Serum High-Density Lipoprotein Cholesterol, Metabolic Profile, and Breast Cancer Risk

Anne-Sofie Furberg, Marit Bragelien Veierød, Tom Wilsgåard, Leslie Bernstein, Inger Thune

Background: The prevalence of metabolic syndrome (obesity, glucose intolerance, low serum high-density lipoprotein cholesterol [HDL-C], high serum triglycerides, hypertension) is high and increasing in parallel with an increasing breast cancer incidence worldwide. HDL-C represents an important aspect of the syndrome, yet its role in breast cancer is still undefined. Methods: In two population-based screening surveys during 1977–1983 and 1985–1987, serum HDL-C was assayed enzymatically among 38 823 Norwegian women aged 17–54 years at entry. Height, weight, blood pressure, serum lipids, fat and energy intake, physical activity, parity, oral contraceptive use, hormone therapy use, alcohol intake, and tobacco use were also assessed. We used Cox proportional hazards modeling to estimate the relative risk (RR) of breast cancer associated with serum HDL-C levels and to adjust for potential confounding variables. We performed stratified analyses to evaluate effect modification by body mass index (BMI) and menopausal status. All statistical tests were two-sided. Results: During a median follow-up of 17.2 years, we identified 708 cases of invasive breast cancer. In multivariable analysis, the risk of postmenopausal breast cancer was inversely related to quartile of HDL-C (P_trend = .02). Among women with HDL-C above 1.64 mmol/L (highest quartile) versus below 1.20 mmol/L (lowest quartile), the relative risk was 0.75 (95% confidence interval [CI] = 0.58 to 0.97). The HDL-C association was confined to women in the heavier subgroup (BMI ≥25 kg/m²), for whom the relative risk of postmenopausal breast cancer in those with HDL-C above 1.64 mmol/L versus below 1.20 mmol/L was 0.43 (95% CI = 0.28 to 0.67; P_trend < .001; P_interaction = .001). Conclusion: Low HDL-C, as part of the metabolic syndrome, is associated with increased postmenopausal breast cancer risk. [J Natl Cancer Inst 2004;96:1152–60]

The metabolic syndrome, which is characterized by visceral obesity, glucose intolerance, hypertension, and dyslipidemia (i.e., low serum high-density lipoprotein cholesterol [HDL-C] and high serum triglycerides), has a high and increasing prevalence in parallel with increasing breast cancer incidence worldwide (1,2). Several studies have implicated increased levels of insulin and insulin-like growth factor I (IGF-I) in metabolic syndrome as being causally linked to breast cancer (3–7). However, the role of other biomarkers, such as HDL-C, in metabolic syndrome is still undefined.

In vitro studies have shown that HDL-C stimulates the growth of human breast cancer cells (8,9), especially hormone-independent cells (10). However, androgens have been found to lower HDL-C levels in women (11), and androgens have also been positively associated with breast cancer risk (12–14).

We previously reported that high energy intake, physical inactivity, high body mass index (BMI), and weight gain were associated with increased breast (15) and endometrial (16) cancer risk and that endometrial cancer risk was increased by hyperglycemia and hypertension in overweight and obese women (16) in a cohort of Norwegian women established in 1974–1976. Interestingly, several studies have reported lower levels of HDL-C in breast cancer patients than in control subjects (17–20). However, data from prospective studies are limited (21–23).

We hypothesize that HDL-C, as an important component of the metabolic syndrome, may influence the risk of breast cancer and that HDL-C may be an important clinical marker of breast cancer risk that may be more pronounced in women with positive energy balance (i.e., with long-term excessive energy intake relative to requirements, as reflected in a high BMI) (2). Our current study was based on 21 years of follow-up in 38 823 women from the Norwegian cohort (15,16,22,24) with repeated assessments of serum lipids and data on height and weight, diet, and lifestyle factors.

METHODS AND SUBJECTS

Participants

The women in our study participated in two population-based screening surveys during 1977–1983 and 1985–1987 in three counties in Norway (Finnmark, Oppland, and Sogn og Fjordane) as part of the Norwegian National Health Screening Service’s program to explore the association of lifestyle with chronic diseases. The screening procedures were almost identical in the two surveys (25,26). In the 1977–1983 survey, we invited all women aged 35–52 years in Finnmark, all women aged 40–54 years in Oppland and Sogn og Fjordane, and a random sample of women aged 20–39 years in all counties (17–39 years in Sogn og Fjordane) to participate. A total of 34 378 women received a mailed invitation, and 31 209 (90.8%) attended. All 1977–1983 survey attendees had a non-fasting blood sample drawn at screening, and 30 546 (88.8% of invited) samples satisfied the technical requirements for HDL-C estimation.

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See “Notes” following “References.”

