available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Metabolic syndrome after risk-reducing salpingo-oophorectomy in women at high risk for hereditary breast ovarian cancer: A controlled observational study

Trond M. Michelsen[a,b,*], *Are H. Pripp*[c], *Serena Tonstad*[d], *Claes G. Tropé*[e], *Anne Dørum*[e]

[a]*Department of Gynaecology, Sørlandet Hospital Arendal, Service Box 605, N-4809 Arendal, Norway*
[b]*National Resource Centre for Women's Health, Rikshospitalet University Hospital, 0027 Oslo, Norway*
[c]*Biostatistics Unit, Rikshospitalet University Hospital, 0027 Oslo, Norway*
[d]*Department of Internal Medicine, Ullevål University Hospital, University of Oslo Division, 0407 Oslo, Norway*
[e]*Department of Gynaecologic Oncology, The Norwegian Radium Hospital, Rikshospitalet University Hospital, University of Oslo Division, 0310 Oslo, Norway*

ARTICLE INFO

Article history:
Received 19 July 2008
Received in revised form
12 September 2008
Accepted 30 September 2008
Available online 12 November 2008

Keywords:
Genes, BRCA1
Genes, BRCA2
Oophorectomy
Metabolic syndrome X
Cardiovascular diseases

ABSTRACT

Surgical menopause may increase the risk of cardiovascular diseases (CVDs). The aim of this study was to determine the risk of metabolic syndrome in women who had undergone risk-reducing salpingo-oophorectomy (RRSO) because of increased risk of hereditary breast ovarian cancer (HBOC).

A sample of 326 (65% of invited) women at risk of HBOC who had undergone RRSO was compared to 679 women from the general population. Mean follow-up after surgery was 6.5 years (standard deviations [SD] 4.4). RRSO was significantly associated with metabolic syndrome according to the 2005 National Cholesterol Education Program Adult Treatment Panel III criteria (odds ratio [OR] 2.46 [95% confidence interval (CI) 1.63, 3.73]) and according to the International Diabetes Federation criteria (OR 2.49 [CI 1.60, 3.88]), as were increasing age and body mass index (BMI).

RRSO in women at risk of HBOC is significantly associated with the metabolic syndrome, and the follow-up after RRSO should take these findings into consideration.

1. Introduction

Ovarian cancer is the fifth most common cancer among women, and hereditary forms represent about 10% of cases.[1] The lifetime risk of ovarian cancer is about 40% for BRCA1 and 18% for BRCA2 mutation carriers,[2] while the risk of sporadic ovarian cancer in the general population is 1.7%.[2] In women at risk of hereditary breast ovarian cancer (HBOC), risk-reducing bilateral salpingo-oophorectomy (RRSO) is frequently performed. The procedure reduces the risk of ovarian cancer by 80% and the risk of breast cancer considerably, but leads to an estimated 4% cumulative incidence of peritoneal cancer after 20 years.[3–5]

Cardiovascular disease (CVD) is the main contributor to morbidity and mortality among women in the Western world,[6,7] and premature menopause is associated with CVD. In a meta-analysis of 18 studies, early natural menopause (<50 years) was associated with an increased risk of CVD.[8] Furthermore, surgical menopause or bilateral oophorectomy performed before the age of 50 years substantially increased

* *Corresponding author:* Address: Department of Gynaecology, Sørlandet Hospital Arendal, Service Box 605, N-4809 Arendal, Norway. Tel.: +47 37014000; fax: +47 37014041.
E-mail address: trond.melbye.michelsen@sshf.no (T.M. Michelsen).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.09.028

