Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

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

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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

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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 (6.940	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)

[a]Measured in subgroup with baseline measurement of BMI.

[b] Measured 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)
P_{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)
P_{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)
P_{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)
P_{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)
P_{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)
P_{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)
P_{trend}	0.49	0.12
Total cholesterol/HDL ratio[c,d]		
<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_{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)
P_{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)
P_{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)
P_{trend}	0.28	0.49

[a]Not adjusted for glucose.
[b]Not adjusted for triglycerides.
[c]Not adjusted for total cholesterol.
[d]Measured 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/m^2) 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

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References

1. Kulie T, Slattengren A, Redmer J, Counts H, Eglash A, 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, Salmon YM. The relationship of serum vitamin A, cholesterol, and triglycerides to the incidence of ovarian cancer. Biochem Med Metab Biol 1987;37:213–9.
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;10:1240–3.
4. Tania M, Khan MA, 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 2012;130:2118–28.
7. Lambe M, Wigertz A, Garmo H, Walldius G, Jungner I, Hammar N. Impaired glucose metabolism and diabetes and the risk of breast, endometrial, and ovarian cancer. Cancer Causes Control 2011;22:1163–71.
8. Jacobs EJ, Gapstur SM. Cholesterol and cancer: answers and new questions. Cancer Epidemiol Biomarkers Prev 2009;18:2805–6.