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In 1985–1987, a similar survey that included blood collection was carried out in all three counties, but the HDL-C assay was run in samples from Oppland and Sogn og Fjordane only. In these two counties, all women who had been invited for the 1977–1983 survey, all women aged 40–54 years, and random samples of women aged 20–39 and 55–59 years were invited to participate. Altogether, 28 685 women were invited, 25 683 (89.5%) attended, and 25 397 (88.5%) had serum HDL-C estimated. In total, 16 028 of the women in Oppland and Sogn og Fjordane registered in both surveys, and of these, 15 781 had serum HDL-C assessed twice. The majority of the women in our study participated in a similar survey 3–5 years before the 1977–1983 survey, but HDL-C was not assessed (15,16).

The study was approved by the Norwegian Data Inspectorate, and the Norwegian Board of Health permitted access to medical record files. Informed consent to participate was implied by the return of the completed questionnaire.

Clinical Parameters and Laboratory Procedures

Body weight was measured to the nearest half kilogram with participants dressed in lightweight clothing. Height was measured in centimeters. BMI was calculated as a measure of body mass relative to height (kg/m²).

The serum lipid analyses were conducted within 2 weeks after blood sampling by the Central Laboratory, Ullevål University Hospital, Oslo, except for the determination of HDL-C in samples from Finnmark in the 1977–1983 survey (n = 7729). The latter were assayed by the Institute of Medical Biology, University of Troms; the majority of these serum samples (n = 5577; 72%) were kept frozen for 12 months until analysis. HDL-C was assayed enzymatically after precipitation of lipoproteins with a density of less than 1.063 g/mL by the addition of heparin and MnCl₂, according to the method of Burstein et al. (27). The concentration of HDL-C in frozen sera was consistently lower than that in fresh sera, and a constant of 0.12 mmol/L, estimated by Thelle et al. (28), was added to the measured HDL-C levels obtained from frozen sera, as described in former studies using these data (22). The concentration of total cholesterol and triglycerides was estimated enzymatically (29,30), except for the use of the Liebermann–Burchard method for cholesterol measurement and a fluorimetric method for triglycerides measurement in samples from Finnmark in the 1977–1983 survey (n = 7729) (31). The latter cholesterol and triglycerides values were converted to the enzymatic scale by multiplying by a factor calculated from a 4-month parallel run of assays (26).

Lifestyle Parameters and Diet

The written invitation included a questionnaire on ethnicity, chronic diseases, tobacco use, alcohol intake (1985–1987 survey only), and usual level of physical activity during the past year (15,25). The same team of trained nurses conducted interviews with the participants at the screening in both the 1977–1983 and the 1985–1987 surveys to confirm the information and to collect data on time since last meal, menopausal status, primary amenorrhea, hysterectomy, oral contraceptive use, and hormone therapy use. Information on hysterectomy, oral contraceptive use, and hormone therapy use were collected only during the 1985–1987 survey.

A semiquantitative food frequency questionnaire was distributed at the screening and returned by mail by 25 892 women (83%) in the 1977–1983 survey and by 22 799 (89%) women in the 1985–1987 survey. The food frequency questionnaire, its reproducibility and validity, and the method of estimating total energy intake have been described (24,32). Information was considered insufficient if estimated daily energy intake was less than 2250 kJ or if fewer than two-thirds of the questions were answered; analyses involving energy and fat intake were not performed for these women.

Menopausal Status

To calculate pre- and postmenopausal years of follow-up, we used information on menopausal status from both surveys. If a woman had not reported being postmenopausal upon survey at a younger age, we defined her as postmenopausal from age 50, assuming that she did not report any menstrual bleeding at that age or later (consistent with other studies of breast cancer in this cohort) (15).

Follow-up and Case Identification

The study population was followed from the date of blood sampling in the 1977–1983 or 1985–1987 survey through December 31, 1998, with respect to incidence of breast cancer, other malignancies, death, and emigration. Breast cancer and other cancer cases were identified by linkage to the Cancer Registry of Norway, while information on death, emigration, and reproductive history was gathered by linkage to Statistics Norway. A unique national 11-digit registration number assigned by the Population Register at Statistics Norway (Oslo) to each resident in Norway ensured the linkages. Among the 30 546 participants who had their HDL-C levels measured in the 1977–1983 survey, we excluded women with missing BMI information, pregnancy, primary amenorrhea (n = 820), or prevalent cancer (n = 439; Fig. 1). To ensure that undiagnosed cancer or severe illness did not influence the results, we included only the 29 199 women who were cancer-free and alive 1 year after participation in the 1977–1983 survey in the 1977–1983 cohort. Among women in the 1977–1983 cohort, the 15 175 women who had their HDL-C levels measured in the 1985–1987 survey, had their BMI recorded, and had not reported pregnancy or primary amenorrhea in the 1985–1987 survey were included in the “repeat cohort.” Among 9953 women who had their HDL-C levels measured in the 1985–1987 survey, 158 were excluded because of missing BMI or report of pregnancy or primary amenorrhea in the 1985–1987 survey, and 171 were excluded because of cancer or death within 1 year after participation in the survey. Thus, a compound cohort of 38 823 women met the inclusion criteria in one or both surveys.