the risk.[8] Rocca et al. prospectively studied a cohort of 2390 women who had undergone unilateral or bilateral oophorectomy.[9] They found an increased mortality risk in the subpopulation whose bilateral oophorectomy was performed before age 45 years [hazard ratio (HR) 1.67] compared to age-matched referent women. In a recent Danish cohort study, rates of ischaemic heart disease were higher in women who had undergone bilateral oophorectomy before age 45 years compared to after age 45 years.[10] Oophorectomy before natural menopause induces an immediate decrease in sex hormones different from the slow decline of the oestrogen and testosterone levels that characterises natural menopause. Some data suggest that oestrogens have a cardio-protective effect before menopause, and that reduction of this protection increases the risk of CVD.[11] It is not yet clear, however, by what mechanisms the reduction of oestrogen levels leads to increased risk of CVD or what risk factors are influenced by oophorectomy. Further studies of CVD risk factors in women with rapidly induced, premature menopause are needed to delineate these mechanisms. Metabolic syndrome is one of the most prevalent risk conditions for CVD and type 2 diabetes. Metabolic syndrome is a constellation of metabolic abnormalities including glucose intolerance, insulin resistance, central obesity, dyslipidemia and hypertension.[12] Several definitions of metabolic syndrome have been proposed. The 2005 criteria of the International Diabetes Federation (IDF)[13] and the revised 2005 National Cholesterol Education Program Adult Treatment Program III criteria (ATP)[14] are among the latest, both designed to facilitate clinical diagnosis of metabolic syndrome. The IDF definition differs from the ATP definition, in that (1) the cut-off values for central obesity measured by waist circumference are lower, and the values are gender and ethnic-group specific and (2) central obesity is mandatory for the diagnosis of metabolic syndrome. The rationale for this requirement is that central obesity is highly correlated with metabolic syndrome and with insulin resistance.[13] The prevalence of metabolic syndrome according to IDF is expected to be higher than according to ATP. However, the prevalence of the components of the syndromes may vary between populations, as risk factors are influenced by differences in genetic background, diet, levels of physical activity, age and sex.

In a European prospective cohort study, Hu et al. followed 6156 men and 5356 women aged 30–89 years for a median of 8.8 years.[15] Among women, metabolic syndrome implied an increased risk of death from all causes and of death from CVD. Postmenopausal status has been found to be associated with a 60% increased risk of metabolic syndrome, after adjusting for age, body mass index (BMI), income and physical inactivity.[16] Menopause affects body fat distribution and lipid metabolism leading to higher levels of total and LDL cholesterols, triglycerides and lipoproteins(a).[17] Data are scarce regarding the association between surgical menopause and metabolic syndrome. Recently, an association between premenopausal oophorectomy and metabolic syndrome was demonstrated by Dørum and colleagues. They found that patients with bilateral oophorectomy before 50 years of age had a higher prevalence of metabolic syndrome than age-matched controls in a large Norwegian population-based health study.[18] This study included patients with both hysterectomy and oophorectomy, and the indications for the procedures were uterine or ovarian benign diseases. Taking the study by Dørum and colleagues one step further, we wanted to examine the prevalence of metabolic syndrome among women who had undergone RRSO as a cancer preventive method.

As RRSO is mostly offered to otherwise healthy women at risk of HBOC, any effects of RRSO causing increasing risk of metabolic syndrome are of interest. In the present study, we examined the risk of metabolic syndrome in women after RRSO compared to controls with intact ovaries from the general population.

2. Materials and methods

2.1. Sample selection

We identified a sample of 503 Norwegian women from HBOC families who had undergone RRSO after they had received genetic counselling at The Norwegian Radium Hospital. The sample was recruited from hospital surgical records, and RRSO was performed in three University Hospitals between 1980 and 2005. The women were sent a mailed questionnaire and were asked to visit their general practitioner for blood pressure and waist circumference measurements and blood tests. Non-responders were sent a reminder three weeks later. Of the women invited, 361 (72%) responded, and 326 (65%) returned complete questionnaires, physical measurements and blood samples. We did not have medical information about the non-respondents, and could therefore not perform a full attrition analysis.

2.2. Control sample

The Health Study of Nord-Trøndelag County of Norway (HUNT-2) was conducted in 1995–1997. All inhabitants aged $\geqslant$20 years were invited to a general health study, described in detail elsewhere.[19] Potential participants received a mailed questionnaire and an appointment for physical measurements and blood tests. Among the 46,709 women invited, 34,518 (74%) between 20 and 98 years of age participated, and 28,025 were between 30 and 79 years of age. Among these, 25,529 participated in the part of the study which included a second questionnaire. The women who had not answered the second questionnaire were excluded, as well as 1192 women with a history of cancer. We then excluded women who responded 'yes' or 'do not know' to these questions: 'Have you had one or both of your ovaries removed?' (N = 1710) and 'Have you had your uterus removed?' (N = 975).

Altogether, these exclusions left 21,650 potential controls, and among them, 679 controls had blood samples drawn in the fasting state (defined as fasting nine hours or more) including glucose, triglycerides and HDL-cholesterol, and complete waist and blood pressure measurements. A selection of 679 of 21,650 controls increases the risk of a selection bias, and we therefore made a comparison between our controls and the total HUNT sample.

