

Lipid Profiles and Risk of Breast and Ovarian Cancer in the Swedish AMORIS Study

Jennifer C. Melvin¹, Divya Seth^{1,2}, Lars Holmberg^{1,3,4}, Hans Garmo^{1,3}, Niklas Hammar^{5,8}, Ingmar Jungner⁶, Göran Walldius⁵, Mats Lambe^{3,7}, Annette Wigertz³, and Mieke Van Hemelrijck¹

Abstract

Background: Obesity is a risk factor for breast and ovarian cancer; the mechanisms of action are not completely understood. Perturbed lipid metabolism often accompanies obesity; we therefore ascertained the associations between lipid components and breast and ovarian cancer risk in a prospective cohort study.

Methods: A total of 234,494 women with baseline measurements of triglycerides and total cholesterol and glucose were selected from the AMORIS database. A total of 27,394 had measurements of high-density lipoprotein, low-density lipoprotein, apolipoprotein (Apo) B, and A-I. Associations between quartiles and dichotomized values of lipid components and breast and ovarian cancer risk were analyzed using Cox proportional hazard models.

Results: We identified 6,105 women diagnosed with breast cancer and 808 women diagnosed with ovarian cancer. A weak trend was observed between triglycerides and breast cancer (HR, 1.01, 95% Confidence Interval, 0.94–1.09; 0.93 (0.86–1.00) 0.91 (0.84–0.99), second, third, and fourth quartiles; $P = 0.01$). No other associations between lipid components and risk of breast cancer or ovarian cancer showed statistical significance.

Conclusions: A weak protective association was found between levels of triglycerides and risk of breast cancer.

Impact: An analysis including information on tumour characteristics of ovarian cancer and breast cancer may provide more insight in possible links between lipid metabolism and the risk of these cancers. *Cancer Epidemiol Biomarkers Prev*; 21(8); 1381–4. ©2012 AACR.

Background

Several studies have investigated whether the lipid metabolism is associated with risk of developing breast cancer and ovarian cancer, given their association to obesity and overweight (1). Variations in the normal lipid metabolism—particularly of serum triglycerides—have been observed in breast cancer and ovarian cancer patients. Two studies that illustrate examples of such results are those by Das and colleagues and Capasso

and colleagues (2, 3), both of which present evidence for a positive association between triglycerides and the risk of developing these cancers. It has been suggested for both breast cancer and ovarian cancer that low levels of HDL (high-density lipoprotein; a common comorbidity of obesity) could be reflective of an unfavorable hormonal profile which, in turn, would increase the risk (4, 5).

The association between lipid components and both breast cancer and ovarian cancer biology remains poorly understood. We studied the link between levels of serum lipid components and risk of breast cancer and ovarian cancer in a Swedish population, as a possible underlying mechanism of the association between obesity and cancer.

Methods

The Swedish AMORIS database has been described in detail elsewhere (6). The database includes data from 351,487 male and 338,101 female healthy individuals. We selected all females aged 25 years or older who did not have a previous diagnosis of breast cancer, ovarian cancer, or an oophorectomy, with baseline measurements of triglycerides, total cholesterol, and glucose ($n = 234,494$). The association between glucose, breast, and ovarian cancer risk has been studied in detail previously

Authors' Affiliations: ¹King's College London, School of Medicine, Division of Cancer Studies, Cancer Epidemiology Group, London, United Kingdom; ²Harvard College, Harvard University, Cambridge, Massachusetts; ³Regional Cancer Centre, Uppsala-Örebro; ⁴Department of Surgical Sciences, Uppsala University Hospital, Uppsala; ⁵Department of Epidemiology, Institute of Environmental Medicine, Karolinska Institutet; ⁶Department of Medicine, Clinical Epidemiological Unit, Karolinska Institutet and CALAB Research; ⁷Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm; and ⁸AstraZeneca Sverige, Södertälje, Sweden

J.C. Melvin and D. Seth contributed equally to this work.

Corresponding Author: Jennifer C. Melvin, King's College London, School of Medicine, Division of Cancer Studies, Cancer Epidemiology Group, Research Oncology, 3rd Floor, Bermondsey Wing, Guy's Hospital, London SE1 9RT, United Kingdom. Phone: 020-7188-7904; Fax: 44-(0)20-7188-9986; E-mail: jennifer.melvin@kcl.ac.uk

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Table 1. Descriptive characteristics by cancer status.