Statistical Analyses

To estimate the relative risks (RRs) for breast cancer associated with serum HDL-C levels and covariates, we used Cox proportional hazards regression modeling. The proportional hazards assumption was verified by evaluating the parallelism between the curves of the log-log survivor function for different categories of the variables. To study in more detail the importance of the biologic variation in serum HDL-C level, we used equal-sized quartiles of serum HDL-C concentration (<1.20, 1.20–1.40, 1.41–1.64, >1.64 mmol/L) for the total population in
the 1977–1983 survey for categorization of the women. The 1977–1983 data were adjusted for age and compared by analysis of covariance. Relative risks for pre- and postmenopausal breast cancer were estimated separately, using the accumulated number of covariance. Relative risks for pre- and postmenopausal breast cancer were estimated separately, using the accumulated number of time-dependent covariates that were updated 1 year after the repeated (second) assessment.

We also used Cox proportional hazards regression models that expressed hazard ratios as a function of age and observed minimal alterations in the relative risks. Thus, we present the results of the analyses that used follow-up time as the scale of interest. All statistical tests were two-tailed, and the level of statistical significance was set at 5%. The analyses were performed with SAS, version 8.2 (SAS Institute, Cary, NC).

**RESULTS**

Among the 38 823 women in the compound cohort, we observed 708 cases of incident breast cancer during a median follow-up of 17.2 years (maximum = 21.8 years). Two hundred of these breast cancer cases were defined as premenopausal (mean age at diagnosis = 45.8 years, range = 27.1–51.6 years), and 508 were defined as postmenopausal (mean age at diagnosis = 58.4 years, range = 43.4–72.9 years). Among the 29 199 women in the 1977–1983 cohort, we observed 579 cases of incident breast cancer during a median follow-up of 17.7 years. One hundred thirty-five of these breast cancer cases were defined as premenopausal (mean age at diagnosis = 45.7 years, range = 36.3–51.6 years), and 444 were defined as postmenopausal (mean age at diagnosis = 59.1 years, range = 43.4–72.9 years).

Table 1 shows the characteristics of the women in the 1977–1983 cohort at entry. The age-adjusted mean HDL-C in the frozen sera from Finmark was statistically significantly higher than in the fresh sera ($P < .001$). Women who participated in the 1977–1983 survey had lower BMI, a higher level of recreational physical activity, and a lower percentage of women who smoked with increasing quartile of serum HDL-C ($P_{\text{trend}} < .001$). In the 1985–1987 survey, 7% of those asked (n = 9606) confirmed use of hormone therapy.

In age-adjusted analyses of the 1977–1983 data, height was positively related and parity and occupational activity were inversely related to both pre- and postmenopausal breast cancer risk. Overweight and obese women (BMI $\geq 25$ kg/m$^2$) had a relative risk of premenopausal breast cancer that was 0.67 (95% confidence interval [CI] = 0.45 to 1.01) times that of women with a BMI of less than 25 kg/m$^2$ and a relative risk of postmenopausal breast cancer of 0.87 (95% CI = 0.72 to 1.06). Age at first birth was positively related to postmenopausal breast cancer risk (data not shown).

