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Original article

No signs of subclinical atherosclerosis after risk-reducing salpingo-oophorectomy in *BRCA1/2* mutation carriers

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ABSTRACT

Background: *BRCA1/2* mutation carriers are generally exposed to early menopause due to risk-reducing salpingo-oophorectomy (RRSO) around the age of 40 years. This risk-reducing intervention is based on a 10–40% life-time risk of ovarian cancer in this population. Although effective, premature and acute menopause induces non-cancer related morbidity in both the short and long term. Little is known about the impact of RRSO on the cardiovascular system.

Methods: This cross-sectional study explored the relationship between time since RRSO and signs of subclinical atherosclerosis, as measured by carotid intima-media thickness (CIMT) and pulse wave velocity (PWV), in 165 *BRCA1/2* mutation carriers. All participants, aged 40 to 63 years, underwent RRSO before the age of 45 years, and at least 5 years ago. Cardiovascular risk factors were assessed by questionnaires and a single screening visit. Data were analyzed using linear regression models.

Results: Mean CIMT was 692.7 μm (SD 87.0), and mean central PWV 6.40 m/s (SD 1.42). After adjustment for age and several relevant cardiovascular risk factors, time since RRSO was not associated with CIMT (β=0.68 μm; 95% CI −4.02, 5.38) and PWV (β=44 mm/s; 95% CI −32, 120). Compared to women of a reference group from the general population, lower systolic blood pressure [mean difference 12 mmHg; 95% confidence interval (CI) 10, 14] was found in *BRCA1/2* mutation carriers.

Conclusions: We found that, in *BRCA1/2* mutation carriers, at 5 to 24 years follow-up, time since RRSO is not related to development of subclinical atherosclerosis. However, the follow-up period in these relatively young women might have been too short.

Introduction

BRCA1/2 mutation carriers have a lifetime risk for breast and ovarian cancer of 49–57% and 18–40%, respectively [1]. Approximately 2% and 15% of all women with respectively breast or ovarian cancer carry a germline mutation in the *BRCA1* or *BRCA2* gene [2]. To reduce ovarian cancer risk, *BRCA1/2* mutation carriers are strongly advised to undergo a risk-reducing salpingo-oophorectomy (RRSO) around the age of 40 years, which is a highly effective strategy [3]. Until now, little is known about the potential long-term health effects of premature surgical menopause due to RRSO, such as earlier occurrence of atherosclerosis.

Germline mutations in the *BRCA1/2* genes were discovered only two decades ago; therefore, data on cardiovascular diseases (CVD)

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after premenopausal RRSO are scarce. Nevertheless, *BRCA1/2* mutation carriers may have an elevated risk for CVD for several reasons [4]. Firstly, in the general population, early menopause negatively affects morbidity and mortality caused by CVD [5,6]. Secondly, a more unfavorable lipid profile and higher body mass index (BMI) are observed after early surgical menopause, whereas its effects on blood pressure and glucose metabolism are less consistent [7]. Hormone replacement therapy (HRT) is advised in women undergoing early menopause, until average age of menopause, with potentially beneficial effects on vascular function, lipid levels, and glucose metabolism [8]. However, HRT is contraindicated in women with prior breast cancer. A significant proportion of *BRCA1/2* mutation carriers will receive adjuvant chemotherapy or radiotherapy for breast cancer which may also have cardiotoxic effects [9]. A possible role of deficient DNA repair mechanisms, as in *BRCA1/2* mutation carriers, in the cardiovascular (CV) system is suggested in animal studies [10,11], but this is yet to be investigated in humans.

A way of providing evidence of CVD risk in oophorectomized *BRCA1/2* mutation carriers is to study the level and extent of arterial damage. Both carotid intima-media thickness (CIMT) and pulse wave velocity (PWV) are subclinical atherosclerosis measurements that reflect long-term exposure to unfavorable levels of increased risk factors. Measurements of increased CIMT and PWV are strong predictors for future CV events in middle-aged subjects [12,13].

Thus far, studies on CIMT and PWV after premature surgical menopause are scarce, with conflicting results on the association with time since menopause [14-17]. The objective of this study was to evaluate whether RRSO is a potential risk factor in *BRCA1/2* mutation carriers for early development of subclinical atherosclerosis as measured by CIMT and PWV.

