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Impact of risk-reducing salpingo-oophorectomy on lipid determinants, HbA1c and CRP

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ABSTRACT

Objective: Risk-reducing salpingo-oophorectomy (RRSO) is advised before 40–45 years of age for BRCA1/2 mutation carriers. This study describes the effect of RRSO on lipid determinants, hemoglobin A1c (HbA1c) and C-reactive protein (CRP).

Methods: A total of 142 women with increased risk of ovarian cancer were included, 92 premenopausal and 50 postmenopausal. Serum levels of low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol and total cholesterol, triglycerides, HbA1c and CRP were determined at three points in time: before (T0) and 6 weeks (T1) and 7 months (T2) following RRSO. The Hot Flush Rating Scale was administered at the same time points.

Results: In premenopausal women, levels of HDL-cholesterol, the cholesterol ratio and HBA1c increased significantly over time, although still staying within the reference range. In this group, hot flushes increased over time ($p < 0.001$). In postmenopausal women, no significant changes were observed following RRSO. At T2, serum LDL-cholesterol, triglycerides, HbA1c and CRP were significantly lower in premenopausal women compared to postmenopausal women, whereas HDL was increased.

Conclusions: Seven months after RRSO, the lipid profile in premenopausal women had changed, although still staying within the reference range. For postmenopausal women, we did not observe any significant changes. Our results do not suggest a worsening of cardiovascular risk within 7 months of RRSO.

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Introduction

Approximately 10–15% of all ovarian cancer is related to inherited gene mutations and familial inheritance of breast and ovarian carcinomas [1]. Approximately 39% and 16% of BRCA1/2 mutation carriers, respectively, will develop ovarian carcinoma before the age of 70 years [1–3]. To reduce the risk of ovarian cancer, risk-reducing salpingo-oophorectomy (RRSO) is advised. This procedure leads to a risk reduction for ovarian cancer of 80–96% [4]. In premenopausal women, a major side effect of RRSO is the acute onset of menopause. Menopause can cause an increase of non-cancer-related morbidity, including osteoporosis, urogenital atrophy and vasomotor symptoms such as hot flashes and night sweats [5]. Early menopause before the age of 45 years is also related to an increased risk of cardiovascular diseases (CVD) [6,7]. Estrogens protect against CVD [8]. Although not all mechanisms are fully understood, the lowered estrogens due to the menopausal transition alter the lipid profile unfavorably. This means an increase in low-density lipoprotein (LDL), an increase of total cholesterol and triglyceride levels and a decrease in high-density lipoprotein (HDL) [9–11]. A changed lipid profile contributes to the formation of atherosclerosis, potentially causing CVD [12]. Another risk factor of RRSO in premenopausal women is the metabolic syndrome [13], comprising multiple metabolic abnormalities such as glucose intolerance/insulin resistance, central obesity, dyslipidemia and hypertension [14]. In order to foretell cardiovascular events, serum triglycerides, cholesterol (especially the proportion between LDL-cholesterol and HDL-cholesterol), glucose and hemoglobin A1c (HbA1c) levels have been demonstrated to be valid predictors of CVD [15]. In addition, moderate changes in C-reactive protein (CRP) are also considered a predictor for cardiovascular events [16]. The increase of CRP is part of the inflammatory cascade that starts as a reaction to injury of the endothelium, which can lead to atherosclerosis [16]. Climacteric symptoms are reported to be more severe

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after RRSO than after natural menopause [17]. Vasomotor symptoms, especially hot flushes, are thought to be associated with (cardio)vascular changes [18,19]. However, a causal relation between RRSO in premenopausal women and an increased risk of CVD has not been clearly established [10,20]. Moreover, BRCA1/2 mutation carriers might have an intrinsically increased risk of CVD. Due to loss of the cardio-protective role of BRCA genes, these women have an increased risk of insulin resistance and venous thromboembolisms [21].

With this background, we hypothesize that predictors of increased CVD risk as evidenced in blood values will be more prominent among women who undergo RRSO at premenopausal age than in women who experience a natural menopause. The first aim of this study was to investigate the influence of RRSO on serum lipids, HbA1c and CRP in both premenopausal and postmenopausal women at increased risk of ovarian cancer. The second aim was to compare serum values 7 months following RRSO in women whose menopause was precipitated by the surgery versus those who were already 'naturally' postmenopausal at the time of surgery. Finally, we examined the association between changes in lipid spectrum, HbA1c and CRP after RRSO and self-reported vasomotor symptoms.

