No	Hysterectomy with adnexae
62	endometrioid	BRCA1	2008	40	EEC gr1	n.a.	n.a., considered *TP53* wildtype	n.a.	Other[e]	No	No	No	Hysterectomy with adnexae
4	endometrioid	BRCA2	2015	64	EEC gr1	EEC gr1	mutant[d]	No	Other[f]	Yes, 6.9	No	Yes	Hysterectomy without adnexae (history RRSO)
12	endometrioid	BRCA2	2004	62	EEC gr2	EEC gr1	wildtype[d]	No	Other	Yes, 1.0	No	Yes	Hysterectomy without adnexae (history RRSO)
24	endometrioid	BRCA2	2011	67	EEC gr2	EEC gr1	wildtype[d]	No	Other	No	No	Yes	Hysterectomy with adnexae
27	endometrioid	BRCA2	2009	61	EEC gr1	EEC gr1	wildtype[d]	No	Other	No	No	Yes	Hysterectomy with adnexae
31	endometrioid	BRCA2	2011	50	EEC gr2	EEC gr1	wildtype[d]	No	Other	No	Simultaneous bilateral EOC	Yes	Hysterectomy, adnexae removed shortly before
45	endometrioid	BRCA2	1989	65	adenocarcino-ma NOS, gr1	n.a.	n.a., considered *TP53* wildtype	n.a.	Other[e]	No	No	No	Hysterectomy with adnexae
52	endometrioid	BRCA2	2001	67	EEC gr2	EEC gr1	wildtype	No	Other	No	No	Yes	Hysterectomy with adnexae

Continue

Continued

Case ID[a]	Final histological subgroup[b]	BRCA mutation	Year	Age	Original diagnoses	Diagnoses after pathology review	P53-status[c]	Category change histologic subgroup after review	Molecular subgroup	RRSO, years in between RRSO-EC	Adnexal involvement/ (history of) ovarian malignancy	Adnexal specimens available for revision	Hysterectomy with/ without adnexae
58	endometrioid	BRCA2	2009	38	EEC gr1	n.a.	n.a., considered *TP53* wildtype	n.a.	Other[e]	yes, 5.0	No	No, unknown if removed	Unknown
5	serous-like	BRCA1	2015	68	serous	ambiguous	mutant[d]	No	p53-abnormal	Yes, 9.4	No	Yes	Hysterectomy without adnexae (history RRSO)
6	serous-like	BRCA1	2008	64	EEC gr3	serous	mutant[d]	Yes	p53-abnormal	No	No	Yes	Hysterectomy with adnexae
7	serous-like	BRCA1	2010	65	EEC gr1	ambiguous	mutant[d]	Yes	p53-abnormal	Yes, 11.7	No	Yes	Hysterectomy without adnexae (history RRSO)
8	serous-like	BRCA1	2009	65	EEC gr3	ambiguous	mutant[d]	Yes	p53-abnormal	Yes, 7.4	No	Yes	Hysterectomy without adnexae (history RRSO)
14	serous-like	BRCA1	2000	49	carcinosarcoma	carcinosarcoma, serous	mutant[d]	No	p53-abnormal	No	No	Yes	Hysterectomy with adnexae
16	serous-like	BRCA1	1996	59	adenocarcinoma NOS, gr2-3	sereus	mutant[d]	Yes	p53-abnormal	No	No	Yes	Hysterectomy with adnexae
22	serous-like	BRCA1	2015	63	carcinosarcoma, serous	carcinosarcoma, ambiguous	mutant[d]	No	Other[f]	Yes, 4.7	No	Yes	Hysterectomy without adnexae (history RRSO)
26	serous-like	BRCA1	2012	49	EEC gr3	carcinosarcoma, ambiguous	mutant[d]	Yes	p53-abnormal	Yes, 4.0	No	Yes	Hysterectomy without adnexae (history RRSO)
39	serous-like	BRCA1	2003	65	EEC gr2	ambiguous	mutant[d]	Yes	p53-abnormal	Yes	No	Yes	Hysterectomy without adnexae (history RRSO)
40	serous-like	BRCA1	2006	58	EEC gr3	serous	mutant[d]	Yes	p53-abnormal	Yes, 6.8	No	Yes	Hysterectomy without adnexae (history RRSO)
43	serous-like	BRCA1	2006	60	serous	serous	mutant	No	p53-abnormal	No	No	Yes	Hysterectomy with adnexae
44	serous-like	BRCA1	2001	73	adenocarcinoma NOS, gr3	serous	mutant	Yes	p53-abnormal	No	Unknown	No, no hysterectomy/ adnexextirpation	No hysterectomy/adnexextirpation performed, diagnosis based on cervical biopsy, vagina wand biopsy and curretage
48	serous-like	BRCA1	1989	47	adenocarcinoma NOS, gr1	serous	mutant	Yes	p53-abnormal	No	No	No, not removed	Hysterectomy without adnexae
49	serous-like	BRCA1	1997	65	EEC gr3	ambiguous	mutant	Yes	p53-abnormal	No	Unknown	No	Hysterectomy with adnexae
53	serous-like	BRCA1	2001	65	carcinosarcoma, unspecified	carcinosacoma, serous	mutant	No	p53-abnormal	No	No	Yes	Hysterectomy with adnexae