Materials and methods

Participants

The Cardiovascular Risk after RRSO in *BRCA1/2* Mutation Carriers (CARSOBRA) study was a single-center cohort study performed in the Radboud University Medical Center (Radboudumc) in the Netherlands between June and November 2015. All germline *BRCA1/2* mutation carriers known to the Department of Human Genetics or the Department of Obstetrics and Gynecology were invited by letter to participate in the CARSOBRA study. Women were asked to participate when RRSO was performed at a maximum age of 45 years and at least five years previously. Women with previous ovarian cancer or current treatment for metastatic breast cancer were excluded from participation. The study is in accordance with the Helsinki Declaration and was approved by the Medical Ethics Committee of the Radboudumc (CMO:2014–1430). All participants provided written informed consent before entering the study. The study consisted of a digital questionnaire and a single CV screening visit. General characteristics included age, race, education level, type of *BRCA* mutation, and time since RRSO.

Measures of subclinical atherosclerosis

Participants were instructed to avoid strenuous physical activity 24 h before testing, to abstain from smoking for 14 h, and to fast at least six hours, to minimize these effects on the vascular system. Tests were performed under standardized conditions in a quiet, partially darkened, temperature-controlled room (22.5 ± 1.0 °C). All measurements were performed by the same sonographer (MA).

High-resolution B-mode ultrasound carotid artery images were acquired using a linear array 10-MHz transducer attached to a Terason T3000 (Burlington, MA, USA). The intima-media thickness of the left common carotid artery (CCA) was measured two cm proximal to the bulbus [18]. Wall thickness was measured continuously for at least ten seconds, and this was repeated from a different perpendicular plane (±90°, compared with previous measurement). From the two measurements, mean wall thickness was calculated and used for analysis. Post-test analysis wall thickness was performed by a researcher (MA) who was blinded to subject identity. Custom-designed edge-detection and wall-tracking Digital Imaging and Communications in Medicine-based (DICOM) software was used, which is largely independent of investigator bias [19].

Arterial stiffness was determined using central PWV. It is a measure of wave velocity, which is propagated by contraction of the heart and travels along the arterial tree. PWV is calculated by dividing travelled distance by transit time [20]. A three-lead electrocardiogram was used for R-wave detection. The pulse wave was measured by echo-Doppler ultrasound (WakiLoki Doppler, 4 MHz, Atys Medical, Soucieu en Jarrest, France) at the left CCA and the right common femoral artery (FA). The distance between CCA to sternal notch (SN) was measured over the body surface, whereas the height from the ground to SN, umbilicus (UMB), and FA were obtained in standing position in front of a measuring rod. The path length for aortic distance was obtained by the formula: [(SN to UMB) + (UMB to FA)] – (CCA – SN). PWV was calculated automatically by echo-tracking subsystem using the intersecting tangent algorithm to measure pulse transit time difference. The reported value was the average of at least eight consecutive beats.

Cardiovascular risk factors and other potential covariates

A fasting venous blood sample was analyzed for glucose, insulin, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides. Insulin resistance was estimated using the Homeostasis Model Assessment (HOMA-IR) formula [fasting serum insulin (mU/l) x fasting plasma glucose (mmol/l)/22.5] [21]. After 15 min of rest in supine position, blood pressure was determined using a semiautomatic oscillometric device (Vital Signs Monitor 300 Series, Model 5300P; Welch Allyn Inc, Beaverton, OR, USA) with a cuff size appropriate for arm circumference, at five-minute intervals for 30 min. The median of seven measures of systolic blood pressure (SBP) was used for analysis. Hypertension was defined as SBP ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg, or the use of blood pressure-lowering medication [22]. Measures consisted of height (m) and body weight (kg) to calculate BMI (kg/m^2), and waist and hip circumferences (cm) to calculate waist–hip ratio (WHR).

Self-reported data were obtained on smoking status, medication use (blood pressure-lowering, lipid-lowering, glucose-lowering, and HRT), history of hypertensive pregnancy disorders and/or gestational diabetes, history of CVD, prior breast cancer treated with chemotherapy and/or radiotherapy, and family history of premature CVD (myocardial infarction/stroke in first-degree family members aged under 60 years). Framingham Risk Scores were calculated according to D'Agostino et al. [23]. Self-reported physical fitness was assessed by the 12-item Duke Activity Status Index (DASI) [24]. Activities representing major aspects of physical function (personal care, ambulation, household tasks, sexual function, and recreational activities) were determined and weighted by their known metabolic cost to predict an individual's maximal exercise capacity. A total DASI score ranges from 0 (worst) to 58.2 (best), and correlates well with peak oxygen uptake [24].