Methods

This prospective, observational, multicenter study was carried out at the Netherlands Cancer Institute and the Leiden University Medical Center in the Netherlands. The institutional review boards of both centers approved the study and written informed consent was obtained from all participants. Between November 2006 and April 2012, all women with a proven BRCA1/2 mutation or women from a family with hereditary breast and ovarian cancer whose risk of ovarian cancer was estimated to exceed 10% and who were scheduled to undergo RRSO were asked to participate. Excluded were women who received cancer treatment at the time of RRSO. Postmenopausal status was defined as having amenorrhea for at least 12 months. If information about menstrual periods was unspecified, the age of 51 years was used as a proxy indicator of menopausal status [22]. We refer to 'premenopausal women' if women were premenopausal before RRSO and to 'postmenopausal women' if women were naturally postmenopausal before RRSO. Questionnaires and blood samples were obtained at three time points: T0 (within 1 week before RRSO), T1 (6 weeks after RRSO) and T2 (7 months after RRSO). We choose these time points because the regular follow-up after surgery took place 6 weeks after RRSO and T2 was 6 months after that consultation. The respondents' age, parity, menopausal status, use of hormone replacement, body mass index (BMI), comorbidities, history of breast cancer, mutation status, education, employment status and relationship status were obtained by self-report. The Hot Flush Rating Scale (HFRS) was used to assess the perceived burden of hot flushes and night sweats over the past week. The HFRS score is the mean of three 1–10 numerical scales assessing the extent to which hot flushes and night sweats were problematic, distressing and caused interference in daily life. Higher scores indicate more problematic symptoms [23]. Blood samples for total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides and CRP were collected in serum separator tubes. After centrifuging according to standard procedures, serum samples were stored at −80 °C until measurement. For the analysis of HbA1c, one 3 ml EDTA tube was used. All measurements were performed using the Cobas® 6000 analyzer (Roche Diagnostics, Mannheim, Germany). The cholesterol assays and the triglycerides were measured using an enzymatic, colorimetric method and CRP using a particle-enhanced immunoturbidimetric method with a limit of detection of 0.1 mg/l. The cholesterol ratio was calculated by dividing total cholesterol by HDL-cholesterol levels, with higher ratios indicating a higher risk of heart disease [24–26] whereas single higher HDL-cholesterol levels indicate a more cardioprotective profile. HbA1c determination is based on the turbidimetric inhibition immunoassay for hemolyzed whole blood. Reference ranges used for all of the conducted measurements were according to the those of the Netherlands Cancer Institute: total cholesterol 3.1–7.0 mmol/l, LDL-cholesterol 1.7–4.5 mmol/l, HDL-cholesterol 1.0–2.5 mmol/l, triglycerides 0.4–2.3 mmol/l, CRP <8 mg/l and HbA1c 20–42 mmol/mol. Intermediate precisions at a normal value were: total cholesterol 0.7%, LDL-cholesterol 0.9%, HDL-cholesterol 0.7%, triglycerides 0.8%, CRP 2.3% and HbA1c 1.1%.

Data were presented as the mean and standard deviation (SD). The premenopausal and postmenopausal groups were analyzed separately. We conducted a short-term (T0–T1) and longer-term (T0–T2) analysis of the within-group biochemical changes over time using repeated-measures mixed-effect models with random intercept and with a maximum likelihood estimator and the best fitted covariance structure [27]. Models with different covariance structures were compared using the Bayesian information criterion and the Akaike information criterion. Both criteria are used to compare non-nested models and both penalize the number of model parameters. The Bayesian information criterion also penalizes small sample sizes [28–30]. Models with lower Bayesian information criterion or Akaike information criterion values are considered to be better fitting models. All models were adjusted for age. We also looked at loss to follow-up and their impact on the data but this did not change the outcome. Differences in short-term and longer-term mean change over time were accompanied by effect sizes (ESs), which were calculated as $2*t/\sqrt{\text{degrees of freedom}}$. An ES of 0.20–0.50 was considered small, 0.50–0.80 moderate and greater than 0.80 large [31]. We compared baseline values of lipids, HbA1c and CRP of postmenopausal women (T0) to the follow-up values at 6 weeks (T1) and 7 months (T2) of premenopausal women who became surgically postmenopausal after RRSO. Spearman correlation coefficients were used to investigate correlations between the biochemical changes in blood with changes in HFRS sum scores and BMI. We used the Statistical Package for the Social Sciences (IBM SPSS statistics®, version

22) to analyze our data. p-Values of <0.05 were considered statistically significant.