2.3. Physical measurements and blood sampling

2.3.1. RRSO

General practitioners measured systolic and diastolic blood pressures. After at least 5 min rest, the mean of the second

and third measurements was used. Cuff size was adjusted after measuring the arm circumference. General practitioners also measured waist circumferences in a standardised manner above the iliac crest.

Fasting blood samples were analysed at Sørlandet Hospital, Arendal, Norway, on a Hitachi 911 auto-analyser. Glucose was measured with an enzymatic hexokinase method, triglycerides with an enzymatic colorimetric method and total and HDL-cholesterols with an enzymatic colorimetric cholesterolesterase method.

2.3.2. *Controls*

Systolic and diastolic blood pressures were measured in a standardised manner by trained nurses using a Dinamap 845XT (Criticon) based on oscillometry. The measurements were started after the participant had been seated for 2 min with the cuff on the arm, and blood pressure was measured three times at 1-min intervals. The mean of the second and third readings was used in this study. Waist circumference was measured above the iliac crest.

Fasting blood samples were analysed at Levanger Hospital, Norway, on a Hitachi 911 auto-analyser. Glucose was measured with an enzymatic hexokinase method, triglycerides with an enzymatic colorimetric method and total and HDL-cholesterols with an enzymatic colorimetric cholesterolesterase method.

2.3.3. *Demographic variables*

The questionnaire both for the RRSO sample and participants in HUNT-2 covered demographic characteristics, somatic and mental morbidity, physical impairment, use of medication as well as lifestyle and health-related behaviour. Somatic diseases were self-reported and queried using the following formulation: 'Has your doctor ever said that you suffer from…?' Diagnoses were not confirmed by general practitioners or hospital records.

Educational level was separated into low (⩽10 years) and high (>10 years) based on the number of completed school years. A *family history* of myocardial infarction was defined as a first degree relative with myocardial infarction before age 60. Employment was dichotomised into *paid work* or *not paid* work. *Not paid work* included housewives, participants on sick leave, students and pensioners. Women who were married or living in a paired relation were defined as *cohabiting*. *Current use of hormonal replacement therapy* (*HRT*) defined as use of oestrogen and use of *antihypertensives* was self-reported. *Physical activity* was self-reported, and the participants were categorised as having 'minimal' or 'moderate or more' physical activity, as published by Thorsen et al.[20] *Smoking* was rated as daily cigarette smokers.

2.3.4. *Metabolic syndrome definitions*

We used two definitions of metabolic syndrome as outcome variables:

(1) The International Diabetic Federation (IDF) defines metabolic syndrome as waist circumference ⩾80 cm plus two of the following four criteria: raised triglycerides, lowered HDL-cholesterol, raised blood pressure or raised fasting plasma glucose.[18] Raised triglycerides is defined as >1.7 mmol/l or specific treatment for this abnormality, lowered HDL-cholesterol as values <1.29 mmol/l or specific treatment, raised blood pressure as systolic pressure ⩾130, diastolic pressure ⩾85, treatment for hypertension or earlier diagnosed hypertension and raised fasting plasma glucose as values ⩾5.6 mmol/l or previously diagnosed type 2 diabetes.
(2) The National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (ATP) defines metabolic syndrome as fulfilling any three of the following criteria: abdominal obesity (>88 cm), raised triglycerides (>1.7 mmol/l), lowered HDL-cholesterol (<1.29 mmol/l) elevated blood pressure (systolic blood pressure ⩾130 and/or diastolic blood pressure ⩾85) or fasting glucose ⩾5.6 mmol/l.[19]

In our samples, we did not have data on treatment of abnormalities in triglycerides or HDL-cholesterol, and therefore we have only used increased values to define raised triglycerides and lowered HDL-cholesterol. Drugs to lower triglycerides and increase HDL-cholesterol, e.g. fibrates, are not registered in Norway.

2.4. *Ethics approval*

The HUNT-2 study was approved by the Regional Ethics Committee of the Mid-Norway Health Region, and all participants delivered written informed consent. The RRSO study was approved by the Regional Ethics Committee of the Southern Norway Health Region and the Data Inspectorate of Social Sciences. All participants provided written informed consent.

