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

Running title: Lipid profiles and risk of breast and ovarian cancer

Jennifer C Melvin[1*], Divya Seth[1, 2*], Lars Holmberg[1,3,4], Hans Garmo[1,3], Niklas Hammar[5,6], Ingmar Jungner[7], Göran Walldius[5], Mats Lambe[3,8], Annette Wigertz[3], Mieke Van Hemelrijck[1].

Affiliations:

1. King's College London, School of Medicine, Division of Cancer Studies, Cancer Epidemiology Unit, London, UK
2. Harvard College, Harvard University, Cambridge, MA.
3. Regional Cancer Centre, Uppsala-Örebro, Sweden
4. Department of Surgical Sciences, Uppsala University Hospital, Uppsala, Sweden
5. Department of Epidemiology, Insitute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
6. AstraZeneca Sverige, Södertalje, Sweden
7. Department of Medicine, Clinical Epidemiological Unit, Karolinska Institutet and CALAB Research, Stockholm, Sweden
8. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

*Both authors contributed equally.

Corresponding author: Jennifer 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, UK

Phone: 020 7188 7904

Email: jennifer.melvin@kcl.ac.uk

Email addresses co-authors: dseth@college.harvard.edu; lars.holmberg@kcl.ac.uk; hans.garmo@kcl.ac.uk; niklas.hammar@ki.se; ingmar.jungner@ki.se; goran.walldius@ki.se; mats.lambe@ki.se; Annette.wigertz@akademiska.se; mieke.vanhemelrijck@kcl.ac.uk

Word count: 195 (abstract) and 781 (manuscript)

Running title: Lipid profiles and risk of breast and ovarian cancer

Abstract

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

Methods: 234,494 women with baseline measurements of triglycerides (TG) and total cholesterol (TC) and glucose were selected from the AMORIS database. 27,394 had measurements of HDL, LDL, apolipoprotein (Apo) B and A-I. Associations between quartiles and dichotomized values of lipid components and BCa and OCa risk were analysed using Cox proportional hazard models.

Results: We identified 6,105 women diagnosed with BCa and 808 women diagnosed with OCa. A weak trend was observed between TG and BCa (HR: 1.01 (CI95% 0.94-1.09), 0.93 (0.86-1.00) 0.91 (0.84-0.99) 2^{nd} 3^{rd} and 4^{th} quartiles; P = 0.01). No other associations between lipid components and risk of BCa or OCa showed statistical significance.

Conclusions: A weak protective association was found between levels of TG and risk of BCa.

Impact: An analysis including information on tumour characteristics of OCa and BCa may provide more insight in possible links between lipid metabolism and the risk of these cancers.

Keywords: breast cancer, ovarian cancer, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, apolipoprotein B, apolipoprotein A-I

Background

Several studies have investigated whether the lipid metabolism is associated with risk of developing breast cancer (BCa) and ovarian cancer (OCa) given their association to obesity and overweight [1]. Variations in the normal lipid metabolism – particularly of serum triglycerides – have been observed in BCa and OCa patients. Two studies which illustrate examples of such results are those by Das *et al.* and Capasso *et al.* [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 BCa and OCa that low levels of HDL (a common co-morbidity of obesity) could be reflective of an unfavourable hormonal profile which, in turn, would increase the risk [4-5].

The association between lipid components and both BCa and OCa biology remains poorly understood. We studied the link between levels of serum lipid components and risk of BCa and OCa 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 BCa, OCa or an oophorectomy, with baseline measurements of triglycerides (TG), total cholesterol (TC), and glucose (n=234,494). The association between glucose and BCa and OCa risk has been studied in detail previously in AMORIS, so will not be considered in depth here [7]. Of those, 27,394 had baseline measurement of body-mass index (BMI, kg/m^2) and 34,057 had baseline information of LDL, HDL, apolipoprotein (apo) B, and A-I. Multivariate Cox proportional hazard regression models were used to calculate the relative risk of BCa or OCa 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, TG and TC (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, Cary, NC) and R version 2.7.2 (R Foundation for Statistical Computing, Vienna, Austria). This study complied with the Declaration of Helsinki and was approved by the Ethics board of the Karolinska Institute.

