

Hypertriglyceridemia is Frequent in Endometrial Cancer Survivors

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Objective: Previous studies have reported an association between endometrial cancer and the risk of metabolic syndrome; however, the pattern of endometrial cancer-associated dyslipidemia is not well understood. The standard therapy for endometrial cancer is total abdominal hysterectomy and bilateral salpingo-oophorectomy. Premenopausal bilateral salpingo-oophorectomy may cause adverse events, including dyslipidemia. Gynecologists have to care dyslipidemia in endometrial cancer survivors at cancer follow-up clinic.

Methods: This study included 693 patients who had undergone bilateral salpingo-oophorectomy, and included 412 women with incident endometrial cancer and 281 controls. We divided the patients into two categories according to whether they had a premenopausal or postmenopausal bilateral oophorectomy. Serum lipid levels were measured and statistically analyzed.

Results: Hypertriglyceridemia was statistically more frequent in patients who had undergone bilateral salpingo-oophorectomy both before and after menopause than in the corresponding non-endometrial cancer controls. High levels of low-density lipoprotein cholesterol and a high low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio were statistically more frequent in patients who had undergone bilateral salpingo-oophorectomy before menopause than in non-endometrial cancer controls.

Conclusions: Our report highlights the importance of the relationship between endometrial cancer and lipid metabolism, which may aid in preventing cerebrovascular or cardiovascular diseases due to dyslipidemia and improving the quality of life in endometrial cancer survivors.

Key words: dyslipidemia – endometrial cancer – hypertriglyceridemia – cancer survivor

INTRODUCTION

Endometrial cancer (EC) is the most common invasive neoplasm of the female genital tract in Europe and North America. Worldwide, ~150 000 cases are diagnosed each year, making EC the fifth most common cancer in women (1). Although the highest rates of EC are seen in Europe and North America, reports from many other countries have shown an increased incidence of EC http://ganjoho.jp/public/statistics/backnumber/2011_en.html. While the incidence rates in developing countries and Japan are four to five times lower (1), the age-adjusted incidence rate of EC in Japan has been increasing since the 1970s.

Like breast cancer, EC is an estrogen-dependent tumor. The predominant treatment for EC is total abdominal hysterectomy and bilateral salpingo-oophorectomy (BSO), and this operation should be performed in all cases whenever feasible (2). Due to the rise in the onset of EC at a young age in many countries, the number of premenopausal EC survivors who will undergo BSO will increase in the near future. BSO places premenopausal women at a high risk for multiple adverse events, including early postmenopausal symptoms (hot flashes, fatigue, shoulder stiffness and palpitations), and can lead to further presentation of symptoms such as coital pain, atrophic (senile) vaginitis, urethritis, urinary incontinence, rough and dull skin

accompanying skin atrophy and obesity. In addition, other long-term conditions, such as osteoporosis or osteopenia, dyslipidemia, atherosclerosis, and subsequent cerebrovascular and cardiovascular diseases may manifest. These illnesses can be difficult to diagnose and have a direct effect on the quality of life (QOL) when they progress, necessitating management from an early stage. Management of postmenopausal symptoms should be carried out in addition to surveillance for recurrence.

The incidence and mortality rates of coronary heart disease are lower in Japanese populations than in Caucasian populations (3–6); however, the increasingly Westernized lifestyle in Japan is the cause for rapidly increasing rates of dyslipidemia or coronary heart diseases (7–10).

The proposed risk factors for EC are obesity, diabetes and hormonal stimulation caused by an early age at menarche, advanced age at menopause, nulliparity, estrogen replacement therapy and tamoxifen treatment, among other risk factors (1). A few studies have reported an association between EC and the risk of metabolic syndrome (MetS) (11,12), including the pattern of dyslipidemia, hyper-low-density lipoprotein (LDL) cholesterolemia, hypertriglyceridemia or hypo-high-density lipoprotein (HDL) cholesterolemia. Furthermore, the LDL-cholesterol (LDL-C)/HDL-C ratio may represent the effects of both LDL-C and HDL-C. The LDL-C/HDL-C ratio has been reported to correlate with ischemic heart disease (13), but the patterns of dyslipidemia associated with EC are not well understood.