Continue

Continued

Case ID[a]	Final histological subgroup[b]	BRCA mutation	Year	Age	Original diagnoses	Diagnoses after pathology review	P53-status[c]	Category change histologic subgroup after review	Molecular subgroup	RRSO, years in between RRSO-EC	Adnexal involvement/ (history of) ovarian malignancy	Adnexal specimens available for revision	Hysterectomy with/ without adnexae
25	serous-like	BRCA2	2015	64	serous	serous	mutant[d]	No	p53-abnormal	Yes, 4.5	No	Yes	Hysterectomy without adnexae (history RRSO)
29	serous-like	BRCA2	2006	57	serous	serous	mutant[d]	No	p53-abnormal	Yes, 6.1	No	Yes	Hysterectomy without adnexae (history RRSO)
32	serous-like	BRCA2	2009	62	serous	serous	mutant[d]	No	p53-abnormal	No	No	Yes	Hysterectomy with adnexae
55	serous-like	BRCA2	2009	68	large cell carcinoma NOS	ambiguous	mutant	Yes	p53-abnormal	No	Unknown	No, no hysterectomy/ adnexextirpation	No hysterectomy/ adnexextirpation performed, diagnoses based on vaginal and cervical biopsy
36	sarcoma	BRCA1	2007	33	low-grade ESS	low-grade ESS	wildtype	No	Other	No	No	Yes	Hysterectomy without adnexae, fallopian tubes were removed shortly prior to hysterectomy during uterine biopsy
42	sarcoma	BRCA2	1995	53	leiomyosarcoma	leiomyosarcoma	wildtype	No	Other	No	No	No, not removed	Hysterectomy without adnexae
46	sarcoma	BRCA2	2001	54	adenosarcoma	adenosarcoma	wildtype	No	Other	No	No	No, not removed	Hysterectomy without adnexae
59	clear cell	BRCA1	2003	59	clear cell carcinoma	n.a.	n.a., considered *TP53* wildtype	n.a.	Other[e]	No	No	No	Unknown
Endometrial cancer outside observation period main analyses													
10	serous-like	BRCA2	2016	49	EEC gr1	carcinosarcoma, serous	mutant[d]	Yes	p53-abnormal	Yes, 4.3	No	Yes	Hysterectomy without adnexae (history RRSO)
54	serous-like	BRCA1	1988	62	adenocarcinoma NOS, gr3	serous	mutant	Yes	p53-abnormal	No	No	Yes, only left side resected	Hysterectomy and left adnex
57	endometrioid	BRCA2	2012	65	EEC gr2	n.a.	n.a., considered *TP53* wildtype	n.a.	Other[e]	yes, 12.1	No	No	Hysterectomy without adnexae (history RRSO)
Not considered endometrial cancer after revision, outside observation period													
9	No EC	BRCA1	1983	45	endocervical adenocarcinoma	n.a.	n.a.	n.a.		Yes, no EC after revision	No	No	Unknown, RRSO one month before resection