CV risk factors of *BRCA1/2* mutation carriers were compared with age-matched women from a Dutch general population study to indicate which CV risk factors might have influenced the subclinical atherosclerosis measures in our study population [25]. These data were collected in 2009–2010 and pooled outcomes on the measures BMI, SBP, DBP, TC, HDL-C, and glucose were reported. Metabolic syndrome was defined as the presence of

Table 1
Characteristics of study participants.

Characteristics	*BRCA1/2* mutation carriers
(*n* = 165)	
Demographics	
Age, median (range), years	49.1 (40 - 63)
Higher education, *n* (%)	49 (29.7)
Clinical data	
Time since RRSO, median (range), years	9.5 (5 - 24)
Medication, *n* (%)	
Blood pressure-lowering	10 (6.1)
Lipid-lowering	8 (4.8)
Glucose-lowering[a]	3 (1.8)
Hormone replacement therapy	33 (20.0)
Cardiovascular risk factors in pregnancy, *n* (%)	26 (18.3)
Prior breast cancer treated with CT/RT, *n* (%)	44 (26.7)
Family history of premature CVD, *n* (%)	32 (19.4)
Currently smoking, *n* (%)	22 (13.3)
DASI score, median (range)	52.2 (7.2 - 58.2)
Physical examination	
Systolic blood pressure, mmHg	112 (11)
Diastolic blood pressure, mmHg	70 (8)
Body mass index, kg/m^2	25.3 (4.4)
Waist-hip ratio	0.82 (0.06)
Laboratory data, median (range)	
Total cholesterol, mmol/l	5.5 (3.2 – 8.8)
LDL cholesterol, mmol/l	3.4 (1.2 – 6.1)
HDL cholesterol, mmol/l	1.6 (0.7 – 5.4)
Triglycerides, mmol/l	1.0 (0.2 – 3.9)
HOMA-IR	1.4 (0.3 – 11.3)

RRSO, risk-reducing salpingo-oophorectomy; CT, chemotherapy; RT, radiotherapy; CVD, cardiovascular disease; DASI score, Duke Activity Status Index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment-Insulin Resistance.
[a] Only the use of oral blood glucose-lowering medication.

three or more of the following risk factors: abdominal obesity; SBP ≥130 mmHg and/or DBP ≥85 mmHg and/or blood pressure-lowering medication; HDL-C <1.30 mmol/l and/or lipid-lowering medication; fasting glucose ≥5.6 mmol/l and/or glucose-lowering medication; triglyceride ≥1.7 mmol/l.

Data analysis

Data were expressed as means and standard deviations (SD). When distributions of variables were skewed, log-transformation was applied prior to analysis. Continuous data were compared by Student's *t*-test for independent samples. Proportions were compared by chi-square test.

In univariable analysis, associations of age-adjusted common CIMT and age-adjusted central PWV with (potential) CVD risk factors were tested (SBP, blood pressure-lowering medication, HOMA-IR, glucose-lowering medication, TC, lipid-lowering medication, BMI, WHR, current smoking, use of HRT, DASI, CV risk in pregnancy, prior breast cancer treated with chemotherapy and/or radiotherapy, family history of CVD). Those variables with a *p*-value <0.10 were included in linear regression models for further adjustment when testing the association of time since RRSO with CIMT and PWV. Statistical analyses were performed using Statistical Package for the Social Sciences software version 22.0 (SPSS Inc., Chicago, IL, USA). A *p*-value <0.05 was considered significant.

Results

In total, 268 women were invited to participate; of these, 165 (62%) gave informed consent. General characteristics of the participants are displayed in Table 1. A total of 112 had a *BRCA1* mutation (68%), 51 had a *BRCA2* mutation (31%), and 2 had both *BRCA1* and *BRCA2* mutations. All but three women were Caucasians. A total of 111 *BRCA1/2* mutation carriers (67%) did not have prior breast cancer. Of these women, 82 (74%) had ever used HRT with a mean duration of 6.6 years (SD 4.1). Only one woman had a history of CVD including a transient ischemic attack and an abdominal aneurysm of the aorta. Fifty percent of all participants had the maximal DASI score of 58.2 (median 52.2, range 7.2–58.2).