Results

In total, 210 women at high risk of ovarian cancer were invited to participate, of whom 68 chose not to participate or were excluded from analysis. The most common reason for choosing not to participate was lack of interest ($n = 32$). Other reasons included RRSO having not been performed, RRSO was performed before baseline data were collected or postmenopausal status was caused by earlier cancer treatment. In total, 142 women who underwent RRSO were included. Data of 92 premenopausal and 50 postmenopausal women at T0 were analyzed; six women were defined postmenopausal by age because of missing data (all aged above 53 years). Follow-up data were obtained from 124 participants at T1 (6 weeks after RRSO) and from 99 participants at T2 (7 months after RRSO). In total, 18 women started hormone replacement during follow-up and thus were excluded from further analysis. Figure 1 presents the flow chart including numbers of missing data during follow-up. Baseline characteristics are presented in Table 1. Table 2 present serum levels at baseline and changes following RRSO in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, HbA1c and CRP for premenopausal and postmenopausal women.

In the premenopausal group, the overall model effects of time indicated significant within-group changes over time for HDL-cholesterol, cholesterol ratio and HbA1c ($p < 0.01$ for all; Table 2). More specifically, premenopausal women exhibited significant short-term and longer-term increases in HDL-cholesterol (ES = 0.43 and 0.58, respectively), cholesterol