2.5. *Statistics*

Data were described by mean and standard deviations (SD) for continuous and by proportions for categorical variables. Differences between groups were assessed with two sample *t*-tests and χ^2-tests. The tables covering demography and risk factors present the crude data in addition to age-adjusted data. Age adjusted *p*-values for differences between women with RRSO and controls were estimated with linear regression or binary logistic regression, respectively. The age-adjusted odds ratios express the risk of each outcome given RRSO. The age-adjusted mean differences express age-adjusted differences between mean scores in the RRSO and in the control groups. The RRSO group and control groups were not systematically matched for age or other demographic and lifestyle factors. Risks of metabolic syndrome as defined by IDF and ATP were therefore modelled by multiple logistic regressions with age, education, civil status, smoking, BMI, RRSO, physical activity, BRCA mutation status, history of cancer, level of total cholesterol and HRT as independent variables. We examined possible presence of multicollinearity in the multiple regression model. The contribution made by each covariate was expressed as odds ratio (OR) with 95% confidence intervals (CI). The level of significance was set at $p < 0.05$, and all

tests were two-tailed. SPSS (version 15.0) was used for the statistical analyses.

3. Results

3.1. Demographic variables

The mean age in the RRSO group and in the control group was 54.4 years (SD 8.9) and 48.5 years (SD 13.1), respectively ($p < 0.001$) (Table 1). In the RRSO group, 93/326 (29%) had a history of cancer, and 75/326 (26%) had a history of breast cancer. A significantly larger proportion of the RRSO group had more than 10 years of education, more paid work, and were more frequently cohabiting compared to controls (Table 1). These differences remained significant after adjustment for age (Table 1).

3.2. Lifestyle variables and medication

More RRSO patients were current users of HRT, even after adjustment for age (Table 1). The RRSO group reported more physical activity with a significantly larger proportion being 'moderately active or more' (Table 1).

The RRSO group included fewer daily smokers than the control group (Table 2).

3.3. Physical measures and blood tests

The RRSO patients had higher HDL-cholesterol, lower systolic blood pressure and lower BMI than the controls. After age-adjustment, the RRSO group also had lower diastolic blood pressure, total cholesterol, blood glucose and triglycerides (Table 2).

The RRSO patients had significantly higher waist circumference, and met the central obesity criteria of the IDF and ATP definitions more frequently compared to controls (Table 2). The unadjusted data showed no differences between the groups in the blood pressure criteria of the IDF and ATP definitions, but after age-adjustment, a lower proportion of the RRSO group filled these criteria compared to the control group (Table 2).

3.4. Metabolic syndrome and contributors of risk

The prevalence of metabolic syndrome was similar in the RRSO group and in the control group after age-adjustment, and according to both the IDF and ATP definitions (Table 2). In the multiple logistic model having performed RRSO was significantly associated with metabolic syndrome (both IDF and ATP definitions) as were increasing age and BMI (Table 3). Multicollinearity was not present in the multiple model according to our analyses (data not shown).

3.5. Controls versus the whole HUNT sample

The controls used in this study ($N = 679$) were significantly younger than the whole HUNT sample ($N = 20,911$) (Table 4). After age-adjustment, the controls from this study had lower level of education, more paid work, more diabetes, higher total cholesterol, higher waist circumference, higher systolic blood pressure, higher diastolic blood pressure, higher Framingham total point score and more smokers compared to the whole HUNT sample (Table 4).

4. Discussion

The major finding in this controlled study is that RRSO for breast and ovarian cancer prevention was significantly associated with metabolic syndrome (both according to IDF and ATP definitions), when compared to controls from the general population without such surgery after adjustment for age, educational level, paid work, cohabiting, physical activity, daily smoking, BRCA mutation status, history of cancer, use of HRT, BMI and levels of total cholesterol.

Table 1 – Demographic, somatic and lifestyle variables in the RRSO and in the control groups.

	RRSO ($N = 326$)	Controls ($N = 679$)	p	Age-adjusted[b]
				OR (95% CI) p
	Mean (SD)	*Mean (SD)*		
Age at survey	54.4 (8.9)	48.5 (13.1)	<0.001	
Age at RRSO	48.0 (7.8)			
Years since RRSO	6.5 (4.4)			
	N/total (%)	*N/total (%)*		
Having cancer	97/326 (30)			
Having breast cancer	75/326 (23)			
Higher education	152/312 (49)	133/654 (20)	<0.001	6.26 (4.42, 8.88) <0.001
BRCA mutation positive	58/273 (21)			
Family history of MI[a]	56/315 (18)	137/679 (20)	0.37	0.84 (0.59, 1.20) 0.34
Paid work	205/313 (65)	337/664 (51)	<0.001	2.89 (2.12, 3.93) <0.001
Cohabiting	262/315 (83)	403/679 (59)	<0.001	3.08 (2.19, 4.32) <0.001
Current use of HRT	127/326 (39)	51/679 (8)	<0.001	8.11 (5.56, 11.84) <0.001
Physically active	283/305 (93)	465/601 (77)	<0.001	3.69 (2.55, 5.34) <0.001