As the incidence rates of dyslipidemia and EC are simultaneously increasing, we hypothesize that serum lipids play a role in endometrial carcinogenesis. Currently, effective diagnostic serum markers for EC have not been identified, and mass screening of the population for EC is not practical (2). In this study, we report the serum lipid characteristics of patients with EC compared with those of non-EC cases following BSO to establish a QOL surveillance system for EC survivors. This attempt to determine the biological characteristics of EC, in addition, might enable the development of preventive or therapeutic targets and biomarkers associated with serum lipids in the future.

PATIENTS AND METHODS

This study was conducted using data from 693 patients who had undergone BSO [412 women with incident EC and 281 without incident EC (non-EC controls)], who visited the menopausal clinic or cancer follow-up clinic of the Department of Obstetrics and Gynecology, Keio University Hospital (Tokyo, Japan), from 2007 to 2011 (Table 1). Because patients experienced dyslipidemia thereafter due to ovarian dysfunction caused by premenopausal oophorectomy (14), they were divided into two groups depending on whether they had undergone BSO before (premenopausal BSO group) or after (postmenopausal BSO group) menopause. The premenopausal BSO group included 169 non-EC patients and 181 EC patients, and the postmenopausal BSO group included 112

non-EC patients and 231 EC patients. Age, time interval from surgical menopause in the premenopausal BSO group, time interval from natural menopause in the postmenopausal BSO group and body mass index (BMI) were analyzed (Table 1). This study was conducted with the approval from the ethics committee of the School of Medicine, Keio University (approval number: 20070081).

Serum lipid, triglyceride (TG), LDL-C and HDL-C levels and the LDL-C/HDL-C ratio were measured. Blood collected after fasting was used to measure serum lipids levels, thereby avoiding any dietary influences that would cause conflicting results among the studies. The Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases were used to diagnose dyslipidemia (15). To be eligible for participation, patients were required to meet the following criteria: patients (i) who had undergone BSO, (ii) aged ≥ 20 years and (iii) not deemed to be ineligible for participation for any other reason. Exclusion criteria for this study included the presence of non-epithelial tumors, multiple primary cancers accompanying EC, hypothyroidism, diabetes mellitus, familial hypercholesterolemia and the administration of antihyperlipidemic drugs.

Statistical analysis was performed with Excel: Mac 2011 (Microsoft, USA) with the add-in software Statcel 3 (OMS, Japan) and Prism 6 (GraphPad Software, USA) using the indicated tests. The *F*-test was used to verify the heterogeneity of variances. Normally distributed variables were compared by Student's *t*-test, and non-parametric distributed variables compared by the Mann-Whitney *U* test. The χ^2 for independence test was carried out for 2×2 contingency tables. The results with $P < 0.05$ were considered significant.

RESULTS

Table 1 lists the patient characteristics of the EC cases and non-EC controls by oophorectomy status. In the overall patient population, patients who received premenopausal BSO and patients who received postmenopausal BSO, the EC and non-EC groups did not differ with regard to age ($P = 0.89$, 0.68 , 0.92 , respectively). The interval from surgical menopause and the interval from natural menopause were not significantly different between the EC and non-EC groups in patients who received premenopausal BSO and those who received postmenopausal BSO, respectively ($P = 0.86$ and 0.27 , respectively). The BMI was significantly higher in the EC group than in the non-EC group in the overall patient population, in those who received premenopausal BSO and in those who received postmenopausal BSO ($P = 8.3 \times 10^{-11}$, 3.6×10^{-8} and 3.9×10^{-5} , respectively).