In analyses of the 1977–1983 cohort, there was no association between total serum cholesterol and postmenopausal breast cancer among overweight and obese women, and a test of interaction (cutoff for BMI, 25 kg/m$^2$) was not statistically significant.
Table 1. Age-adjusted means (95% confidence intervals) and proportions of characteristics among all women and women in each quartile of serum high-density lipoprotein cholesterol (HDL-C) in the 1977–1983 survey*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total population (N = 29,199)†</th>
<th>&lt;1.20 (n = 6994)‡</th>
<th>1.20–1.40 (n = 7264)‡</th>
<th>1.41–1.64 (n = 7387)‡</th>
<th>&gt;1.64 (n = 7554)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>43.6 (43.5 to 43.7)</td>
<td>43.5 (43.4 to 43.7)</td>
<td>43.2 (43.0 to 43.4)</td>
<td>43.5 (43.3 to 43.7)</td>
<td>44.0 (43.9 to 44.2)</td>
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<tr>
<td><strong>Reproductive history</strong></td>
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<tr>
<td>Parity‡</td>
<td>2.64 (2.62 to 2.65)</td>
<td>2.67 (2.63 to 2.71)</td>
<td>2.65 (2.61 to 2.68)</td>
<td>2.64 (2.60 to 2.67)</td>
<td>2.59 (2.56 to 2.63)</td>
</tr>
<tr>
<td>Age at first birth, y</td>
<td>23.1 (23.0 to 23.2)</td>
<td>22.7 (22.7 to 22.8)</td>
<td>22.9 (22.9 to 23.0)</td>
<td>23.2 (23.1 to 23.2)</td>
<td>23.5 (23.4 to 23.5)</td>
</tr>
<tr>
<td><strong>Clinical parameters</strong></td>
<td></td>
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<tr>
<td>Height, cm</td>
<td>162.8 (162.7 to 163.5)</td>
<td>162.9 (162.8 to 163.1)</td>
<td>162.9 (162.8 to 163.1)</td>
<td>162.8 (162.7 to 162.9)</td>
<td>162.6 (162.5 to 162.8)</td>
</tr>
<tr>
<td>Body mass index (BMI), kg/m²</td>
<td>24.6 (24.6 to 24.7)</td>
<td>26.0 (25.9 to 26.1)</td>
<td>24.8 (24.7 to 24.9)</td>
<td>24.2 (24.1 to 24.3)</td>
<td>23.6 (23.5 to 23.7)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>81.8 (81.6 to 81.9)</td>
<td>83.0 (82.7 to 83.2)</td>
<td>81.7 (81.5 to 82.0)</td>
<td>81.0 (80.8 to 81.3)</td>
<td>81.4 (81.1 to 81.6)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>130.4 (130.2 to 130.6)</td>
<td>132.1 (131.7 to 132.5)</td>
<td>130.2 (129.8 to 130.6)</td>
<td>129.3 (128.9 to 129.7)</td>
<td>130.2 (129.8 to 130.6)</td>
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<tr>
<td><strong>Serum lipids, mmol/L</strong></td>
<td></td>
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<tr>
<td>Triglycerides</td>
<td>1.41 (1.40 to 1.42)</td>
<td>1.95 (1.93 to 1.97)</td>
<td>1.43 (1.42 to 1.45)</td>
<td>1.24 (1.22 to 1.25)</td>
<td>1.05 (1.04 to 1.07)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>6.10 (6.09 to 6.11)</td>
<td>6.06 (6.03 to 6.08)</td>
<td>6.01 (5.99 to 6.04)</td>
<td>6.07 (6.05 to 6.10)</td>
<td>6.25 (6.22 to 6.28)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.45 (1.44 to 1.45)</td>
<td>1.04 (1.04 to 1.04)</td>
<td>1.30 (1.30 to 1.31)</td>
<td>1.52 (1.52 to 1.52)</td>
<td>1.90 (1.89 to 1.90)</td>
</tr>
<tr>
<td>Fresh sera</td>
<td>1.43 (1.43 to 1.44)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sera frozen for 1 year</td>
<td>1.52 (1.51 to 1.53)</td>
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<tr>
<td><strong>Dietary factors</strong></td>
<td></td>
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<tr>
<td>Energy, 10³ kJ/day</td>
<td>5.53 (5.51 to 5.55)</td>
<td>5.43 (5.39 to 5.47)</td>
<td>5.55 (5.51 to 5.59)</td>
<td>5.57 (5.53 to 5.61)</td>
<td>5.59 (5.54 to 5.63)</td>
</tr>
<tr>
<td>Fat, g/day</td>
<td>55.5 (55.2 to 55.7)</td>
<td>54.0 (53.5 to 54.6)</td>
<td>55.3 (54.8 to 55.8)</td>
<td>56.0 (55.5 to 56.5)</td>
<td>56.4 (55.9 to 56.9)</td>
</tr>
<tr>
<td>Saturated fat, g/day</td>
<td>23.8 (23.7 to 24.0)</td>
<td>23.2 (23.0 to 23.5)</td>
<td>23.8 (23.6 to 24.0)</td>
<td>24.0 (23.8 to 24.3)</td>
<td>24.2 (24.0 to 24.5)</td>
</tr>
<tr>
<td>Monounsaturated fat, g/day</td>
<td>18.5 (18.4 to 18.6)</td>
<td>18.1 (17.9 to 18.2)</td>
<td>18.4 (18.3 to 18.6)</td>
<td>18.6 (18.5 to 18.8)</td>
<td>18.7 (18.6 to 18.9)</td>
</tr>
<tr>
<td><strong>Lifestyle habits, %</strong></td>
<td></td>
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</tr>
<tr>
<td>Physically active in leisure time</td>
<td>82.8</td>
<td>79.4</td>
<td>83.1</td>
<td>83.9</td>
<td>84.6</td>
</tr>
<tr>
<td>Physically active at work</td>
<td>85.1</td>
<td>85.1</td>
<td>85.0</td>
<td>84.9</td>
<td>85.5</td>
</tr>
<tr>
<td>Daily smoking</td>
<td>36.4</td>
<td>44.2</td>
<td>37.8</td>
<td>34.3</td>
<td>30.1</td>
</tr>
<tr>
<td><strong>Disease history, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-reported hypertension</td>
<td>5.8</td>
<td>9.2</td>
<td>6.2</td>
<td>4.7</td>
<td>3.4</td>
</tr>
<tr>
<td>Self-reported diabetes</td>
<td>0.6</td>
<td>0.8</td>
<td>0.4</td>
<td>0.4</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*Women were invited from three counties in Norway (Finnmark, Oppland, and Sogn og Fjordane) to participate as part of the Norwegian National Health Screening Service’s program to explore the association of lifestyle with chronic diseases.
†Number may vary because of missing information on certain variables.
‡Parity throughout follow-up.