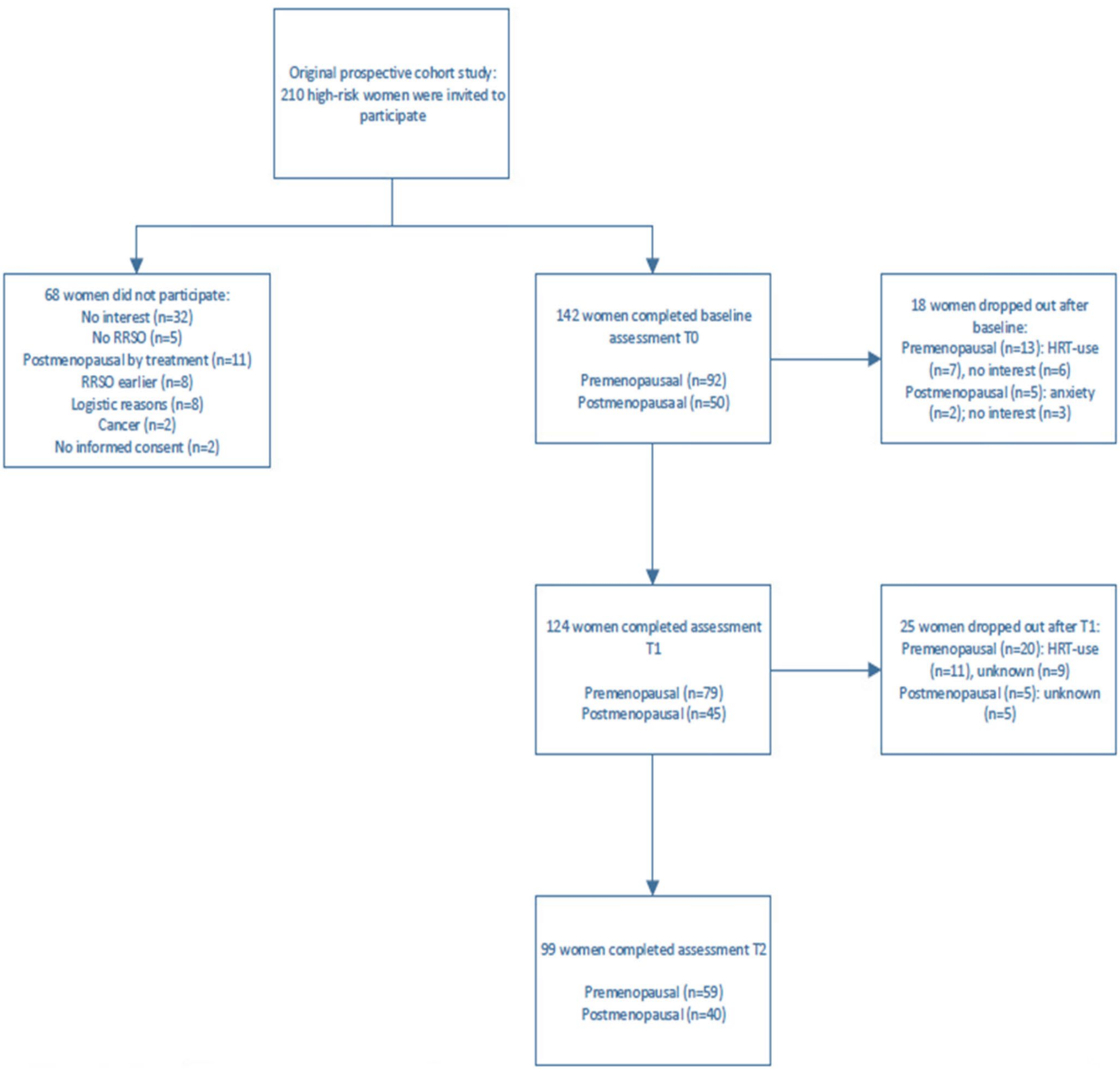

Figure 1. Flow chart describing the numbers of participants at each follow-up moment. HRT, hormone replacement therapy; RRSO, risk-reducing salpingo-oophorectomy.

Table 1. Baseline characteristics of the study population.

Characteristic	*Premenopausal* (n = 92, 65%)	*Postmenopausal* (n = 50, 35%)	p-*Value overall*	p-*Value*
Age, mean (SD)	43 (5)	58 (6)		<0.001[a]
BMI, mean (SD)	24.5 (3.4)	26.1 (4.1)		0.018[a]
Marital status, *N* (%)			0.963	
Married/cohabitating	80 (87)	41 (87)		
Unmarried/without partner	12 (13)	6 (13)		
Educational level, *N* (%)			0.120	
Primary school/lower-level high school	19 (21)	18 (38)		
Middle-level high school	7 (7)	4 (9)		
Vocational	32 (35)	10 (21)		
Advanced vocational/university	34 (37)	15 (32)		
Employment status, *N* (%)			0.002[a]	
(Un)Paid job (full-time or part-time)	77 (89)	31 (66)		
Full-time housewife	10 (11)	16 (34)		
Parity				
None	12 (14)	9 (23)	0.217	
≥1	73 (86)	30 (77)		
Breast cancer, *N* (%)				
Yes	26 (28)	21 (43)	0.080	
No	66 (72)	28 (57)		
DNA status, *N* (%)			0.007[a]	
BRCA1/2 carrier	78 (91)	30 (68)		
Negative	8 (9)	14 (32)		
Comorbidities, *N* (%)				
Pulmonary disease	0 (0)	5 (12)		0.007[a]
Cardiac disease	0 (0)	0 (0)		n.a.
Hypertension	5 (7)	10 (23)		0.014[a]
Stroke	0	0		n.a.
Renal disease	0	0		n.a.
Diabetes	0	2 (5)		0.143
Arthralgia	0	15 (35)		<0.001[a]
Psychological problems	2 (3)	4 (9)		0.199
Malignancies (other than breast and ovarian)	2 (3)	3 (7)		0.367
Time (days) from baseline blood sample to RRSO, median (IQR)	3 (1–7)	4 (1–7)	0.545	

[a] $p < 0.05$.

BMI, body mass index; IQR, interquartile range; *N*, number of participants; n.a., not applicable; RRSO, risk-reducing salpingo-oophorectomy; SD, standard deviation.

ratio (ES = 0.80 and 0.70, respectively) and HbA1c serum levels (ES = 0.86 and 1.30, respectively). We also found a significant short-term and longer-term increase in hot flushes (HFRS sum scores; ES = 1.30 and 1.50, respectively). All short-term and longer-term effects were clinically relevant (ES ≥ 0.20) in the premenopausal group. No significant within-group changes were observed in premenopausal women in total cholesterol, LDL-cholesterol, triglyceride, CRP or BMI. In the postmenopausal group, there were no significant overall within-group changes over time in any of the outcomes analyzed. Table 3 presents the comparison of lipids, HbA1c and CRP between postmenopausal women at T0 and premenopausal women at T1 and T2 after RRSO. At baseline, mean total cholesterol was significantly lower for premenopausal than for postmenopausal participants (5.2 ± 0.9 vs. 6.1 ± 1.2 mmol/l, $p < 0.001$, respectively), whereas 7 months after RRSO those levels for the premenopausal women were comparable with those of the postmenopausal women. The same pattern was observed for LDL-cholesterol. At baseline, HDL-cholesterol was not significantly different for the premenopausal group and postmenopausal group (mean ± SD: 1.7 ± 0.4 vs. 1.6 ± 0.6). Six weeks after RRSO, mean HDL-cholesterol was similar for both groups, but 7 months after RRSO, mean HDL-cholesterol of the premenopausal group was significantly higher (1.9 ± 0.5 vs. 1.6 ± 0.6, $p = 0.012$). The mean levels of triglycerides were significantly lower for the premenopausal group at baseline (mean ± SD: 0.9 ± 3.2 vs. 0.6 ± 1.8, $p < 0.001$) and remained significantly lower 6 weeks (mean ± SD: 0.7 ± 1.8) and 7 months (mean ± SD: 0.6 ± 1.7) after RRSO compared to the postmenopausal group. The premenopausal group had a significantly lower cholesterol ratio and HbA1c at all time points. Finally, Table 4 presents the correlations of the biochemical changes in blood with changes in HFRS scores and BMI. No significant correlations were observed between the changes in serum levels and scores on the HFRS questionnaires for either the premenopausal or the postmenopausal group. For the postmenopausal group, the only significant correlation observed, although still small, was between a decrease in BMI and a decrease in HDL-cholesterol ($p = 0.034$) and an increase in triglycerides ($p = 0.024$) 7 months after RRSO. There were no significant correlations observed between change in BMI and blood levels for the premenopausal group.