RRSO: risk-reducing salpingo-oophorectomy; OR: odds ratio; CI: confidence interval; SD: standard deviation; MI: myocardial infarction; and HRT: hormonal replacement therapy.

a $\geqslant 1$ relative with MI < 60 years.

b The age-adjusted ORs give an estimated age-adjusted risk of outcome given RRSO.

Table 2 – Variables related to metabolic syndrome (IDF and 2005 ATP definition).

	RRSO (N = 326)	Controls (N = 679)	p	Age-adjusted[a]
				Mean difference (95% CI) p (RRSO – controls)
	Mean (SD)	*Mean (SD)*		
Total cholesterol mmol/l	5.8 (1.2)	6.1 (1.4)	0.05	–0.54 (–0.70, –0.38) <0.001
BMI kg/m^2	25.1 (4.0)	27.4 (5.0)	<0.001	–2.57 (–3.25, –1.89) <0.001
Waist circumference cm	87 (12)	84 (12)	<0.001	2.12 (0.48, 3.75) 0.01
Triglycerides mmol/l	1.2 (0.7)	1.3 (0.7)	0.62	–0.12 (–0.21, –0.03) 0.009
HDL-cholesterol mmol/l	1.7 (0.4)	1.5 (0.4)	<0.001	0.16 (0.10, 0.21) <0.001
Blood pressure mmHg				
Systolic BP	128 (17)	134 (24)	<0.00	–11.3 (–13.8, –8.80) <0.001
Diastolic BP	79 (10)	80 (11)	1 0.39	–2.14 (–3.54, –0.72) 0.003
Fasting glucose in mmol/l	5.2 (1.3)	5.4 (1.2)	0.11	–0.29 (–0.45, –0.13) <0.001
	N (%)	*N* (%)	*p*	Age-adjusted[b] OR (95% CI) p
Smoking	70 (22)	289 (43)	<0.001	0.45 (0.33, 0.62) <0.001
Waist circumference ⩾80 cm (IDF)[c]	236 (72)	402 (59)	<0.001	1.49 (1.10, 2.00) 0.009
Waist circumference ⩾88 cm (ATP)[c]	159 (49)	232 (34)	<0.001	1.56 (1.19, 2.06) 0.002
Blood glucose ⩾5.6 mmol/l[c]	89 (27)	159 (23)	0.18	0.96 (0.70, 1.31) 0.79
Triglycerides ⩾1.7 mmol/l[c]	58 (18)	133 (20)	0.50	0.73 (0.51, 1.03) 0.08
Blood pressure ⩾130 or ⩾85 mmHg or antihypertensives[c]	186 (57)	368 (54)	0.39	0.62 (0.46, 0.85) 0.003
HDL-cholesterol <1.29 mmol/l[c]	56 (17)	188 (28)	<0.001	0.57 (0.40, 0.80) 0.001
Metabolic syndrome				
IDF[d]	102 (31)	185 (27)	0.18	0.83 (0.77, 1.40) 0.83
2005 ATP[e]	85 (26)	163 (24)	0.48	1.12 (0.82, 1.54) 0.47

IDF: International Diabetes Federation; ATP: The National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults; RRSO: risk-reducing salpingo-oophorectomy; CI: confidence interval; BMI: body mass index; HDL-cholesterol: high density lipoprotein cholesterol; BP: blood pressure; and OR: odds ratio.

a The age-adjusted mean differences express age-adjusted differences between mean scores in the RRSO and in the control groups.

b The age-adjusted ORs give an estimated age-adjusted risk of outcome given RRSO.

c Risk determinants of metabolic syndrome.

d IDF definition: includes central obesity and ⩾2 of 4 risk determinants present.

e ATP-definition: ⩾3 of 5 risk determinants present.

To our knowledge, this is the first study to examine the associations between RRSO in women at risk of HBOC and metabolic syndrome. It has previously been demonstrated that oophorectomy before the age of 45 is associated with increased mortality.[9] However, it is still unclear whether this association is due to a causal effect or to a worse risk

Table 3 – Multiple binary logistic analysis of variables associated with metabolic syndrome in the total sample (RRSO + control groups).