Abbreviations: EEC: Endometrioid endometrial carcinoma, n.a.: not available, NOS: Not otherwise specified, RRSO: Risk-reducing salpingo-oophorectomy, EC: Endometrial cancer [a]CaseIDs number 1-41 correspond with CaseIDs from our previous publication; De Jonge and colleagues, CCR 2019. [b]Based on diagnoses after pathology review when available. [c]P53-status based on IHC, molecular analyses or most common pattern based on literature in case no FFPE blocks were available. "Mutant" includes both overexpression pattern and null-pattern. [d]P53-status based on mutational analyses (see de Jonge and colleagues, CCR 2019). [e]Molecular subgroup based on most prevalent p53 status for the histologic subtype, no FFPE-tumour tissue block was available for determining p53-status. [f]Tumour was also mismatch repair deficient and therefore considered as "other" molecular subgroup. [g]Ovaries were previously removed (without fallopian tubes); this was not considered as RRSO. [h]History of therapeutic ovariectomy because of ovarian clear cell carcinoma.

Supplementary Table 6. Characteristics of endometrial cancers that occurred in the non-*BRCA1/2* mutation carrier cohort

Case ID	Final histological subgroup[a]	Year	Age	Original diagnoses	Diagnoses after pathology review	P53 status[b]	Molecular subgroup	Category change histologic subgroup after review	RRSO, years in between RRSO-EC	Adnexal involvement/ (history of) ovarian malignancy	Adnexal specimens available for revision	Hysterectomy with/ without adenxae
Included as endometrial cancer in main analyses												
101	Endometrioid	1990	46	adenocarcinoma NOS, gr3	n.a.	n.a., considered *TP53* mutant	p53-ab-normal[c]	n.a.	No	No	No	Hysterectomy with adnexae
102	Endometrioid	2010	53	EEC gr1	EEC gr1	wildtype	other	No	No	No	No	Hysterectomy with adnexae
104	Endometrioid	2004	54	EEC gr2	EEC gr1	wildtype	other	No	No	Simultaneous EOC gr1 right side, considered as second primary	Yes	Hysterectomy with adnexae
105	Endometrioid	2000	54	EEC, gr not specified	EEC gr1	wildtype	other	No	No	No	Yes	Hysterectomy with adnexae
106	Endometrioid	1998	65	Adenocarcinoma NOS gr2	EEC gr2	wildtype	other	No	No	No	No	Hysterectomy with adnexae
108	Endometrioid	2009	58	EEC gr1	EEC gr1	wildtype	other	No	No	No	Yes	Hysterectomy with adnexae
110	Endometrioid	2005	60	adenocarcinoma NOS gr1	EEC gr1	n.a., considered *TP53* wildtype	other[c]	No	No	No	Yes	Hysterectomy with adnexae
111	Endometrioid	2003	37	adenocarcinoma NOS gr1	EEC gr1	wildtype	other	No	Unknown	No	No, not removed	Hysterectomy without adnexae
112	Endometrioid	2007	49	adenocarcinoma NOS gr1	EEC gr1	wildtype	other	No	No	Simultaneous EOC right side, considered as second primary	Yes, left side not removed	Hysterectomy with right adnex
113	Endometrioid	1997	48	EEC gr1	EEC gr1	wildtype	other	No	No	No	yes	Hysterectomy with adnexae
114	Endometrioid	2008	57	EEC gr 2	EEC gr3	wildtype	other	No	No	No	yes	Hysterectomy with adnexae
115	Endometrioid	2007	67	EEC gr1	EEC gr1	wildtype	other	No	No	No	yes	Hysterectomy with adnexae
116	Endometrioid	2002	66	adenocarcinoma NOS gr2	EEC gr1	wildtype	other	No	No	Simultaneous bilate-ral serous borderline tumour/low-grade serous carcinoma.	yes	Hysterectomy with adnexae