	Breast cancer N = 6,083	Ovarian cancer N = 786	Breast and ovarian cancer N = 22	No cancer N = 227,603
Age (y)				
Mean (SD)	51.31 (11.58)	53.04 (11.64)	47.68 (7.09)	46.68 (13.68)
Year of birth, n (%)				
<1920	501 (8.24)	74 (9.41)	0 (0.00)	15,217 (6.69)
1920–1939	2,775 (45.62)	406 (51.65)	8 (36.36)	69,397 (30.49)
1940–1949	2,061 (33.88)	229 (29.13)	12 (54.55)	65,964 (28.98)
1950–1959	643 (10.57)	69 (8.78)	2 (9.09)	48,465 (21.29)
1960–	103 (1.69)	8 (1.02)	0 (0.00)	28,560 (12.55)
Parity, n (%)				
0 children	1,363 (22.41)	224 (28.50)	4 (18.18)	62,414 (27.42)
1 child	1,330 (21.86)	186 (23.66)	5 (23.73)	44,589 (19.59)
2 children	2,267 (37.27)	262 (33.33)	8 (36.36)	78,439 (34.46)
3+ children	1,123 (18.46)	114 (14.50)	5 (22.73)	42,161 (18.52)
Age at birth of first child, n (%)				
<20	560 (11.86)	75 (13.35)	3 (16.67)	23,544 (14.25)
20–25	1,740 (36.86)	201 (35.77)	7 (38.39)	64,226 (38.88)
25–30	1,552 (32.88)	187 (33.27)	5 (27.78)	52,092 (31.53)
30–34	563 (11.93)	60 (10.68)	3 (16.67)	17,163 (10.39)
34+	305 (6.94)	39 (6.94)	0 (0.00)	8,164 (4.94)
SES				
White collar	1,953 (32.11)	222 (28.24)	3 (13.64)	67,027 (29.45)
Blue collar	3,223 (52.98)	434 (55.22)	19 (86.36)	123,124 (54.10)
Not gainfully employed or missing	907 (14.91)	130 (16.54)	0 (0.00)	37,452 (16.45)
Fasting status				
Fasting	3,630 (59.67)	490 (62.34)	13 (59.09)	126,294 (55.49)
Nonfasting	1,738 (28.57)	213 (27.10)	3 (13.64)	75,605 (33.22)
Missing	715 (11.75)	83 (10.56)	6 (27.27)	25,704 (11.29)
BMI (kg/m ²) ^a				
<18.5	10 (1.49)	1 (1.11)	0 (0.00)	823 (3.09)
18.5–24.99	453 (67.51)	58 (64.44)	1 (50.00)	17,833 (66.96)
25–29.99	161 (23.99)	24 (26.67)	0 (0.00)	6,000 (22.53)
>30	47 (7.78)	7 (7.78)	1 (50.00)	1,975 (7.42)
Total cholesterol				
Mean (SD)	5.81 (1.17)	5.93 (1.21)	5.73 (1.13)	5.61 (1.17)
Triglycerides (mmol/L)				
Mean (SD)	1.15 (0.78)	1.20 (0.87)	0.99 (0.39)	1.11 (0.73)
Glucose (mmol/L)				
Mean (SD)	4.93 (1.15)	4.94 (1.02)	4.58 (0.73)	4.87 (1.13)
Apolipoprotein A-I (mmol/L) ^b				
Mean (SD)	1.54 (0.25)	1.52 (0.27)	1.27 (0.16)	1.51 (0.24)
Apolipoprotein B (mmol/L) ^b				
Mean (SD)	1.22 (0.32)	1.27 (0.35)	1.61 (0.40)	1.16 (0.34)
HDL cholesterol (mmol/L) ^b				
Mean (SD)	1.77 (0.45)	1.70 (0.50)	1.95 (0.52)	1.72 (0.43)
LDL cholesterol (mmol/L) ^b				
Mean (SD)	3.62 (1.07)	3.76 (1.10)	3.94 (0.71)	3.49 (1.09)
ApoB/ApoA-I ratio ^b				
Mean (SD)	0.82 (0.26)	0.89 (0.31)	0.80 (0.10)	0.79 (0.27)
LDL/HDL ratio ^b				
Mean (SD)	2.27 (1.29)	2.66 (1.68)	2.05 (0.18)	2.25 (1.24)
Total cholesterol/HDL ratio ^b				
Mean (SD)	3.64 (1.73)	4.16 (2.32)	3.22 (1.10)	3.61 (1.64)
Triglycerides/HDL ratio ^b				
Mean (SD)	0.82 (1.20)	1.11 (1.62)	0.39 (0.19)	0.80 (1.11)

^aMeasured in subgroup with baseline measurement of BMI.^bMeasured in subgroup with baseline measurements of apoA-I, apoB, HDL, and LDL.