Discussion

In this study we found that, in premenopausal women, blood levels of HbA1c, HDL-cholesterol and cholesterol ratio increased after RRSO, although still staying within the reference range. In women who were postmenopausal at the time of RRSO, there were no relevant changes in any of the blood levels after RRSO.

Table 2. Baseline to follow-up differences in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, HbA1c and CRP within premenopausal and postmenopausal women who opted for RRSO.

		T0		T1		T2		Within-group changes T0–T1					Within-group changes T0–T2				
Parameter	p-Value, main effect	Mean	SE	Mean	SE	Mean	SE	Mean change	SE	95% confidence interval		ES	Mean change	SE	95% ionfidence interval		ES
Premenopausal																	
Total cholesterol (mmol/l)	0.45	5.2	0.09	5.7	0.09	5.7	0.10	–0.70	0.62	–1.92	0.52	–0.19	–1.02	0.94	–2.88	0.84	–0.16
HDL-cholesterol (mmol/l)	**0.002**	1.7	0.04	1.8	0.05	1.9	0.05	0.08	0.03	0.02	0.14	**0.43**[a]	0.12	0.04	0.05	0.20	**0.58**[b]
LDL-cholesterol (mmol/l)	0.16	3.1	0.08	3.5	0.09	3.5	0.09	–0.63	0.52	–1.67	0.40	**–0.20**[a]	–1.55	0.81	–3.15	0.05	**–0.29**[a]
Cholesterol ratio	**0.002**	3.1	0.09	3.4	0.11	3.4	0.13	0.22	0.06	0.10	0.35	**0.80**[b]	0.26	0.09	0.10	0.44	**0.70**[b]
Triglyceride (mmol/l)	0.43	1.2	0.08	1.3	0.08	1.2	0.08	0.05	0.08	–0.11	0.22	0.14	–0.02	0.08	–0.18	0.13	–0.07
HbA1c (mmol/mol)	**<0.001**	30.0	0.30	31.0	0.3	31.6	0.30	1.0	0.2	0.6	1.4	**0.86**[c]	1.6	0.2	1.2	2.0	**1.30**[c]
CRP (mg/l)	0.52	2.5	0.52	2.0	0.35	1.8	0.28	–0.45	0.58	–1.60	0.70	–0.16	–0.08	0.27	–0.62	0.47	–0.08
HFRS sum	**<0.001**	1.3	0.09	2.3	0.17	2.6	0.19	0.99	0.17	0.64	1.33	**1.29**[c]	1.24	0.19	0.85	1.63	**1.54**[c]
BMI (kg/m²)	0.53	24.4	0.36	24.6	0.37	24.4	0.38	0.19	0.17	–1.60	0.70	**0.20**[a]	0.06	0.19	–0.31	0.43	0.06
Postmenopausal																	
Total cholesterol (mmol/l)	0.33	6.1	0.16	6.2	0.16	6.2	0.17	0.14	0.10	–0.06	0.34	**0.30**[a]	0.12	0.11	–0.09	0.33	**0.25**[a]
HDL-cholesterol (mmol/l)	0.46	1.6	0.09	1.6	0.08	1.7	0.10	–0.01	0.04	–0.08	0.07	–0.06	0.06	0.05	–0.04	0.16	0.38
LDL-cholesterol (mmol/l)	0.52	3.8	0.14	3.9	0.14	3.8	0.14	0.08	0.08	–0.08	0.24	**–0.29**[a]	–0.01	0.08	–0.17	0.16	–0.02
Cholesterol ratio	0.38	4.3	0.31	4.3	0.28	4.1	0.23	0.04	0.14	–0.24	0.32	0.08	–0.17	0.15	–0.48	0.14	**–0.30**[a]
Triglyceride (mmol/l)	1.00	2.2	0.31	2.2	0.24	2.2	0.28	–0.01	0.23	–0.47	0.44	–0.02	–0.01	0.16	–0.34	0.31	–0.03
HbA1c (mmol/mol)	0.14	34.4	0.60	34.4	0.6	34.9	0.60	0.0	0.3	–0.5	0.5	–0.02	0.5	0.3	–0.1	1.1	0.40
CRP (mg/l)	0.69	2.8	0.50	2.7	0.54	2.5	0.41	–0.65	0.58	–1.80	0.49	**–0.23**[a]	–0.34	0.40	–1.15	0.46	**–0.25**[a]
HFRS sum	0.39	1.9	0.22	1.8	0.23	2.1	0.24	–0.03	0.19	–0.41	0.35	0.08	0.23	0.20	–0.17	0.63	**0.3**[a]
BMI (kg/m²)	0.69	26.1	0.59	26.1	0.59	26.0	0.59	–0.08	0.11	–1.80	0.49	–0.18	–0.08	0.11	–0.30	0.15	–0.2