Continue

Continued

Case ID	Final histological subgroup[a]	Year	Age	Original diagnoses	Diagnoses after pathology review	P53 status[b]	Molecular subgroup	Category change histologic subgroup after review	RRSO, years in between RRSO-EC	Adnexal involvement/ (history of) ovarian malignancy	Adnexal specimens available for revision	Hysterectomy with/ without adenxae
117	Endometrioid	1999	53	adenocarcinoma NOS gr2	EEC gr2	wildtype	other	No	No	No	No	Hysterectomy with adnexae
118	Endometrioid	2002	62	EIN/ adenocar-cioma NOS gr1	EEC gr1	wildtype	other	No	No	No	No	Hysterectomy with adnexae
121	Endometrioid	2011	60	EEC gr1	EEC gr1	wildtype	other	No	No	No	Yes	Hysterectomy with adnexae
124	Endometrioid	1999	56	adenocarcinoma NOS, gr1-2	EEC gr1	wildtype	other	No	No	No	Yes	Hysterectomy with adnexae
126	Endometrioid	2004	52	adenocarcinoma NOS gr1	EEC gr1	wiltype	other	No	No	No	No, not removed	Hysterectomy without adnexae
129	Endometrioid	2011	64	EEC gr3	n.a.	n.a., considered *TP53* wildtype	other[c]	n.a.	No	No	No	Hysterectomy with adnexae
130	Endometrioid	2000	57	EEC gr1	n.a.	n.a., considered *TP53* wildtype	other[c]	n.a.	Unknown	No	No, unknown if removed	Unknown
131	Endometrioid	2002	63	EEC gr2	n.a.	n.a., considered *TP53* wildtype	other[c]	n.a.	No	No	No, unknown if removed	Unknown
132	Endometrioid	2010	74	EEC gr2	n.a.	n.a., considered *TP53* wildtype	other[c]	n.a.	No	No	No	Hysterectomy with adnexae
133	Endometrioid	2010	53	EEC gr2	n.a.	n.a., considered *TP53* wildtype	other[c]	n.a.	Yes, 2.7[d]	No	No	Unknown
134	Endometrioid	2008	58	EEC gr2	n.a.	n.a., considered *TP53* wildtype	other[c]	n.a.	No	No	No, unknown if removed	Unknown
135	Endometrioid	2002	49	EEC gr1	n.a.	n.a., considered *TP53* wildtype	other[c]	n.a.	No	No	No	hysterectomy with right adnex
136	Endometrioid	2007	72	EEC gr1	n.a.	n.a., considered *TP53* wildtype	other[c]	n.a.	No	No	No	hysterectomy with right adnex
137	Endometrioid	2011	29	EEC gr1	n.a.	n.a., considered *TP53* wildtype	other[c]	n.a.	No	Simultaneous bilate-ral serous borderline tumour	No	Hysterectomy with adnexae
138	Endometrioid	1999	60	adenocarcinoma NOS gr2	n.a.	n.a., considered *TP53* wildtype	other[c]	n.a.	No	No	No, unknown if removed	Unknown
139	Endometrioid	1999	51	adenocarcinoma NOS gr unspe-cified	n.a.	n.a., considered *TP53* wildtype	other[c]	n.a.	No	No	No	Hysterectomy with adnexae

Continue

Continued

Case ID	Final histological subgroup[a]	Year	Age	Original diagnoses	Diagnoses after pathology review	P53 status[b]	Molecular subgroup	Category change histologic subgroup after review	RRSO, years in between RRSO-EC	Adnexal involvement/ (history of) ovarian malignancy	Adnexal specimens available for revision	Hysterectomy with/ without adenxae
140	Endometrioid	2007	53	EEC gr 1	n.a.	n.a., considered *TP53* wildtype	other[c]	n.a.	No	No	No, unknown if removed	Unknown
103	Serous-like	1997	53	carsinocarcoma, unspecified	carcinosarcoma, endometrioid	wildtype	other	No	No	No	Yes	Hysterectomy with adnexae
123	Serous-like	2007	72	carcinosarcoma, endometrioid	carcinosarcoma, serous	mutant	other	No	No	Simultaneous bilateral serous adenocarcinoma	No	Hysterectomy with adnexae
128	Serous-like	2009	79	serous	serous	mutant	p53-abnormal	No	No	No	Yes	Hysterectomy with adnexae
Endometrial cancer outside follow-up window main analyses												
107	Endometrioid	2012	55	EEC gr1	EEC gr1	wildtype	other	No	No	No	Yes	Hysterectomy with adnexae
109	Endometrioid	2013	69	EEC gr1	EEC gr1	wildtype	other	No	No	No	Yes	Hysterectomy with adnexae
119	Endometrioid	2012	56	undifferentiated/ dedifferentiated carcinoma	dedifferentiated carcinoma	wildtype	other	No	No	No	Yes	Hysterectomy with adnexae
120	Endometrioid	2014	71	EEC gr1	EEC gr2	wildtype	other	No	No	No	Yes	Hysterectomy with adnexae
127	Serous-like	2012	65	carcinosarcoma, unspecified	carcinosarcoma, serous	mutant	p53-abnormal	No	No	No	No	No hysterectomy/adnex extirpation performed (diagnosis based on endometrial curretage)
Not considered endometrial cancer after revision												
122	No EC	1990	59	adenosquamous EC	adenosquamous carcinoma	mutant	No EC	No EC	Unknown	No	No, not removed	Hysterectomy without adnexae
125	No EC	2003	60	EEC gr2	HGSOC	mutant	No EC	No EC	No	Bilateral HGSOC with endometrial involvement	Yes	Hysterectomy with adnexae