Table 2. HRs of breast cancer, ovarian cancer, and breast and ovarian cancer combined in quartiles of lipoprotein components and ratios, adjusted for age, glucose (continuous), parity, triglycerides (continuous), total cholesterol (continuous), fasting status, and SES

	Breast Cancer N = 6,105 HR (95% CI)	Ovarian cancer N = 808 HR (95% CI)
Glucose (mmol/L)^a		
<4.40	1.00 (ref)	1.00 (ref)
4.40–4.70	1.10 (1.02–1.18)	1.02 (0.84–1.26)
4.70–5.10	1.07 (0.99–1.16)	1.16 (0.95–1.43)
≥5.10	1.16 (1.07–1.25)	1.03 (0.83–1.28)
<i>P</i> _{trend}	0.00	0.53
Triglycerides (mmol/L)^b		
<0.70	1.00 (ref)	1.00 (ref)
0.70–0.90	1.01 (0.94–1.09)	1.02 (0.82–1.26)
0.90–1.30	0.93 (0.86–1.00)	0.87 (0.71–1.07)
≥1.30	0.91 (0.84–0.99)	0.93 (0.75–1.17)
<i>P</i> _{trend}	0.01	0.31
Total cholesterol (mmol/L)^c		
<4.80	1.00 (ref)	1.00 (ref)
4.80–5.50	1.13 (1.05–1.22)	1.12 (0.91–1.38)
5.50–6.30	1.06 (0.98–1.14)	1.11 (0.90–1.38)
≥6.30	0.97 (0.89–1.05)	1.07 (0.85–1.38)
<i>P</i> _{trend}	0.20	0.68
LDL-cholesterol (mmol/L)^{c, d}		
<2.72	1.00 (ref)	1.00 (ref)
2.72–3.37	1.10 (0.91–1.32)	1.00 (0.56–1.77)
3.37–4.14	1.00 (0.82–1.22)	1.13 (0.64–1.98)
≥4.14	0.92 (0.75–1.13)	0.95 (0.53–1.71)
<i>P</i> _{trend}	0.29	0.94
HDL cholesterol (mmol/L)^{c, d}		
<1.45	1.00 (ref)	1.00 (ref)
1.45–1.70	0.95 (0.79–1.15)	0.97 (0.57–1.64)
1.70–1.98	1.02 (0.84–1.25)	0.91 (0.51–1.60)
≥1.98	1.05 (0.86–1.29)	0.95 (0.54–1.67)
<i>P</i> _{trend}	0.45	0.81
Apolipoprotein B (g/L)^d		
<0.93	1.00 (ref)	1.00 (ref)
0.93–1.11	1.09 (0.91–1.32)	0.92 (0.54–1.58)
1.11–1.35	1.03 (0.85–1.25)	0.68 (0.38–1.21)
≥1.35	0.95 (0.76–1.17)	0.78 (0.43–1.40)
<i>P</i> _{trend}	0.53	0.29
Apolipoprotein A-I (g/L)^d		
<1.35	1.00 (ref)	1.00 (ref)
1.35–1.49	0.99 (0.82–1.19)	0.64 (0.38–1.07)
1.49–1.65	0.96 (0.80–1.19)	0.65 (0.39–1.07)
≥1.65	1.08 (0.90–1.29)	0.68 (0.41–1.14)
<i>P</i> _{trend}	0.49	0.12
Total cholesterol/HDL ratio^{c, d}		
<2.72	1.00 (ref)	1.00 (ref)

(Continued on the following column)

Table 2. HRs of breast cancer, ovarian cancer, and breast and ovarian cancer combined in quartiles of lipoprotein components and ratios, adjusted for age, glucose (continuous), parity, triglycerides (continuous), total cholesterol (continuous), fasting status, and SES (Cont'd)

	Breast Cancer N = 6,105 HR (95% CI)	Ovarian cancer N = 808 HR (95% CI)
2.72–3.27	1.02 (0.84–1.23)	0.76 (0.44–1.30)
3.27–4.05	1.06 (0.88–1.29)	0.64 (0.36–1.12)
≥4.05	0.93 (0.75–1.17)	0.75 (0.41–1.36)
<i>P</i> _{trend}	0.74	0.28
LDL/HDL ratio^{c, d}		
<1.52	1.00 (ref)	1.00 (ref)
1.52–2.01	1.05 (0.87–1.27)	0.76 (0.44–1.32)
2.01–2.67	1.09 (0.90–1.31)	0.69 (0.39–1.21)
≥2.67	0.95 (0.76–1.17)	0.91 (0.52–1.60)
<i>P</i> _{trend}	0.76	0.71
ApoB/ApoA-I ratio^d		
<0.60	1.00 (ref)	1.00 (ref)
0.60–0.75	1.11 (0.93–1.34)	0.93 (0.54–1.61)
0.75–0.94	1.08 (0.89–1.30)	0.77 (0.43–1.36)
≥0.94	0.91 (0.74–1.12)	0.96 (0.55–1.68)
<i>P</i> _{trend}	0.43	0.77
Triglycerides/HDL ratio^{b, c, d}		
<0.37	1.00 (ref)	1.00 (ref)
0.37–0.54	0.91 (0.75–1.09)	0.76 (0.43–1.34)
0.54–0.89	0.83 (0.69–1.01)	0.76 (0.43–1.35)
≥0.89	0.92 (0.76–1.11)	0.79 (0.39–1.61)
<i>P</i> _{trend}	0.28	0.49

^aNot adjusted for glucose.