(P interaction = .13). However, women with total serum cholesterol above 6.82 mmol/L (highest quartile) had a lower risk of postmenopausal breast cancer than women with total serum cholesterol below 5.24 mmol/L (lowest quartile) (age-adjusted RR = 0.63, 95% CI = 0.48 to 0.82; P trend = .005).

We initially observed a positive association between increasing quartile of serum HDL-C and the incidence of premenopausal breast cancer in the compound cohort (mean follow-up = 8.9 years) (Table 2). However, after inclusion of multiple covariates in the Cox model, the association between serum HDL-C and premenopausal breast cancer incidence in the compound cohort, like that for the 1977–1983 cohort, was not statistically significant.

In contrast, after adjustments for covariates, we observed a statistically significant trend of decreasing risk of postmenopausal breast cancer with increasing quartile of HDL-C in the 1977–1983 cohort (mean follow-up = 12.9 years; multivariable trend = .03). The risk of postmenopausal breast cancer was reduced in women in the highest quartile of HDL-C (above 1.64 mmol/L) compared with women in the lowest quartile (below 1.20 mmol/L) (multivariable RR = 0.73, 95% CI = 0.55 to 0.95) (Table 2). In an analysis confined to women with HDL-C assayed from fresh sera in the 1977–1983 cohort, similar results of decreasing risk of postmenopausal breast cancer with increasing quartile of HDL-C were observed (data not shown).

In analyses of the compound cohort using time-dependent covariates, the reduced risk of postmenopausal breast cancer in women in the highest HDL-C quartile as compared with women in the lowest HDL-C quartile was confirmed (mean follow-up = 11.2 years; multivariable RR = 0.75, 95% CI = 0.58 to 0.97; P trend = .02) (Table 2). The results were similar in analyses confined to women in the compound cohort with HDL-C assayed from fresh sera in both the 1977–1983 and the 1985–1987 surveys (data not shown).

In stratified analyses of underweight or normal weight and overweight or obese women in the 1977–1983 cohort and the compound cohort, the data suggested a possible positive association between serum HDL-C (all sera or fresh sera separately) and premenopausal breast cancer among underweight or normal weight women. However, the trends were not statistically significant (Table 3).

In contrast, the observed association between serum HDL-C and the risk of postmenopausal breast cancer was confined to overweight and obese women. Among overweight and obese women in the 1977–1983 cohort with HDL-C assayed from fresh sera, risk was reduced in women in the second HDL-C quartile (RR = 0.60, 95% CI = 0.40 to 0.89), in the third quartile (RR = 0.50, 95% CI = 0.32 to 0.78), and in the highest quartile (RR = 0.34, 95% CI = 0.19 to 0.59) relative to women in the lowest quartile (P trend < .001) (Table 2).
Among overweight and obese women in the compound cohort, the highest versus the lowest serum HDL-C quartile was associated with a decreased risk in an analysis restricted to women with HDL-C assayed from fresh sera (RR = 0.43, 95% CI = 0.28 to 0.67; \( P_{\text{trend}} < .001 \)) (Table 4). There was statistically significant interaction between the dichotomized BMI variable (cutoff, 25 kg/m\(^2\)) and quartile of serum HDL-C in both the 1977–1983 and the compound cohorts (\( P_{\text{interaction}} = .006 \) and \( P_{\text{interaction}} = .001 \), respectively). The association remained in an analysis adjusted for BMI (continuous term). In analyses of the 1977–1983 and the compound cohorts that included overweight and obese women with HDL-C assayed from frozen sera, the association between quartiles of serum HDL-C and postmenopausal breast cancer risk was slightly weakened (data not shown).

We also performed analyses of the relationship between HDL-C and the risk of breast cancer in subgroups defined by other BMI criteria (e.g., quartiles of BMI, or BMI ≥30 kg/m\(^2\)). However, we found no other BMI thresholds for an interaction or stronger associations than those reported among overweight and obese postmenopausal women (data not shown).