[a]ES of 0.20–0.50, considered small.
[b]ES of 0.50–0.80, considered moderate.
[c]ES greater than 0.80, considered large.
All bold values are p <0.05 or ES > (–) 0.2. BMI, body mass index; CRP, C-reactive protein; ES, effect size; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HFRS, Hot Flush Rating Scale; LDL, low-density lipoprotein; RRSO, risk reducing salpingo oophorectomy; SE, standard error; T0, within 1 week before RRSO; T1, 6 weeks after RRSO; T2, 7 months after RRSO.

Table 3. Comparison of lipids, HbA1c and CRP between postmenopausal women (T0) and premenopausal women at 6 weeks (T1) and 7 months (T2) after RRSO.

Parameter	Postmenopausal T0 (N = 50)	Premenopausal T0 (N = 92)	p-Value compared to postmenopausal at T0	Premenopausal T1 (N = 79)	p-Value compared to postmenopausal at T0	Premenopausal T2 (N = 59)	p-Value compared to postmenopausal at T0
Total cholesterol (mmol/l)	6.1 (1.2)	5.2 (0.9)	<0.001[b]	5.7 (0.9)	0.06	5.8 (0.9)	0.25
LDL-cholesterol (mmol/l)	3.8 (1.0)	3.1 (0.8)	<0.001[b]	3.5 (0.8)	0.04[a]	3.6 (0.8)	0.16
HDL-cholesterol (mmol/l)	1.6 (0.6)	1.7 (0.4)	0.39	1.8 (0.4)	0.09	1.9 (0.5)	0.012[a]
Cholesterol ratio	4.3 (2.2)	3.1 (0.8)	0.001[b]	3.3 (1.0)	0.005[b]	3.3 (1.2)	0.006[b]
Triglycerides (mmol/l)	2.2 (2.2)	1.2 (0.8)	0.01[b]	1.3 (0.7)	0.008[b]	1.2 (0.7)	0.002[b]
HbA1c (mmol/mol)	34.4 (4.6)	30.0 (2.4)	<0.001[b]	30.9 (2.7)	<0.001[b]	31.7 (2.5)	<0.001[b]
CRP (mg/l)	2.8 (3.6)	2.5 (5.0)	0.66	2.0 (3.1)	0.18	1.8 (2.2)	0.09

[a]$p < 0.05$.
[b]$p < 0.01$.
Data presented as mean (standard deviation). CRP, C-reactive protein; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RRSO, risk reducing salpingo oophorectomy; T0, within 1 week before RRSO; T1, 6 weeks after RRSO; T2, 7 months after RRSO.

Table 4. Spearman rho correlation matrix and *p*-values for independent laboratory values in correlation to HFRS score and BMI.