Of the nonparticipants ($n = 97$), eight did not fulfill the inclusion criteria, twenty-two did not respond or were not reached, and 67 were not interested in participation for several reasons. In a random sample of these nonparticipants ($n = 32$), 38% were known to be smokers, whereas 13% of the participants smoked, other CVD risk factors were unknown.

Table 2 summarizes (potential) CVD risk factors compared with women from a Dutch reference group divided into two age-categories (40–49 and 50–59 years) [25]. Two *BRCA1/2* mutation carriers were excluded from this comparison because of age above 59 years. Oophorectomized *BRCA1/2* mutation carriers did not differ from women of the reference group with regard to BMI, diabetes, TC, HDL-C, and smoking. However, *BRCA1/2* mutation carriers had lower SBP [mean difference 12 mmHg (95% CI 10, 14); $p<0.01$] and DBP [mean difference 7 mmHg (95% CI 5, 9); $p<0.01$]. The presence of hypercholesterolemia was higher in women aged 40–49 years, and less abdominal obesity and metabolic syndrome in women aged 50–59 years were observed compared with the reference group.

Subclinical atherosclerosis measures

Mean CIMT in *BRCA1/2* mutation carriers was 692.7 μm (SD 87.0, median 675.5, range 527.5–1073.0). Time since RRSO was not associated with CIMT in the age-adjusted model (Table 3). Univariate associations were tested between age-adjusted CIMT and CVD risk factors, in which SBP, HOMA-IR, TC, and BMI were significantly associated with CIMT. After adjustment for these additional factors, time since RRSO was still not associated with CIMT (Table 3). After selecting women without HRT, still no association was found between time since RRSO and CIMT (model 1: $p = 0.78$, model 2: $p = 0.85$, model 3a: $p = 0.73$).

Data on PWV analyses failed for 10 *BRCA1/2* mutation carriers, because of arrhythmia ($n = 1$) and technical problems ($n = 9$). In 155 *BRCA1/2* mutation carriers, mean PWV was 6.40 m s^{-1} (SD 1.42, median 6.01, range 4.14–11.79). No association was found between time since RRSO and age-adjusted PWV (Table 3). Univariate analysis for age-adjusted PWV showed significant associations with SBP, TC, WHR, HOMA-IR, and prior breast cancer treated with chemotherapy and/or radiotherapy. In linear regression analysis, time since RRSO was not associated with age-adjusted PWV after adjustment for relevant CVD risk factors. Also when analyzing women without HRT only, no association was found between time since RRSO and PWV (model 1: $p = 0.55$, model 2: $p = 0.83$, model 3b: $p = 0.90$).

Framingham risk score was significantly associated with time since RRSO ($R = 0.349$, $p < 0.00$).

Discussion

In this relatively young cohort of oophorectomized *BRCA1/2* mutation carriers, time since RRSO was not related to signs of subclinical atherosclerosis as measured by CIMT and PWV. In contrast, we found that *BRCA1/2* mutation carriers 5 to 24 years after RRSO had a relatively healthy CVD risk profile.

At the moment, this is the first study in which time since early surgical menopause and signs of subclinical atherosclerosis in *BRCA1/2* mutation carriers are investigated. Our findings support previous studies indicating that time since surgical menopause is not associated with increased CIMT at a maximum of 24 years follow up [14,15,26]. However, two smaller studies did find a positive

Table 2
Cardiovascular risk factors in *BRCA1/2* mutation carriers compared with a reference group[24].