Differences between the serum lipid levels of each group were analyzed using the Mann-Whitney *U* test (Fig. 1). TG levels were significantly higher in all EC groups ($P < 0.0001$). LDL-C levels ($P = 0.0071$) and the LDL-C/HDL-C ratio ($P = 0.0020$) were significantly higher in the EC patients of the premenopausal BSO group.

Table 1. Characteristics of endometrial cancer patients and non-endometrial cancer controls by oophorectomy status

	Total		Premenopausal bilateral oophorectomy		Postmenopausal bilateral oophorectomy	
	Non-EC	EC	Non-EC	EC	Non-EC	EC
Number	281	412	169	181	112	231
	Ovarian tumor: 146		Ovarian tumor: 68		Ovarian tumor: 78	
	Cervical cancer: 69		Cervical cancer: 53		Cervical cancer: 16	
	Myoma or endometriosis: 51		Myoma or endometriosis: 43		Myoma or endometriosis: 8	
	Others: 15		Others: 5		Others: 10	
Age, years						
Average	54.1	59.9	48.1	51.6	62.4	66.3
<i>P</i> (<i>F</i> test)	0.89		0.68		0.92	
Interval from surgical menopause						
Average			5.2	7.0	NA	
<i>P</i> (<i>F</i> test)			0.86			
Interval from natural menopause						
Average			NA		11.6	15.1
<i>P</i> (<i>F</i> test)					0.27	
Body mass index, kg/m ²						
Average	21.3	23.2	21.2	23.7	21.4	22.8
<i>P</i> (Mann–Whitney <i>U</i> test)	8.3×10^{-11}		3.6×10^{-8}		3.9×10^{-5}	

BMI, body mass index; EC, endometrial cancer; non-EC, non-endometrial cancer; NA, not applicable.

Table 2 shows the relationship between EC and serum lipid levels. Hyper-LDL cholesterolemia was significantly more frequent in EC than in non-EC patients in the premenopausal BSO group [*P* = 0.0261, odds ratio (OR) = 1.655]. Hypertriglyceridemia was significantly more frequent in EC patients in all groups (total, premenopausal BSO and postmenopausal BSO; *P* < 0.0001, <0.0001 and 0.00154, respectively). This was particularly evident in the premenopausal BSO group, where the OR was 2.259. The LDL-C/HDL-C ratio was significantly higher in EC than that in non-EC patients in the premenopausal BSO group (*P* = 0.0121, OR = 1.719).

DISCUSSION

Hypertriglyceridemia is a marker of MetS and is assuming an increasingly important role in the assessment and management of cardiovascular disease risk (16). MetS, initially defined as a risk factor for cardiovascular disorders, has recently been associated with various cancers (11,17–22). Lipoprotein abnormalities in MetS include hypertriglyceridemia, high remnant lipoproteinemia, small dense LDL particles and low-HDL cholesterolemia. Cases of MetS are increasingly observed during the postmenopausal period.

Several studies have reported a direct association between the EC risk and MetS (11,23), and some have reported

that diabetes is a risk factor for EC, independent of obesity (24–27). A case–control study nested within the European Prospective Investigation into Cancer and Nutrition on 284 women with EC showed that the presence of MetS was associated with EC risk (relative risk = 2.12, 95% confidence interval: 1.51–2.97), and there was a positive trend in risk with an increasing number of MetS components (28). These findings suggest that metabolic abnormalities may act to increase EC risk, but data on dyslipidemia, with details on each type of serum lipid, are limited (29,30).