The relationship between HDL-C and postmenopausal breast cancer among overweight and obese women was relatively robust across strata of potential effect modifiers (Fig. 2); we observed a statistically significant trend of decreasing risk of postmenopausal breast cancer by increasing HDL-C quartile at all strata of height (<163 cm, \( P_{\text{trend}} = .01 \); 163 to 166 cm, \( P_{\text{trend}} = .009 \); >166 cm, \( P_{\text{trend}} = .01 \)) and energy intake (<4390 kJ/day, \( P_{\text{trend}} = .03 \); 4390 to 5195 kJ/day, \( P_{\text{trend}} = .009 \); >5195 kJ/day, \( P_{\text{trend}} = .04 \)). The trend was also statistically significant among women who were never smokers (\( P_{\text{trend}} = .004 \)) or current smokers (\( P_{\text{trend}} = .01 \)) but not among former smokers (\( P_{\text{trend}} = .06 \)). Likewise, there was some evidence of decreasing risk of postmenopausal breast cancer by increasing quartile of HDL-C across all strata of occupational physical activity in overweight and obese women; the trend was statistically significant in women who walked during working hours (\( P_{\text{trend}} < .001 \)) but not in those who were sedentary (\( P_{\text{trend}} = .06 \)) or engaged in lifting/heavy manual work (\( P_{\text{trend}} = .05 \)). However, the trend was less evident in subgroups of recreational physical activity; test for trend of decreasing risk of postmenopausal breast cancer by increasing HDL-C quartile was statistically significant in women who walked 4 hours/week (\( P_{\text{trend}} < .001 \)) but not in women who were sedentary (\( P_{\text{trend}} = .07 \)) or engaged in sports (\( P_{\text{trend}} = .26 \)). In the two subgroups of overweight and obese women who had borne live children, test for trend of decreasing risk of postmenopausal breast cancer by increasing HDL-C quartile was statistically significant (1–2 children, \( P_{\text{trend}} < .001 \); ≥3 children, \( P_{\text{trend}} = .007 \)), but among nulliparous women, HDL-C was unrelated to the risk of postmenopausal breast cancer (\( P_{\text{trend}} = .33 \)).

In the analysis restricted to women with HDL-C assessed in both surveys, that is, the repeat cohort (n = 15 175; mean time between surveys = 5.1 years, range = 3.6–10.8 years), we observed associations with postmenopausal breast cancer similar to the results for the 1977–1983 cohort; HDL-C in the highest quartile versus the lowest quartile was associated with a decrease in risk among all women (multivariable RR = 0.65, 95% CI = 0.43 to 0.99; \( P_{\text{trend}} = .03 \)) and among the subgroup of overweight and obese women (RR = 0.32, 95% CI = 0.15 to 0.69; \( P_{\text{trend}} < .001 \) and \( P_{\text{interaction}} = .01 \)) but not among normal weight or underweight women.

To determine whether recent alterations in metabolic risk profile influence the relationship between HDL-C and postmenopausal breast cancer risk, we divided the women who participated in both surveys and were observed in their postmenopausal years (n = 13 519) according to whether they had a change in weight below or above the median weight change between surveys of 1.5 kg. Among women with a weight gain below 1.5 kg, no association between HDL-C and post-menopausal breast cancer was observed (85 cases; Fig. 3). In contrast, among women with weight gain above 1.5 kg, we observed an inverse association between serum HDL-C and breast cancer risk (100 cases). Women with serum HDL-C in the highest quartile had a lower risk than women in the lowest HDL-C quartile (multivariable RR = 0.51, 95% CI = 0.29 to

<table>
<thead>
<tr>
<th>Cohort</th>
<th>HDL-C mmol/L</th>
<th>No. of case patients</th>
<th>Premenopausal RR (95% CI)†</th>
<th>P_trend</th>
<th>Postmenopausal RR (95% CI)‡</th>
<th>P_trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>1977–1983</td>
<td>&lt;1.20</td>
<td>23</td>
<td>1.00 (referent)</td>
<td>.9</td>
<td>1.00 (referent)</td>
<td>.9</td>
</tr>
<tr>
<td></td>
<td>1.20–1.40</td>
<td>39</td>
<td>1.56 (0.93 to 2.62)</td>
<td>.01</td>
<td>1.50 (0.89 to 2.52)</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>1.41–1.64</td>
<td>35</td>
<td>1.39 (0.82 to 2.36)</td>
<td>.03</td>
<td>1.32 (0.77 to 2.26)</td>
<td>.03</td>
</tr>
<tr>
<td></td>
<td>&gt;1.64</td>
<td>38</td>
<td>1.54 (0.92 to 2.58)</td>
<td>.19</td>
<td>1.43 (0.83 to 2.46)</td>
<td>.19</td>
</tr>
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<td></td>
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<td></td>
<td>†</td>
</tr>
<tr>
<td>1977–1983 and</td>
<td>&lt;1.20</td>
<td>25</td>
<td>1.00 (referent)</td>
<td>.9</td>
<td>1.00 (referent)</td>
<td>.9</td>
</tr>
<tr>
<td>1985–1987 (compound)</td>
<td>1.20–1.40</td>
<td>43</td>
<td>1.20 (0.73 to 1.96)</td>
<td>.01</td>
<td>1.13 (0.69 to 1.86)</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>1.41–1.64</td>
<td>56</td>
<td>1.33 (0.83 to 2.13)</td>
<td>.01</td>
<td>1.24 (0.77 to 1.99)</td>
<td>.01</td>
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<tr>
<td></td>
<td>&gt;1.64</td>
<td>76</td>
<td>1.60 (1.02 to 2.52)</td>
<td>.03</td>
<td>1.44 (0.91 to 2.30)</td>
<td>.03</td>
</tr>
</tbody>
</table>

†Adjusted for age, county of residence, parity, height, body mass index, total serum cholesterol, and recreational and occupational activity. Also considered blood pressure, serum triglycerides, age at first birth, time since last meal, smoking, and dietary energy and fat intake.
‡Adjusted for menopausal status in survey.