Age category	40–49 years CARSOBRA (n = 93)	Reference (n = 518)	p-value	50–59 years CARSOBRA (n = 70)	Reference (n = 553)	p-value
Cardiovascular risk factors,%						
Hypertension	6.5	14.7	<0.05	10.0	31.5	<0.01
Obesity[a]	15.1	10.5	0.20	17.1	14.9	0.63
Abdominal obesity[b]	31.1	33.2	0.69	31.9	44.3	<0.05
Diabetes[c]	1.1	2.3	0.46	4.3	5.0	0.80
Hypercholesterolemia[d]	18.3	10.3	<0.05	30.0	31.9	0.75
Metabolic syndrome	10.8	17.0	0.14	13.0	28.8	<0.01
Current smoking	14.0	21.3	0.11	11.4	20.9	0.06
Framingham Risk Score[e], median (range)	2.4 (1.0–11.7)			3.6 (1.7–13.7)		
Physical examination, mean (SD)						
Systolic blood pressure, mmHg	111 (11)	120 (14)	<0.01	113 (11)	127 (17)	<0.01
Diastolic blood pressure, mmHg	71 (9)	75 (10)	<0.01	70 (8)	78(10)	<0.01
Body mass index, kg/m^2	25.5 (4.5)	24.7 (4.3)	0.12	24.9 (4.5)	25.7 (4.7)	0.17
Waist circumference, cm	86.2 (10.7)	84.5 (11.3)	0.16	85.4 (12.2)	87.7 (11.8)	0.12
Laboratory data, mean (SD)						
Total cholesterol, mmol/l	5.42 (1.08)	5.19 (0.088)	0.06	5.70 (1.03)	5.83 (1.03)	0.36
HDL cholesterol, mmol/l	1.52 (0.36)	1.48 (0.34)	0.32	1.57 (0.37)	1.57 (0.37)	0.09

HDL, High-density lipoprotein.
[a] Body mass index ≥ 30 kg/m^2;
[b] Waist circumference ≥ 88 cm;
[c] Reported in questionnaire or fasting glucose ≥ 7.0 mmol/l;
[d] Total cholesterol ≥ 6.5 mmol/l and/or lipid-lowering medication;
[e] Calculated according to D'Agostino et al. [23].

Table 3
Association of time since RRSO with CIMT and PWV.

	CIMT (µm)^	p-value	PWV (mm/s)^	p-value
Model 1[a]	1.95 (−2.88, 6.78)	0.43	75.1 (−7.4, 157.5)	0.07
Model 2[b]	1.03 (−3.72, 5.77)	0.67	55.0 (−24.3, 134.2)	0.17
Model 3a[c]	0.68 (−4.02, 5.38)	0.77		
Model 3b[d]			43.9 (−31.7, 119.5)	0.25

^values represent β coefficients (95%) of linear regression analyses, reflecting change in outcome per one year increase in time since RRSO.
RRSO, risk-reducing salpingo-oophorectomy; CIMT, carotid intima media thickness; PWV, pulse wave velocity; RRSO, risk-reducing salpingo-oophorectomy; HOMA-IR, Homeostatic Model Assessment-Insulin Resistance.
[a] adjusted for age;.
[b] adjusted for age and systolic blood pressure;.
[c] adjusted for age, systolic blood pressure, HOMA-IR, total cholesterol and body mass index;.
[d] adjusted for age, systolic blood pressure, HOMA-IR, total cholesterol, waist-hip ratio and prior breast cancer treatment with chemotherapy and/or radiotherapy.

association [16,17]. Arterial stiffness, measured with PWV, has only been studied after natural menopause in which a significantly positive association at a mean time interval of 8 years was found [27].

Generally, early menopause is consistently associated with an increased risk for CVD and its mortality [5,6]. Prior studies on early surgical menopause were performed predominantly in women undergoing hysterectomy for benign diseases with or without bilateral oophorectomy. In these premenopausal women undergoing hysterectomy, the CV benefits of conserving ovaries have been highlighted [28,29]. Even in postmenopausal women, retained ovaries are associated with slower rates of thickening of the carotid arteries. Moreover, in a recent meta-analysis both natural and surgical premature menopause have been found to be associated with an increased risk for CVD events among postmenopausal women [30].

In the general population, a small protective CV effect of retained ovaries might outweigh the potential low lifetime risk of ovarian cancer of 1.3% [31]. However, *BRCA1/2* mutation carriers have to be distinguished from the general population because of their elevated ovarian cancer risk (up to 40%), combined with the poor prognosis of ovarian cancer, a salpingo-oophorectomy is advised despite potential side-effects. Furthermore, it is debated whether they are at increased risk for CVD compared to non-carriers [32]. It has been postulated that the *BRCA* gene itself may influence CV risk, on top of the effects of early induced menopause due to RRSO [4]. In previous studies it was found that women undergoing hysterectomy had a more unfavorable CVD risk profile at baseline [33,34]. In contrast, other studies found a healthier CVD risk profile in women who underwent RRSO [35]. These authors suggested that self-selection of healthier women seeking RRSO and their changes in lifestyle after surgery may play an important role [35]. This is in accordance with our results, in which our participants may represent a positive selection, based on the differences in smoking among women who did and did not participate in this study.