Characteristics	IDF metabolic syndrome	ATP metabolic syndrome
	OR (95% CI) p	*OR (95% CI) p*
If RRSO	2.13 (1.31, 3.46) 0.002	2.12 (1.26, 3.57) 0.005
Age	1.04 (1.02, 1.06) <0.001	1.04 (1.02, 1.06) <0.001
If lower education	1.18 (0.78, 1.78) 0.45	1.20 (0.77, 1.88) 0.42
If not having paid work	1.21 (0.84, 1.74) 0.32	1.29 (0.87, 1.91) 0.21
If not cohabiting	1.10 (0.75, 1.60) 0.63	0.99 (0.66, 1.48) 0.96
If not physically active	1.10 (0.72, 1.67) 0.66	0.91 (0.58, 1.42) 0.91
If smoker	1.29 (0.88, 1.89) 0.19	1.39 (0.92, 2.09) 0.12
If BRCA mutation positive	0.94 (0.44, 1.98) 0.86	1.18 (0.54, 2.58) 0.68
If history of cancer	1.49 (0.83, 2.68) 0.18	1.42 (0.76, 2.65) 0.27
If use of HRT	1.18 (0.76, 1.83) 0.47	1.12 (0.70, 1.80) 0.63
Total cholesterol	1.13 (0.98, 1.29) 0.09	1.16 (1.00, 1.34) 0.05
BMI	1.26 (1.21, 1.31) <0.001	1.30 (1.24, 1.36) <0.001

IDF: International Diabetes Federation; ATP: The National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults; OR: odds ratio; CI: confidence interval; RRSO: risk-reducing salpingo-oophorectomy; BRCA: breast cancer gene; HRT: hormonal replacement therapy; and BMI: body mass index.

Table 4 – Controls (N = 679) versus eligible controls from the HUNT sample (N = 20,911).

	HUNT (N = 20,911)	Controls (N = 679)	p*
	Mean (SD)	*Mean (SD)*	
Age at survey	52.0 (14.0)	48.4 (13.1)	
	N/total (%)	*N/total (%)*	
Higher education	5451/19,797 (28)	133/654 (20)	<0.001
Paid work	11,595/20,911 (55)	396/664 (60)	0.02
Current use of HRT	1835/17,159 (11)	51/679 (8)	0.61
History of angina	741/20,175 (4)	17/679 (3)	0.79
History of MI	347/20,930 (2)	8/679 (1)	0.88
History of stroke	321/20,911 (2)	7/671 (1)	0.89
Diabetes	563/20,934 (3)	28/679 (4)	<0.001
Smoker	4901/20,911 (23)	289/679 (43)	<0.001
	Mean (SD)	*Mean (SD)*	
Total cholesterol mmol/l	6.1 (1.3)	6.1 (1.4)	<0.001
Waist circumference cm (mean)	82 (11)	84 (12)	<0.001
HDL-cholesterol mmol/l	1.5 (0.4)	1.5 (0.4)	0.80
Blood pressure			
Systolic BP	137 (23)	134 (24)	0.005
Diastolic BP	80 (12)	80 (11)	0.02
Framingham total point score	14.3 (6.2)	14.4 (6.5)	<0.001

HUNT: The Nord-Trøndelag Health Study; SD: standard deviation; HRT: hormonal replacement therapy; MI: myocardial infarction; HDL: high density lipoprotein; and BP: blood pressure.
* *p*-Values adjusted for age.

profile in the population who underwent early oophorectomy.

Recently, a possible causal relation between metabolic syndrome and breast cancer has been postulated.[21] Putative mechanisms include peripheral oestrogen aromatisation in adipose tissue and insulin resistance. These processes seem to be associated with aggressive and late-stage breast cancer disease.[22–24] In the present study, 23% of the RRSO patients had a history of breast cancer. However, we did not find an increased prevalence of metabolic syndrome in the subpopulation with cancer in our material.