Abbreviations: EEC: Endometrioid endometrial carcinoma, EIN: Endometrioid intra-epithelial neoplasia, n.a.: not available, NOS: Not otherwise specified, RRSO: Risk-reducing salpingo-oophorectomy, EC: Endometrial cancer [a]Based on diagnoses after pathology review when available. [b]P53-status based on IHC, molecular analyses or most common pattern based on literature in case no FFPE blocks were available. "Mutant" includes both overexpression pattern and null-pattern. [c]Molecular subgroup based on most prevalent p53 status for the histologic subtype, no FFPE-tumour tissue block was available for determining p53 status. [d]One ovary previously removed.

Supplementary Table 7. Additional sensitivity analyses endometrial cancer risks *BRCA1/2* mutation carriers versus non-*BRCA1/2* mutation carriers

	BRCA1/2 carriers			non-*BRCA1/2* carriers				
Subgroups	**Total (No.)**	**Events (No.)**	**Person-years at risk**	**Total (No.)**	**Events (No.)**	**Person-years at risk (No.)**	**Hazard Ratio (95% CI)[a]**	***p* value[b]**
Start follow-up from date *BRCA* DNA test, excluding cases for which date of *BRCA1/2* DNA test was unknown								
All histotypes	4104	28	29821	6885	7	30055	3.79 (1.61-8.91)	0.002
Endometrioid	4104	17	29821	6885	6	30055	3.76 (1.41-9.97)	0.01
Serous-like	4104	10	29821	6885	1	30055	12.39 (1.49-103.29)	0.02
p53-abnormal[c]	4104	16	29821	6885	1	30055	20.06 (2.56-157.22)	0.004
BRCA1, all histotypes[d]	2493	22	18744	6885	7	30055	7.26 (2.96-17.82)	<0.001
BRCA2, all histotypes[d]	1640	6	11298	6885	7	30055	2.46 (0.72-8.44)	0.15
End follow-up 01-01-2012 for all included women								
All	5936	48	105609	8451	33	160841	2.37 (1.52-3.69)	<0.001
Endometrioid	5936	29	105609	8451	30	160841	1.51 (0.91-2.52)	0.11
Serous-like	5936	15	105609	8451	3	160841	8.16 (2.36-28.22)	0.001
p53-abnormal[c]	5936	20	105609	8451	3	160841	10.95 (3.25-36.87)	<0.001
BRCA1, all histotypes[d]	3796	36	66700	8451	33	160841	2.78 (1.73-4.46)	<0.001
BRCA2, all histotypes[d]	2181	12	39704	8451	33	160841	1.45 (0.75-2.81)	0.27
Additional censoring BC[e]								
All	5689	32	88493	8311	21	139488	2.83 (1.62-4.95)	<0.001
Endometrioid	5689	22	88493	8311	20	139488	1.75 (0.95-3.24)	0.07
Serous-like	5689	6	88493	8311	1	139488	8.90 (1.04-76.54)	0.05
p53-abnormal[c]	5689	9	88493	8311	1	139488	14.25 (1.77-114.22)	0.01
BRCA1, all histotypes[d]	3610	22	53898	8311	21	139488	2.61 (1.41-4.84)	0.002
BRCA2, all histotypes[d]	2115	10	35239	8311	21	139488	1.97 (0.93-4.19)	0.08
Additional censoring HT-BC including cases for which HT was unknown[e]								
All histotypes	5895	49	110215	8407	30	153443	2.30 (1.44-3.68)	<0.001

Abbreviations: BC: Breast Cancer, HT: Hormone Treatment
[a]Hazard ratios were adjusted for age.
[b]The P values assessing the null hypothesis of HR=1.00.
[c]Includes cases for which p53-status was unknown (no FFPE tumour block available) and for which p53-status was based on the most common p53-status for the histotype.
[d]Women with both a *BRCA1* and a *BRCA2* mutation were included in both analyses stratified for *BRCA1/2*-mutation status.
[e]DCIS was considered as BC.