Table 2. Adjusted relative risks (RRs) of premenopausal and postmenopausal breast cancer in relation to serum high-density lipoprotein cholesterol (HDL-C) in the 1977–1983 and 1985–1987 surveys*
0.93; P\textsubscript{trend} = 0.02). However, the interaction between the dichotomized weight gain variable (cutoff, 1.5 kg) and quartile of HDL-C was not statistically significant (P\textsubscript{interaction} = 0.95).

**DISCUSSION**

Our study provides evidence that low serum HDL-C is independently associated with increased postmenopausal breast cancer risk among women with positive energy balance (i.e., those who are overweight or obese). We found that risk of postmenopausal breast cancer among overweight and obese women in the highest serum HDL-C quartile was one-third the risk of women in the lowest serum HDL-C quartile. In analyses adjusted for BMI, the relationship between HDL-C and the risk of postmenopausal breast cancer was strongest among those who gained weight during follow-up. These findings suggest an interaction between metabolic disturbances (i.e., overweight or obesity and low serum HDL-C) in postmenopausal breast carcinogenesis.

The 25%–30% overall reduction in the risk of postmenopausal breast cancer among women with the highest serum HDL-C levels is in agreement with an expected reduction in the risk of postmenopausal breast cancer among women with a relative androgen deficit, because serum HDL-C may be a marker of androgen status. After menopause, bioavailable estrogens formed in adipose tissue by the aromatization of androgens are a major stimulus for breast carcinogenesis (33). Sex hormones influence levels of serum HDL-C, apparently by regul-
Fig. 2. Data in the 1977–1983 survey and parity throughout the follow-up period. Women were invited from three counties in Norway (Finmark, Oppland, and Sogn og Fjordane) to participate as part of the Norwegian National Health Screening Service’s program to explore the association of lifestyle with chronic diseases. Age-adjusted relative risk of postmenopausal breast cancer among overweight and obese women (body mass index ≥25 kg/m²) by serum high-density lipoprotein cholesterol (HDL-C) quartile and categories of 1) recreational physical activity (upper left panel): open squares = sedentary, solid circles = walked 4 hours/week, solid squares = engaged in sports; occupational physical activity (upper right panel): open squares = sedentary, solid circles = walked during working hours, solid squares = engaged in lifting/heavy manual work; daily energy intake (middle left panel): open squares = ≥4390 kJ/day, solid circles = 4390–5195 kJ/day, solid squares = ≥5195 kJ/day; height (middle right panel): open squares = ≤163 cm, solid circles = 163–166 cm, solid squares = ≥166 cm; parity (lower left panel): open squares = nulliparous, solid circles = 1–2 children, solid squares = ≥3 children; and smoking (lower right panel): open squares = never smoker, solid circles = former smoker, solid squares = current smoker. * = statistically significant test for trend (P<.05). 95% confidence intervals were omitted for clarity.

The suggested positive association between serum HDL-C and the risk of premenopausal breast cancer among relatively lean women in our study should be interpreted with caution because of the small number of cases in the premenopausal follow-up period. This finding may be parallel to the inverse relationship between BMI and risk of premenopausal breast cancer observed in most studies (2). The biologic mechanisms underlying the associations between BMI and related metabolic variables and breast cancer in young women are poorly understood. However, subnormal ovarian production of estradiol and progesterone mediated by insulin and IGF-I may partly explain the suggested reduced risk of breast cancer observed in women with a tendency toward hyperinsulinemia (i.e., overweight and/or low serum HDL-C) (37). Our overall results suggest that the tumor promoting action of HDL-C observed in cell cultures (8–10) may not have an equivalent impact in vivo.

Our finding of an increased risk of postmenopausal breast cancer among women in the lowest quartile of HDL-C is in agreement with a small (51-case) Danish prospective study (21) that reported a relative risk of breast cancer of 0.3 (95% CI = 0.1 to 0.8; P<.01) for women in the highest quartile of HDL-C compared with those in the lowest quartile. However, in a nested case–control study (23), a positive association between HDL-C in serum stored for more than 20 years and postmenopausal breast cancer risk and an inverse association with premenopausal breast cancer risk were observed. There was substantial degradation of the HDL-C during storage (23), however, and...
analyses were not stratified by BMI; this may explain some of the discrepancies between the results of the nested case–control study and our findings.

A prior report from a portion of our cohort of women with follow-up through December 31, 1990 (22), showed no association between HDL-C and breast cancer risk overall or among postmenopausal women. One explanation for the lack of association may be that an increase in the prevalence of overweight and obesity among women in Norway developed primarily after 1990 (41). In addition, we have a longer follow-up period with an increased number of postmenopausal women, performed separate analyses of pre- and postmenopausal breast cancer using the accumulated number of person-years in each period (15), excluded women with HDL-C assayed from frozen sera in the analysis, used repeated measurements of HDL-C and covariates, and conducted stratum-specific analyses among women with the least favorable metabolic profile (i.e., those who were overweight or obese).