Results

6,105 women were diagnosed with BCa and 808 with OCa during mean follow-ups of 8.30 (SD±4.30) and 8.18 years (SD±4.33) respectively. Descriptive statistics are shown in Table 1. No statistically significant trends were seen between lipid component quartiles and BCa or OCa risk (Table 2). Associations using pre-defined medical cut-off values for lipid components were also investigated, but we only found weak negative associations between TC, ApoB and BCa risk (HR for TC ≥6.50mmol/L: 0.91 (95%CI: 0.85-0.97) and HR for ApoB ≥ 1.50mmol/L: 0.82 (95%CI: 0.68-0.98). For OCa, high levels of HDL were found to be protective (HR for HDL ≥ 1.03mmol/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 performed stratified analyses by levels of TC and TG for the association between lipid components and BCa 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 TG was likely visible because less than half of the women who fell into the 4th 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 OCa 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. Further, 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 tumour characteristics.

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

References

[1] Kulie T, Slattengren A, Redmer J, Counts H, Eglash A and Schrager S. Obesity and women's health: an evidence-based review. J Am Board Fam Med 2011; 24: 75-85.

[2] Das NP, Ma CW and Salmon YM. The relationship of serum vitamin A, cholesterol, and triglycerides to the incidence of ovarian cancer. Biochem Med Metab Biol 1987; 37: 213-219.

[3] Capasso I, Esposito E, Pentimalli F, Crispo A, Montella M, Grimaldi M, et al. Metabolic syndrome affects breast cancer risk in postmenopausal women: National Cancer Institute of Naples experience. Cancer Biol Ther 2011; 10: 1240-1243.

[4] Tania M, Khan MA and Song Y. Association of lipid metabolism with ovarian cancer. Curr Oncol 2010; 17: 6-11.

[5] Furberg AS, Jasienska G, Bjurstam N, Torjesen PA, Emaus A, Lipson SF, et al. Metabolic and hormonal profiles: HDL cholesterol as a plausible biomarker of breast cancer risk. The Norwegian EBBA Study. Cancer Epidemiol Biomarkers Prev 2005; 14: 33-40.

[6] Van Hemelrijck M, Garmo H, Hammar N, Jungner I, Walldius G, Lambe M et al. The interplay between lipid profiles, glucose, BMI and risk of kidney cancer in the Swedish AMORIS study. Int J Cancer 2011;

[7] Lambe M, Wigertz A, Garmo H, Walldius G, Jungner I and Hammar N. Impaired glucose metabolism and diabetes and the risk of breast, endometrial, and ovarian cancer. Cancer Causes Control 2011; 22: 1163-1171.

[8] Jacobs EJ and Gapstur SM. Cholesterol and cancer: answers and new questions. Cancer Epidemiol Biomarkers Prev 2009; 18: 2805-2806.

Author Manuscript Published OnlineFirst on May 16, 2012; DOI: 10.1158/1055-9965.EPI-12-0188
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Table 1. *Descriptive characteristics by cancer status.*