^bNot adjusted for triglycerides.

^cNot adjusted for total cholesterol.

^dMeasured in subgroup with baseline measurements of apoA-I, apoB, HDL, and LDL.

in AMORIS, so will not be considered in depth here (7). Of those, 27,394 had baseline measurement of body mass index (BMI, kg/m²) and 34,057 had baseline information of low-density lipoprotein (LDL), HDL, apolipoprotein (apo) B, and A-I. Multivariate Cox proportional hazard regression models were used to calculate the relative risk of breast cancer or ovarian cancer dependent on lipid quartiles or ratios. Quartiles were assigned to an ordinal scale, allowing a linear test for trend. All models took into account continuous levels of glucose, triglycerides, and total cholesterol (except where indicated), as well as age, parity, fasting status, and SES.

Analyses were conducted with Statistical Analysis Systems (SAS) release 9.1.3 (SAS Institute) and R version 2.7.2 (R Foundation for Statistical Computing). This study complied with the Declaration of Helsinki and was approved by the Ethics board of the Karolinska Institute.

Results

A total of 6,105 women were diagnosed with breast cancer and 808 with ovarian cancer during mean follow-ups of 8.30 (SD \pm 4.30) and 8.18 years (SD \pm 4.33), respectively. Descriptive statistics are shown in Table 1. No statistically significant trends were seen between lipid component quartiles and breast cancer or ovarian cancer risk (Table 2). Associations using predefined medical cut-off values for lipid components were also investigated, but we only found weak negative associations between total cholesterol, ApoB, and breast cancer risk [HR for total cholesterol \geq 6.50 mmol/L, 0.91, 95% confidence interval (CI): 0.85–0.97] and HR for ApoB \geq 1.50 mmol/L: 0.82 (95% CI, 0.68–0.98). For ovarian cancer, high levels of HDL were found to be protective (HR for HDL \geq 1.03 mmol/L, 0.48 (95% CI, 0.25–0.91). Further in-depth analysis of these associations, using natural cubical splines, confirmed the association to be weak and showed no clear patterns (results not shown).

We investigated potential effect modifiers: overweight, parity, and menopausal status, but found no statistically significant interaction terms (results not shown). We also carried out stratified analyses by levels of total cholesterol and triglycerides for the association between lipid components and breast cancer risk, but no statistical significance was observed.

Reverse causality was assessed by excluding those with follow-up < 3 years; this did not affect the above findings (results not shown).

Conclusions

Despite having a good proportion of women with elevated lipids, no significant associations were seen. The variation in effect of triglycerides was likely visible because less than half of the women who fell into the fourth quartile ($n = 65,960$) met medical cut-off criteria ($n = 29,971$). This deviation from expected results occurred, at least in part, because the number of women

in whom BMI was measured was relatively modest; and the proportion falling into the "obese" category was small. The association between HDL and ovarian cancer may reflect the effect of other factors thought to impact overall cancer risk, such as inflammation (8).

Strengths of the AMORIS database include its large size, with prospective blood profile measurements for all individuals, measured at the same laboratory (CALAB). One limitation is that no data is available on potential confounders such as diabetes, smoking habits, diet, or hypertension. Furthermore, BMI was measured only in a small number of individuals; however, we do not believe this dramatically impacted our findings. A final limitation was the lack of information on tumor characteristics.

In conclusion, we found some evidence, albeit weak, that perturbed lipid metabolisms may be involved in risk of developing breast cancer and ovarian cancer. An analysis including information on tumor characteristics may provide more insight into possible links between lipid metabolism and these cancers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J.C. Melvin, L. Holmberg, H. Garmo, G. Walldius, M. Lambe, M. Van Hemelrijck

Development of methodology: J.C. Melvin, D. Seth, L. Holmberg, G. Walldius, M. Van Hemelrijck

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Lambe

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.C. Melvin, D. Seth, L. Holmberg, H. Garmo, G. Walldius, M. Van Hemelrijck

Writing, review, and/or revision of the manuscript: J.C. Melvin, D. Seth, L. Holmberg, H. Garmo, N. Hammar, G. Walldius, M. Lambe, A. Wigertz, M. Van Hemelrijck

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L. Holmberg, H. Garmo, I. Jungner, G. Walldius, M. Lambe

Study supervision: L. Holmberg, M. Van Hemelrijck

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