Some studies attempted to investigate whether serum dyslipidemia influences EC risk, but these results are contradictory (28–31). Lindemann et al. (29) examined the association of serum total cholesterol (TC) levels, LDL-C, non-HDL and HDL-C with EC risk in 100 EC cases. The results showed a positive correlation between serum TG levels and EC risk and no association between TC, LDL-C or HDL-C. Cust et al. (28) reported that TG and HDL-C levels were positively and negatively associated with EC risk, respectively, but TC and LDL-C were not. Swanson et al. (30) analyzed serum lipid levels in 256 EC cases and 185 controls <75 years old, and indicated that the EC risk was reduced by 25% in women with the lowest serum TG compared with women in the highest quartile. Zhang et al. reported positive correlations of EC risk with TC, TG and LDL-C, but a negative correlation with HDL-C using fasting blood to measure serum lipid levels

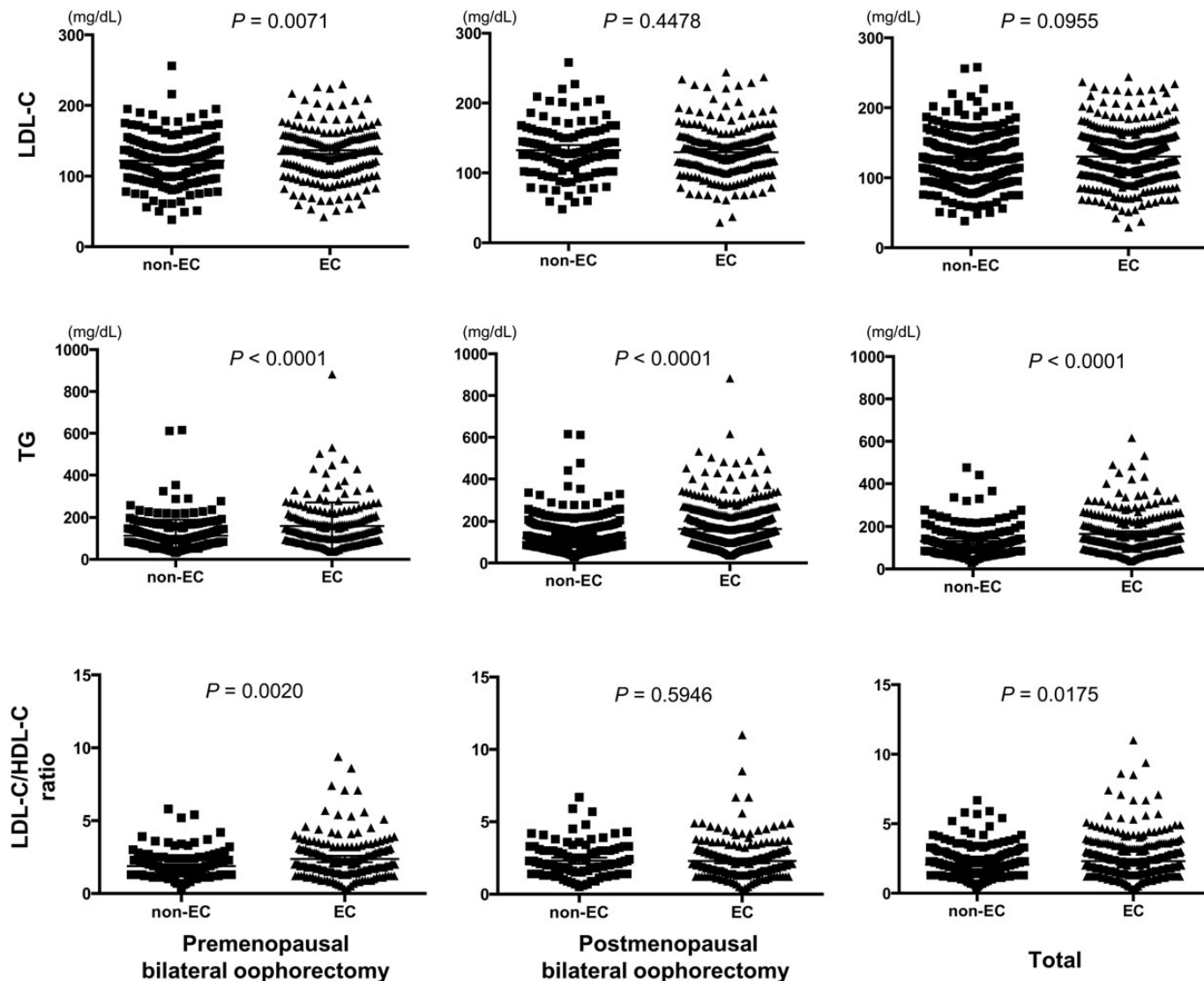


Figure 1. Mann–Whitney *U* test for low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) levels and the LDL-C/high-density lipoprotein cholesterol (HDL-C) ratio in endometrial cancer and non-endometrial cancer groups.