	Breast Cancer N=6083	**Ovarian Cancer** N = 786	**Breast & Ovarian Cancer** N = 22	**No Cancer** N= 227603
Age (years)				
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)	15217 (6.69)
1920-1939	2775 (45.62)	406 (51.65)	8 (36.36)	69397 (30.49)
1940-1949	2061 (33.88)	229 (29.13)	12 (54.55)	65964 (28.98)
1950-1959	643 (10.57)	69 (8.78)	2 (9.09)	48465 (21.29)
1960-	103 (1.69)	8 (1.02)	0 (0.00)	28560 (12.55)
Parity, n (%)				
0 children	1363 (22.41)	224 (28.50)	4 (18.18)	62414 (27.42)
1 child	1330 (21.86)	186 (23.66)	5 (23.73)	44589 (19.59)
2 children	2267 (37.27)	262 (33.33)	8 (36.36)	78439 (34.46)
3+ children	1123 (18.46)	114 (14.50)	5 (22.73)	42161 (18.52)
Age at birth of first child, n(%)				
<20	560 (11.86)	75 (13.35)	3 (16.67)	23544 (14.25)
20-25	1740 (36.86)	201 (35.77)	7 (38.39)	64226 (38.88)
25-30	1552 (32.88)	187 (33.27)	5 (27.78)	52092 (31.53)
30-34	563 (11.93)	60 (10.68)	3 (16.67)	17163 (10.39)
34+	305 (6.94)	39 (6.940	0 (0.00)	8164 (4.94)
SES				
White Collar	1953 (32.11)	222 (28.24)	3 (13.64)	67027 (29.45)
Blue Collar	3223 (52.98)	434 (55.22)	19 (86.36)	123124 (54.10)
Not gainfully employed or Missing	907 (14.91)	130 (16.54)	0 (0.00)	37452 (16.45)
Fasting status				
Fasting	3630 (59.67)	490 (62.34)	13 (59.09)	126294 (55.49)
Non-fasting	1738 (28.57)	213 (27.10)	3 (13.64)	75605 (33.22)
Missing	715 (11.75)	83 (10.56)	6 (27.27)	25704 (11.29)
BMI (kg/m^2)*				
<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)	17833 (66.96)
25-29.99	161 (23.99)	24 (26.67)	0 (0.00)	6000 (22.53)
>30	47 (7.78)	7 (7.78)	1 (50.00)	1975 (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)^				
Mean (SD)	1.54 (0.25)	1.52 (0.27)	1.27 (0.16)	1.51 (0.24)
Apolipoprotein B (mmol/l)^				
Mean (SD)	1.22 (0.32)	1.27 (0.35)	1.61 (0.40)	1.16 (0.34)
HDL-cholesterol (mmol/l)^				
Mean (SD)	1.77 (0.45)	1.70 (0.50)	1.95 (0.52)	1.72 (0.43)
LDL-cholesterol (mmol/l)^				
Mean (SD)	3.62 (1.07)	3.76 (1.10)	3.94 (0.71)	3.49 (1.09)
ApoB/ApoA-I ratio^				
Mean (SD)	0.82 (0.26)	0.89 (0.31)	0.80 (0.10)	0.79 (0.27)
LDL/HDL ratio^				

Mean (SD)	2.27 (1.29)	2.66 (1.68)	2.05 (0.18)	2.25 (1.24)
Total Cholesterol/HDL ratio^				
Mean (SD)	3.64 (1.73)	4.16 (2.32)	3.22 (1.10)	3.61 (1.64)
Triglycerides/HDL ratio^				
Mean (SD)	0.82 (1.20)	1.11 (1.62)	0.39 (0.19)	0.80 (1.11)

Table 2. Hazard ratios 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.

Author Manuscript Published OnlineFirst on May 16, 2012; DOI: 10.1158/1055-9965.EPI-12-0188
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

	Breast Cancer N = 6105		Ovarian Cancer N = 808	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Glucose (mmol/L)[1]				
<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)
P-value for trend	0.00		0.53	
Triglycerides (mmol/L)[2]				
<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)
P-value for trend	0.01		0.31	
Total cholesterol (mmol/L)[3]				
<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)
P-value for trend	0.20		0.68	
LDL-cholesterol (mmol/L)[b3]				
<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)
P-value for trend	0.29		0.94	
HDL-cholesterol (mmol/L) [b3]				
<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)
P-value for trend	0.45		0.81	
Apolipoprotein B (g/L)[b]				
<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)
P-value for trend	0.53		0.29	
Apolipoprotein A-I (g/L)[b]				
<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)
P-value for trend	0.49		0.12	
Total Cholesterol/HDL ratio [b3]				
<2.72	1.00	(ref)	1.00	(ref)
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)

P-value for trend		0.74		0.28
LDL/HDL ratio [b3]				
<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)
P-value for trend		0.76		0.71
ApoB/ApoA-I ratio [b]				
<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)
P-value for trend		0.43		0.77
Triglycerides/HDL ratio [b23]				
<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)
P-value for trend		0.28		0.49

1: Not adjusted for glucose; 2: Not adjusted for TG; 3 Not adjusted for TC; b: Measured in subgroup B

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

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

Jennifer C. Melvin, Divya Seth, Lars Holmberg, et al.

Cancer Epidemiol Biomarkers Prev Published OnlineFirst May 16, 2012.