Supplementary Table 8. Observed and expected endometrial cancer rates in non*BRCA1/2* mutation carriers, compared to the Dutch country-specific incidence rates

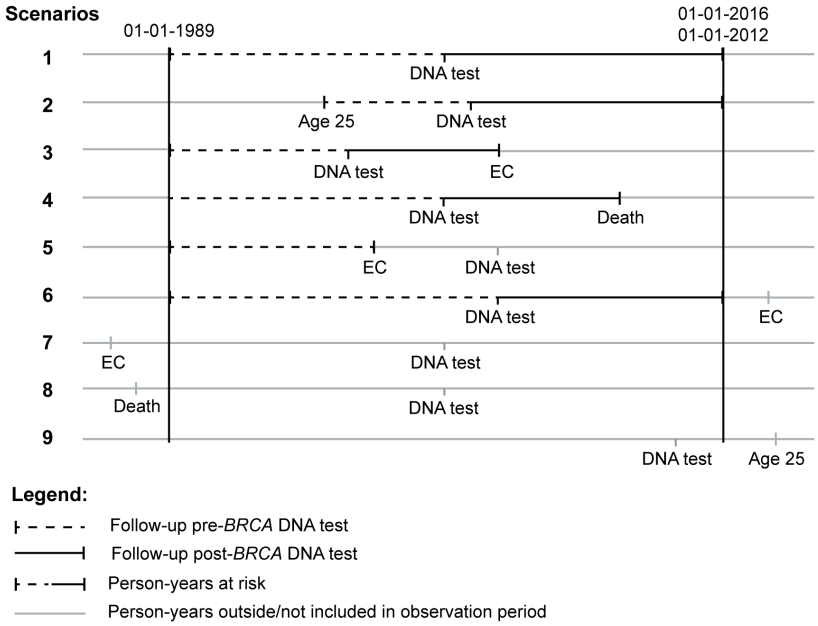
	non-*BRCA1/2* carriers	Dutch population		
EC subtype	**Observed**	**Expected**	**SIR (95% CI)**	***P* value**[a]
All endometrial cancers	33	26.81	1.23 (0.88-1.73)	0.14
Histologic groups				
Endometrioid	30	22.14	1.35 (0.95-1.94)	0.06
Serous-like	3	2.39	1.26 (0.40-3.89)	0.43
Sarcoma	0	1.73	NA	NA
Clear cell	0	0.36	NA	NA

Abbreviations: SIR: Standardized Incidence Ratio, CI: Confidence Interval. NA: not applicable
[a]*p* values were estimated assuming a Poisson distribution.

Supplementary Table 9. Cumulative endometrial cancer risks for *BRCA1/2* mutation carriers by the age of 75 years

EC subtype	**Cumulative risk (%, 95% CI)**
All Endometrial cancers	**2.97 (2.20-3.91)**
BRCA1	3.49 (2.46-4.81)
BRCA2	1.97 (1.09-3.30)
Histologic groups	
Serous-like	**1.14 (0.69-1.80)**
BRCA1	1.42 (0.79-2.37)
BRCA2	0.64 (0.21-1.60)
Endometrioid	**1.70 (1.14-2.44)**
BRCA1	1.97 (1.23-3.01)

Abbreviations, CI: confidence interval



Supplementary Figure 1. Schematic overview of the composition of different observation period scenarios. Follow-up started on the date of nationwide PALGA coverage (01-01-1989) or on the date of attaining 25 years of age (whichever was later). Follow-up ended at date of endometrial cancer diagnosis, date of death, or date of end of follow-up (01-01-2016 for *BRCA1/2* mutation carriers who provided informed consent, 01-01-2012 for all others). The observation period comprised both person-years at risk before *BRCA* DNA testing (dashed line) and person-years at risk after *BRCA* DNA testing (continuous line). Scenario 1 displays the maximum possible observation period. In case endometrial cancer or death occurred before the start of follow-up (scenarios 7 and 8), or age 25 was reached after end of follow-up (scenario 9), cases were excluded. Endometrial cancers that occurred after end of follow-up (scenario 6) were not included as events in the study. Abbreviations; EC: Endometrial cancer