(31). We also have used fasting blood in our study, as we consider it to be the most accurate.

The relationship between EC and lipid metabolism is important for some reasons. First, even if the patient is cancer-free and does not die of EC, the cause of death may be cerebrovascular or cardiovascular disease due to dyslipidemia. Therefore, the prevention of these diseases may lead to an improved QOL for EC survivors. TG levels were elevated in EC patients irrespective of age at BSO, and hyper-LDL cholesterolemia or a high LDL-C/HDL-C ratio was observed in EC survivors who had undergone premenopausal BSO. It is important to prevent cerebrovascular or cardiovascular events in these patients by treating dyslipidemia during follow-up.

Second, serum lipid profiles may be a useful EC biomarker. Mass screening of the population for EC is not practical and no blood test with sufficient sensitivity and specificity has been developed (1,2). Screening for EC or its precursors is

justified for certain high-risk populations, such as postmenopausal women on exogenous estrogens without progestins, women from families with Lynch syndrome and premenopausal women with anovulatory cycles such as those with polycystic ovarian disease (2). On the basis of our findings, we propose that women with dyslipidemia may belong to a high-risk EC group. Clinicians should be advised to refer women with dyslipidemia to a gynecologist for endometrial surveillance. Thus, hypertriglycemia is a potential EC biomarker and could be used for screening of individuals with a high risk for EC.

It is notable that this is the first report to use an optimal study design, including non-EC control patients who had undergone BSO. Moreover, we emphasize that we used fasting blood to measure serum lipid levels, while previous studies used either non-fasting or a mixture of both fasting and non-fasting blood samples.

Table 2. EC and serum lipid levels

	Total				Premenopausal bilateral oophorectomy				Postmenopausal bilateral oophorectomy			
	Non-EC (n = 281)	EC (n = 412)	Odds ratio (95% CI)	P (χ^2 test)	Non-EC (n = 169)	EC (n = 181)	Overall confidence interval)	P (χ^2 test)	Non-EC (n = 112)	EC (n = 231)	OR (95% CI interval)	P (χ^2 test)
LDL-C (mg/dl)												
<140	186	262	1.121 (0.8152–1.541)	0.4821	120	108	1.655 (1.060–2.585)	0.0261	66	154	0.7174 (0.4504–1.143)	0.1611
≥140 ^a	95	150			49	73			46	77		
TG (mg/dl)												
<150	204	225	2.202 (1.589–3.051)	<0.0001	128	100	2.529 (1.600–3.997)	<0.0001	76	125	1.790 (1.115–2.875)	0.0154
≥150 ^b	77	187			41	81			36	106		
LDL-C/HDL-C ratio												
<2	150	193	1.299 (0.9587–1.761)	0.0911	102	85	1.719 (1.125–2.629)	0.0121	48	108	0.8542 (0.5420–1.346)	0.4958
≥2	131	219			67	96			64	123		

TG, triglyceride; CI, confidence interval.

^aHigh-LDL-cholesterolemia.

^bHypertriglyceridemia.

Malignancy, cerebrovascular disease and heart disease accounted for ~54% of all mortality in Japan in 2011 <http://www.mhlw.go.jp/english/database/db-hw/vs01.html>. Our report highlights the importance of the relationship between endometrial cancer and lipid metabolism, which may aid in preventing cerebrovascular or cardiovascular diseases due to dyslipidemia and improving the QOL of endometrial cancer survivors.

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Conflict of interest statement

None declared.

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