Parameter	Laboratory value	Premenopausal Δ baseline–6 weeks	Premenopausal Δ baseline–7 months	Premenopausal Δ 6 weeks–7 months	Postmenopausal Δ baseline–6 weeks	Postmenopausal Δ baseline–7 months	Postmenopausal Δ 6 weeks–7 months
HFRS	Total cholesterol (mmol/l)	0.023 (*p* = 0.85)	0.049 (*p* = 0.72)	0.128 (*p* = 0.37)	−0.045 (*p* = 0.78)	−0.008 (*p* = 0.96)	0.060 (*p* = 0.74)
	LDL-cholesterol (mmol/l)	0.024 (*p* = 0.84)	0.028 (*p* = 0.84)	0.013 (*p* = 0.93)	−0.317 (*p* = 0.05)	0.035 (*p* = 0.85)	−0.051 (*p* = 0.79)
	HDL-cholesterol (mmol/l)	0.080 (*p* = 0.51)	−0.025 (*p* = 0.86)	0.004 (*p* = 0.98)	0.170 (*p* = 0.29)	0.051 (*p* = 0.78)	0.087 (*p* = 0.67)
	Triglycerides (mmol/l)	−0.088 (*p* = 0.47)	0.039 (*p* = 0.78)	0.063 (*p* = 0.66)	−0.049 (*p* = 0.77)	−0.156 (*p* = 0.38)	0.060 (*p* = 0.74)
	CRP (mg/l)	0.093 (*p* = 0.44)	0.131 (*p* = 0.35)	−0.235 (*p* = 0.10)	0.147 (*p* = 0.37)	0.094 (*p* = 0.60)	−0.091 (*p* = 0.62)
	HbA1c (mmol/mol)	0.028 (*p* = 0.83)	0.130 (*p* = 0.35)	−0.205 (*p* = 0.16)	0.030 (*p* = 0.86)	−0.009 (*p* = 0.96)	−0.076 (*p* = 0.71)
	BMI (kg/m^2)	0.111 (*p* = 0.37)	0.113 (*p* = 0.40)	−0.067 (*p* = 0.64)	0.054 (*p* = 0.74)	−0.181 (*p* = 0.31)	0.010 (*p* = 0.96)
BMI	Total cholesterol (mmol/l)	−0.134 (*p* = 0.29)	0.023 (*p* = 0.87)	0.020 (*p* = 0.90)	−0.018 (*p* = 0.92)	−0.256 (*p* = 0.14)	0.062 (*p* = 0.74)
	LDL-cholesterol (mmol/l)	−0.114 (*p* = 0.37)	0.044 (*p* = 0.76)	0.080 (*p* = 0.59)	0.151 (*p* = 0.38)	−0.184 (*p* = 0.31)	0.091 (*p* = 0.64)
	HDL-cholesterol (mmol/l)	−0.081 (*p* = 0.52)	−0.014 (*p* = 0.92)	−0.060 (*p* = 0.69)	0.091 (*p* = 0.59)	−0.364 (**p = 0.03**[a])	−0.049 (*p* = 0.79)
	Triglycerides (mmol/l)	0.069 (*p* = 0.56)	0.192 (*p* = 0.17)	−0.075 (*p* = 0.62)	−0.102 (*p* = 0.54)	0.386 (**p = 0.02**[a])	−0.252 (*p* = 0.17)
	CRP (mg/l)	−0.158 (*p* = 0.21)	0.039 (*p* = 0.78)	0.270 (*p* = 0.07)	0.083 (*p* = 0.62)	0.028 (*p* = 0.87)	−0.073 (*p* = 0.70)
	HbA1c (mmol/mol)	−0.074 (*p* = 0.58)	0.041 (*p* = 0.77)	0.149 (*p* = 0.34)	0.083 (*p* = 0.63)	0.099 (*p* = 0.61)	−0.083 (*p* = 0.69)

[a]$p < 0.05$.
All bold values are *p* <0.05 or ES > (−) 0.2. BMI, body mass index; CRP, C-reactive protein; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HFRS, Hot Flush Rating Scale; LDL, low-density lipoprotein.

The total score of the HFRS increased after RRSO in premenopausal women, but we did not observe any significant correlations between HFRS and changes in blood levels. Lastly, we found that premenopausal women with surgically induced menopause had higher HDL-cholesterol and lower triglyceride, HbA1c and cholesterol ratio levels following RRSO compared to the postmenopausal participants. The increase of cholesterol ratio and HbA1c observed in premenopausal women undergoing RRSO supports our hypothesis that these women undergo changes in serum lipids and HbA1c that are associated with the risk for CVD. In contrast to van der Schouw et al. we also found a significant increase in HDL-cholesterol, which is associated with less carotid atherosclerosis before menopause but with greater carotid atherosclerosis after menopause [7,32]. Whereas LDL-cholesterol increases in women who traverse menopause, the direction of change for HDL-cholesterol varies [9,33]. Higher HDL levels may be a marker of HDL dysfunctionality rather than a true indicator of CVD risk [34].