Although the RRSO participants were older than controls, they had lower BMI, higher HDL-cholesterol and lower systolic blood pressure. In addition to this, they were more physically active, had a higher level of education, included a lower proportion of smokers and a higher proportion in paid work and cohabiting. Some of these findings may have been caused by an adaptation to changing health.[25] The RRSO group might have been more concerned about their general health because of their high HBOC risk and the RRSO status, and adapt to a healthier lifestyle, such as their increased physical activity and reduced smoking habits, all changes known to decrease the risk of CVD.[26] Also, the RRSO women may be aware of studies suggesting that lifestyle variables and weight control through restricted dietary energy intake may reduce the risk of breast cancer.[22] Such lifestyle changes seem to affect breast cancer risk in BRCA individuals as well.[27] Additionally, the rates of genetic testing seem to be higher in groups of higher socioeconomic status.[28] However, when adjusted for these demographic and lifestyle characteristics, RRSO was still significantly associated with metabolic syndrome.

Because of the cross-sectional design of the study, we cannot establish a causal relationship. Nonetheless, our findings indicate that RRSO is significantly associated with metabolic syndrome. Age is a well-known risk factor of metabolic syndrome, and this association is confirmed in our study.[12] Higher BMI is associated with increased waist measurements, and was significantly associated with metabolic syndrome in this study.[29]

This study demonstrates a significantly higher waist circumference in the post-RRSO group, even after age-adjustment. The association between increased waist circumference and cardiovascular risk is well-known. Central obesity, either caused by visceral obesity or subcutaneous fat accumulation, is agreed as essential in the IDF definition of metabolic syndrome because of the strength of the evidence linking waist circumference with cardiovascular disease and other metabolic syndrome components.[13] The most probable explanation of our finding is that the loss of oestrogen caused by RRSO leads to alterations in body fat distribution with increased waist circumference and central obesity. The differences between the RRSO and control groups regarding socioeconomic factors and other cardiovascular risk factors may outweigh differences in each of the single cardiovascular risk factors and therefore the association between RRSO and metabolic syndrome is not revealed unless analysed with multiple models.

A prospective study has previously shown that HRT of any type did not significantly alter the reduction in breast cancer risk after RRSO.[30] Use of oestrogen therapy does not seem to influence the risk of metabolic syndrome in our study, and only 39% in the RRSO group were current users of oestrogens. As about one fourth of the RRSO sample had a history of breast cancer and all carry an increased risk of breast cancer, many patients may have been reluctant to use oestrogen replacement therapy.

4.1. *Strengths and limitations*

Our cohort was large and uniform as all RRSO procedures were performed after evaluation and counselling at the same centre. Measurements were standardised both in the cases and in the controls, and the controls were drawn from a population-based sample. All blood samples were analysed by the same methods. None of the controls had undergone oophorectomy or hysterectomy, and none had a history of cancer.

Our main limitation is the cross-sectional design as measurements were not available among cases prior to surgery. Therefore, we were not able to establish causal relationships. To determine the prevalence of metabolic syndrome, blood samples have to be drawn in the fasting state, and in our population-based control sample, only 679 of 21,650 eligible controls fulfilled these criteria. The comparison between the control sample ($N = 679$) and the total sample of eligible controls ($N = 21,650$) demonstrates differences, confirming the presence of a selection bias. The selection bias limits our ability to generalise the association between RRSO and metabolic syndrome. Overall, our control sample seems to have a worse cardiovascular risk profile than the total HUNT material. Presumably, this worse risk profile would tend to lessen the differences towards the RRSO group.

Women with RRSO may be self-selected in regard to higher education, more paid work, less smoking and a healthier lifestyle. These selections may reduce the risk of CVD. The cardiovascular risk differences between the RRSO and control groups may explain why the association between RRSO and metabolic syndrome is only visible in the multiple model.

5. Conclusion

RRSO was significantly associated with the metabolic syndrome, indicating that women after RRSO may have a higher risk of type 2 diabetes and CVD than controls from the general population with intact ovaries. These findings need to be confirmed in studies with a more robust design. Women at risk of HBOC will be offered RRSO at early ages in the foreseeable future. It is therefore important to evaluate the need for medical follow-up.

Conflicts of interest statement

None declared.

Funding sources

Trond Melbye Michelsen holds a research career grant from Sørlandet Hospital and The National Resource Centre for Women's Health, Rikshospitalet.

Acknowledgements

HUNT is a collaboration between HUNT Research Centre, Faculty of Medicine, Norwegian University of Science and Technology (NTNU, Verdal), Norwegian Institute of Public Health and Nord-Trøndelag County Council.