Comparing CVD risk factors in *BRCA1/2* mutation carriers with women from the reference group, lower SBP and DBP were found in *BRCA1/2* mutation carriers [25]. A lower prevalence of abdominal obesity and metabolic syndrome was observed which is positively associated with a lower blood pressure. In the literature, results on changes in CVD risk factors by hysterectomy with bilateral oophorectomy diverge from no changes [33,34,36], to increased BMI and higher total and LDL-cholesterol [7,37]. Changes in blood pressure, as we found, have not been observed previously.

Healthy lifestyle is the cornerstone for CVD prevention, as highlighted in the European guideline for CVD prevention, and this certainly accounts for women at middle-age [22]. Presumably, in *BRCA1/2* mutation carriers, patient's motivation for healthy lifestyle is focusing mainly on cancer prevention. Healthy lifestyle interventions, such as weight control, healthy diet, and physical activity, have all been shown to lower breast cancer risk [38]. Furthermore, a relatively high level of education has been found in *BRCA1/2* carriers which is associated with a healthy lifestyle in general [39]. In the future, we expect a better reflection of the general population while genetic testing is increasing. For example, universal tumor *BRCA1*/2 testing in all newly diagnosed ovarian cancer patients appears to be feasible, effective, and appreciated by patients and gynecologists in the Netherlands [40]. The current national implementation of this trajectory will lead to population-based genetic analysis with national coverage.

Considering the relatively recent discovery of germline *BRCA1/2* mutations, no data on clinical CVD endpoints are yet available af-

ter premenopausal RRSO. Therefore, we used CIMT and PWV as surrogate endpoints for CV risk [12,13]. Another well-established method, coronary artery calcium (CAC) scoring with computed tomography, is strongly associated with the long-term risk of CVD mortality in young- and middle-aged women [41]. However, this technique uses ionizing radiation which requires special caution, especially in young *BRCA1/2* mutation carriers [42].

Determining the role of menopause in the pathogenesis or progression of CVD is complex, given the dominant effect of aging on the CV system in combination with the presence of CVD risk factors, as is possibly also reflected by the association between time since RRSO and Framingham risk score. It has been suggested that early natural menopause may be caused predominantly by an intrinsic elevated CVD risk [43]. Furthermore, CVD mortality in women increases exponentially throughout all ages with no acceleration at menopause [44]. Recently, menopausal status and chronological aging were found to be both associated independently with CVD risk factors, with a more marked role for the latter [7].

Our results must be interpreted in the context of several strengths and limitations. We are the first group investigating the association between time since RRSO in *BRCA1/2* carriers and signs of subclinical atherosclerosis. In this study clinical data, as well as laboratory data and atherosclerosis measurements are included to provide an insight into the CV risk profile of *BRCA* mutation carriers. However, the cross-sectional design precludes investigating causality, and the lack of a control group for measures of subclinical atherosclerosis is another limitation. Using an external reference cohort to compare CVD risk factors also has some disadvantages, such as potential differences in measurement techniques and laboratory analysis. Furthermore, our study group may reflect a relatively healthy subgroup of all *BRCA* mutation carriers due to selection bias. Moreover, patients with high risk of CV events might have developed CV events within five years after RRSO and might be excluded. Time since RRSO was still rather short with a relatively young age of the study group. Therefore, information on CV events was not yet available.

In conclusion, the present study showed no relation between time since RRSO and signs of subclinical atherosclerosis at intermediate term as measured by CIMT and PWV in oophorectomized *BRCA1/2* mutation carriers. In contrast, a relatively healthy CVD risk profile was observed. From our data, it seems unlikely that RRSO at a maximum age of 45 years in *BRCA1/2* mutation carriers has a major contribution to the CVD risk within several years. However, additional studies with longer follow-up are required to provide more insight in clinical CV events after RRSO.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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