Our findings are supported by observations of lower levels of HDL-C among postmenopausal breast cancer patients in retrospective studies (17–20), although it is possible that the cancer itself may have lowered the HDL-C levels in the patients (20) and may therefore have influenced the results. Furthermore, in agreement with our prospective data, a tendency toward higher levels of HDL-C among premenopausal case patients with a low BMI has been reported (42).

We did not observe the same strong risk associated with total serum cholesterol for postmenopausal breast cancer as we did with HDL-C and postmenopausal breast cancer. One biologically plausible explanation for this difference in risk may be that sex hormones have less influence on total serum cholesterol than they do on serum HDL-C, which is strongly influenced by androgen levels (35). Furthermore, serum HDL-C has been recognized as a better marker of metabolic status than total serum cholesterol (HDL-C is the fraction of circulating cholesterol included in the definition of metabolic syndrome) (43).

Our study has several important strengths. All physicians, hospital departments, and histopathologic laboratories in Norway are obliged to report malignant diseases to the Cancer Registry, and the Cancer Registry matches regularly against the death register at Statistics Norway; therefore, we had a complete follow-up and histopathologic confirmation of all incident breast cancer cases (44). Furthermore, our study had a prospective design, and we excluded women with diagnosis of any cancer within the first year of follow-up, such that data on serum HDL-C and other potential risk factors for breast cancer were collected prior to breast cancer diagnosis. Therefore, misclassification of exposure can be assumed to be non-differential in this study, in contrast to other studies (17–20). Moreover, misclassification was reduced by several means; this is the first study of HDL-C and breast cancer risk based on repeated assessments of exposure (17–23), and blood draws and height and weight measurement were conducted by the same team of trained nurses in both surveys, each participant attended both surveys during the same season, and we used consistent methods in the same laboratory in both surveys to obtain HDL-C levels in fresh sera (26). Finally, the population-based approach in our study, high participation rate, the large number of fresh serum samples assessed in each of the surveys, adjustments for major confounders, and examination of effect modification in our analyses all increase the validity of our results.

One limitation of our study was the lack of information on exact age at menopause; the definition of menopause at age 50 years may have biased our estimates. Age-adjusted mean serum HDL-C was 1.45 mmol/L among postmenopausal women and 1.44 mmol/L among premenopausal women in the 1977–1983 survey ($P_{\text{equality}} = .62$) and we observed risk ratios for postmenopausal breast cancer that were very similar to those presented for postmenopausal breast cancer in analysis restricted to women who had serum HDL-C assessed before menopause (results not shown). Others have observed a reduction in serum HDL-C during the perimenopausal and postmenopausal years (45), but this reduction might have been due to aging and weight gain (46). The physiologic effect of menopause on serum HDL-C is not firmly established, but it is plausible that postmenopausal women experience relative androgen excess (adrenal production) that lowers their serum HDL-C when the ovarian function ceases. To account for this potential drop in HDL-C levels at menopause, we adjusted for age and menopausal status in our analyses.

Another limitation of our study was improper control in the analyses for changes in the use of hormone therapy during follow-up, a potentially important confounder or effect modifier of the relationship between metabolic profile (i.e., serum HDL-C and BMI) and breast cancer risk; exogenous estrogen therapy is an established risk factor for breast cancer—it increases HDL-C levels (34), and more frequent use of hormone therapy among lean women has been observed (47). In addition, a stronger association between BMI and postmenopausal breast cancer risk has been observed among nonusers of hormone therapy (48). Nevertheless, adjustment in our analyses for use of hormone therapy in the 1985–1987 survey did not change the estimated risk of postmenopausal breast cancer associated with HDL-C level. Furthermore, Norwegian women were cautious about using hormone therapy until the 1990s (47), the hormone therapy prescription rates started to increase in the early 1990s, hormone therapy has primarily been recommended to climacteric women, and prophylactic use among older women has been limited (47). In our cohort, younger women were more likely to be users of hormone therapy (1985–1987 survey; mean age [standard deviation] = 49.5 [4.8] years among users and 51.4 [4.4] years among nonusers). Consequently, it is likely that hormone therapy was not an important confounder.

In conclusion, our study demonstrates that low serum HDL-C is an independent predictor of increased postmenopausal breast cancer risk among overweight and obese women. Because low HDL-C is related to increased levels of several cancer-promoting hormones (e.g., androgens, estrogens, insulin, and IGF-I), the observed association may reflect the relative importance and mutual dependence of different disease pathways in malignant breast tumors after menopause. Thus, HDL-C is a potential marker of postmenopausal breast cancer risk that could provide a means for identifying women at higher risk who may be candidates for preventative intervention in the future.

REFERENCES