REFERENCES

1. Narod SA, Risch H, Moslehi R, et al. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. *New Engl J Med* 1998;**339**:424–8.
2. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol* 2007;**25**:1329–33.
3. Finch A, Beiner M, Lubinski J, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 mutation. *JAMA* 2006;**296**:185–92.
4. Narod SA. Modifiers of risk of hereditary breast cancer. *Oncogene* 2006;**25**:5832–6.
5. Kauff ND, Domchek SM, Friebel TM, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. *J Clin Oncol* 2008;**26**:1331–7.
6. Jacobs AK. Women, ischemic heart disease, revascularization, and the gender gap: what are we missing? *J Am Coll Cardiol* 2006;**47**:S63–5.
7. Polk DM, Naqvi TZ. Cardiovascular disease in women: sex differences in presentation, risk factors, and evaluation. *Curr Cardiol Rep* 2005;**7**:166–72.
8. Atsma F, Bartelink ML, Grobbee DE, van der Schouw YT. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. *Menopause* 2006;**13**:265–79.
9. Rocca WA, Grossardt BR, de A, Malkasian GD, Melton LJ. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. *Lancet Oncol* 2006;**7**:821–8.
10. Lokkegaard E, Jovanovic Z, Heitmann BL, Keiding N, Ottesen B, Pedersen AT. The association between early menopause and risk of ischaemic heart disease: influence of hormone therapy. *Maturitas* 2006;**53**:226–33.
11. Clarkson TB. Estrogen effects on arteries vary with stage of reproductive life and extent of subclinical atherosclerosis progression. *Menopause* 2007;**14**:373–84.
12. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005;**365**:1415–28.
13. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome – a new worldwide definition. *Lancet* 2005;**366**:1059–62.
14. Executive Summary of the Third Report of The National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA* 2001;**285**:2486–97.
15. Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Pyorala K. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. *Arch Intern Med* 2004;**164**:1066–76.
16. Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB. The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey 1988–1994. *Arch Intern Med* 2003;**163**:427–36.
17. Carr MC. The emergence of the metabolic syndrome with menopause. *J Clin Endocrinol Metab* 2003;**88**:2404–11.
18. Dorum A, Tonstad S, Liavaag AH, Michelsen TM, Hildrum B, Dahl AA. Bilateral oophorectomy before 50 years of age is significantly associated with the metabolic syndrome and Framingham risk score: a controlled, population-based study (HUNT-2). *Gynecol Oncol* 2008.
19. Holmen J, Midthjell K, Kruger Ø, et al. The Nord-Trøndelag Health Study 1995–1997 (HUNT 2): objectives, contents, methods and participation. *Norwegian J Epidemiol* 2003;**13**:19–32.

20. Thorsen L, Nystad W, Stigum H, et al. The association between self-reported physical activity and prevalence of depression and anxiety disorder in long-term survivors of testicular cancer and men in a general population sample. *Support Care Cancer* 2005;**13**:637–46.
21. Beaulieu LM, Whitley BR, Wiesner TF, et al. Breast cancer and metabolic syndrome linked through the plasminogen activator inhibitor-1 cycle. *Bioessays* 2007;**29**:1029–38.
22. Furberg AS, Veierod MB, Wilsgaard T, Bernstein L, Thune I. Serum high-density lipoprotein cholesterol, metabolic profile, and breast cancer risk. *J Natl Cancer Inst* 2004;**96**:1152–60.
23. Lorincz AM, Sukumar S. Molecular links between obesity and breast cancer. *Endocr Relat Cancer* 2006;**13**:279–92.
24. Vona-Davis L, Howard-McNatt M, Rose DP. Adiposity, type 2 diabetes and the metabolic syndrome in breast cancer. *Obes Rev* 2007;**8**:395–408.
25. Schwartz CE, Sprangers MAG. Adaptation to changing health: response shift in quality of life research; 2000.
26. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature* 2006;**444**:875–80.
27. Nkondjock A, Robidoux A, Paredes Y, Narod SA, Ghadirian P. Diet, lifestyle and BRCA-related breast cancer risk among French–Canadians. *Breast Cancer Res Treat* 2006;**98**:285–94.
28. Lerman C, Narod S, Schulman K, et al. BRCA1 testing in families with hereditary breast-ovarian cancer. A prospective study of patient decision making and outcomes. *JAMA* 1996;**275**:1885–92.
29. Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. *Am J Clin Nutr* 2004;**79**:379–84.
30. Rebbeck TR, Friebel T, Wagner T, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol* 2005;**23**:7804–10.