As others have found, our analysis of the group of women who were already postmenopausal before RRSO also showed no change in any of the laboratory variables, BMI or HFRS [35]. At baseline, we observed some significant differences between premenopausal and postmenopausal women, all explainable by the difference in age and menopausal status [9,36–38]. When we compared premenopausal women (at T1 and T2) with postmenopausal women (T0), there were lower levels of triglycerides and HbA1c and higher levels of HDL-cholesterol in the premenopausal group. We hypothesized that serum lipids and HbA1c of premenopausal women would change after RRSO, reaching baseline levels similar to postmenopausal women 7 months after RRSO. However, this was only true for total cholesterol and LDL-cholesterol, but not for the other serum levels. This indicates a more favorable risk profile for CVD in the first 7 months after RRSO for premenopausal women than postmenopausal women at baseline. The few studies that have compared biochemical profiles of both menopausal groups report inconsistent results [10,20]. One of the possible explanations for these inconsistencies is the difference in the timing of the collection of blood samples after surgery. The longer the period of estrogen deprivation following menopause, the greater the metabolic changes and increase of atherosclerosis, which is expressed in different values of serum lipids and HbA1c. Also, Sari et al. did not observe any significant differences in any of the serum levels between women who had a surgically induced menopause between the age of 40 and 50 years and postmenopausal women of matched age until 6 years after surgery [39]. We also investigated whether the changes in BMI and HFRS scores correlated significantly with the serum levels. For the natural postmenopausal group, the changes in HDL-cholesterol and triglycerides were associated with a decrease in BMI 7 months after RRSO. The decrease in BMI probably leads to the changes in these serum levels [40]. In the group of premenopausal women, there were no significant correlations observed between the changed blood values and BMI or the HFRS scores at any time point. Unexpectedly, in premenopausal women, the total HFRS scores did not show a substantial increase (although statistically significant) after RRSO: the score increased from 1.3 to 2.6 (range 1–10). It could be that the beneficial quality of life effects of RRSO may outweigh the adverse effects and therefore these women experience a relief of cancer-related stress [41]. Also, our premenopausal group had a mean age of 43 years, which could indicate that this group was already close to natural menopause and therefore had fewer symptoms related to RRSO.

Our study had several limitations that should be noted. We did not collect data on lifestyle habits or obstetric history, which are necessary to calculate adequately the risk of CVD [42,43]. We did not collect data on previous chemotherapy (type, duration) and we do not know the fasting status of our study population at time of blood withdrawal. As the literature states that it is not routinely necessary to obtain blood samples while fasting and because we are looking at group variables instead of individuals, we do not think this has influenced our results [44]. Also, the development of atherosclerosis and of actual CVD is both a multifactorial and a gradual process. Our follow-up was limited to 7 months, and thus it is likely that we were unable to capture some of the potentially longer-term, negative effects of RRSO. Longer-term follow-up is needed before drawing more definitive conclusions. A potential bias could also be the loss to follow-up of 32% of the original sample; however, there are no signs that the loss to follow-up is caused by CVD or other conditions related to change these lipid determinants, HbA1c and CRP. So we think this bias will not lead to significant changes in outcome. Our study also had a number of notable strengths, including its prospective design, relatively high follow-up rates, focus on women with a hereditary risk of ovarian cancer and the wide spectrum of serum levels that we used to examine the risk of CVD. Finally, to our knowledge this is one of the first prospective studies in this population that combined laboratory values with a validated questionnaire assessing vasomotor symptoms.

Conclusions

Our results may have several clinical implications. First, our results suggest that there is no clear indication for extra cardiovascular monitoring of premenopausal women up to 7 months after RRSO. The results of the study show that, although there were significant increases in HDL-cholesterol, cholesterol ratio and HbA1c in premenopausal women with early onset of menopause due to RRSO, these values remained within reference ranges. We would note, however, that the HbA1c level was still lower than in those women who had experienced a natural menopause. However, mean age and time since menopause differed significantly between the groups. Ultimately, a prospective study with a longer follow-up of several decades is needed to investigate the long-term changes in serum lipids, HbA1c and CRP, and their influence on the cardiovascular risk profile of women undergoing RRSO. Such a trial is currently being conducted by the group of van Leeuwen et al. registered at ClinicalTrials.gov NCT03835793 [45]. Awaiting these results, we suggest that there is no increased cardiovascular risk in the first 7 months after RRSO as the current guidelines state.

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