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Serum Beta-lipoprotein, Serum Cholesterol and Quetelet's Index as Predictors for Survival of Breast Cancer Patients

Sven Törnberg and John Carstensen

We studied the survival of breast cancer patients in relation to serum cholesterol level, serum beta-lipoprotein level (BLP) and being overweight among women having breast cancer diagnosed during a follow-up period of 20 years. A cohort of 46 570 women attended a general health screening including examination of serum lipid levels, height and weight during 1963–1965. Of these, 1170 women developing breast cancer; 196 were below the age of 50 and 974 were above 50 years of age. 66 of the younger women, and 341 of the older women were reported to have died of breast cancer. A correlation was found between high serum BLP and decreased survival of breast cancer patients < 50 years of age. For women ≥ 60 years of age, BLP was positively correlated to breast cancer survival. No correlation was found between serum cholesterol level and breast cancer survival in any age group. Increasing obesity was statistically significantly correlated to decreased survival with breast cancer. The latter findings were in accordance with other studies which have shown being overweight as a risk factor for breast cancer. As for the relationships between ischaemic heart disease and serum lipid levels, in studies of cancer risks in relation to serum cholesterol level, the different fractions of cholesterol seem to be of importance.
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INTRODUCTION

SUGGESTIONS HAVE been made that factors related to breast cancer development may also interfere with its prognosis [1–3]. Apparently, being overweight is associated with an increased breast cancer risk in postmenopausal women and decreased risk in premenopausal women [4]. Being overweight also seems to have an unfavourable impact on breast cancer survival, which is most pronounced among postmenopausal women [5–15]. High serum cholesterol levels have, in two studies, been correlated to decreased breast cancer survival [9, 15]. However, in studies on serum cholesterol levels and risk of breast cancer, most researchers have failed to demonstrate a positive relationship [16–20].

Serum beta-lipoprotein (BLP) is the electrophoretical correspondent to the ultracentrifugally measured low-density lipoprotein (LDL). BLP has been more strongly correlated to dietary fat intake than total cholesterol [21]. In a recent study of a large Swedish cohort [19], BLP was positively correlated to the risk of developing breast cancer among women less than 50 years of age. However, serum cholesterol level was negatively correlated to breast cancer risk, indicating that the different cholesterol fractions may be of importance in studies on cancer risks in relation to serum lipid levels. In the same study, obesity was positively correlated to breast cancer risk among postmenopausal women, whereas for premenopausal women, the risk relationship was negative, suggesting different aetiological mechanisms in premenopausal and postmenopausal women.

The aim of the present investigation was to study the survival of patients with breast cancer in relation to serum BLP, serum cholesterol levels and Quetelet's index, in a large cohort including 1170 breast cancer cases with a follow-up period of up to 20 years.

SUBJECTS AND METHODS

A general health screening was conducted during the period 1963–1965 in two counties in central Sweden in all women aged 25 years or more. Nearly 60 000 women were invited, and 46 570 (80% of those invited) participated. The mean age was 48 years.

Each woman was examined for 12 serum parameters (including serum BLP and serum cholesterol), height, weight, and blood pressure. The examination was made under non-fasting conditions. All serum samples were analysed at the same laboratory in Stockholm [22]. Cholesterol was analysed according to a modified Liebermann–Burchard method described by Zak *et al.* [23] and BLP by the spectrophotometrical method of Burstein and Samaille [24]. BLP levels were given in units. No data were available on tobacco consumption or dietary habits.

The cohort was followed in the nationwide Swedish Cancer Register (SCR) [25] until 1983 which was searched for all reports of malignant disease. They were also followed-up in the nationwide Swedish Cause of Death Register (SCDR) until 1987. Both date of death as well as cause of death were searched for in the SCDR. The data linkage was made possible due to the Swedish identification numbers used in all population statistics. Each person in Sweden is assigned a unique identification number consisting of 10 digits, representing the year, month and day of birth, supplemented by digits indicating the region and number sequence of birth, sex and by one control digit. The numbers are not affected by changes in name or residence.

During the period of follow-up, 1182 breast cancers were reported in the cohort. Twelve of these were diagnosed at autopsy, so 1170 were included in the survival analyses. Mean age at diagnosis was 62.4 years (S.D. 12.0). Of these, 196 were reported among women younger than 50 years of age. For these cases, patient data, surgical and pathological reports were collected from the hospitals where the patient was diagnosed and treated for their breast cancer. Relevant patient records were found for all but one. As stage is not included in the SCR, these records were used for stage classification. The number of patients, person-years at risk, and cancer deaths in different age groups are listed in Table 1.

The mean cholesterol level was 256.1 mg/dl (S.D. 42.7), mean BLP level 12.3 units (S.D. 3.4), and mean Quetelet's index 24.9 kg/m^2 (S.D. 3.9). For the breast cancer cases, the corresponding levels were 259.8 mg/dl (S.D. 45.3), 12.6 units (S.D. 3.5) and 25.5 kg/m^2 (S.D. 3.9), respectively.

Table 1. Number of person-years at risk, breast cancer patients and cancer deaths in different age groups

Age at diagnosis	No. of person-years at risk*	No. of patients*†	No. of cancer deaths‡
≤ 49	283 482	196	66
50–59	204 837	287	112
≥ 60	332 289	687	229
Total	820 289	1170	407

*Includes cases diagnosed until 31 December 1983. †Cases with date of diagnosis equal to date of death were excluded. ‡Includes deceased subjects until 31 December 1987.

The relationships between breast cancer survival and the different prognostic variables were analysed using Cox's proportional hazards model [26]. In the analysis, deaths due to causes other than breast cancer were treated as censored observations. The correlations between clinical stage and cholesterol, BLP and Quetelet's index, respectively, were tested by means of linear regression analysis [27].

RESULTS

During the period of follow-up, 66 out of 196 patients aged < 50 years at diagnosis, were reported to the SCDR as deceased due to breast cancer. The corresponding numbers for women ≥ 50 years of age were 974 patients and 341 breast cancer deaths.

Serum cholesterol level was not related to survival with breast cancer in any age group (Table 2). Serum BLP, however, was statistically significant negatively related to breast cancer survival among the 196 cases < 50 years of age and positively related to breast cancer survival among the 341 cases ≥ 50 years of age (Table 3). The relative risk of death in breast cancer patients among younger women increased with increasing BLP level ($P < 0.01$) and was 2.4 for those having a BLP level ≥ 16 units. The corresponding risk level was 0.7 ($P < 0.05$) for older women. The interaction between age and BLP was also significant ($P < 0.01$). A graphical illustration of breast cancer survival in relation to BLP level among women < 50 years of age is shown in Fig. 1.

Quetelet's index was positively correlated to breast cancer death among women aged 50–69 years at diagnosis (Table 4), although a non-significant positive trend was also found for younger women.

The stage distribution and mean levels of serum cholesterol, serum BLP and Quetelet's index among the 195 breast cancer cases < 50 years of age are listed in Table 5. When adjustment was made for stage in the analysis of breast cancer survival in relation to serum cholesterol level, serum BLP level and Quetelet's index among women < 50 years of age at diagnosis, serum BLP was no longer significantly related to survival (Table 6).

DISCUSSION

Among women having breast cancer diagnosed before the age of 50, we found a statistically significant positive correlation

Correspondence to S. Törnberg at the Department of General Oncology, Radiumhemmet, Karolinska Hospital, S-104 01 Stockholm, Sweden. J. Carstensen is at the Department of General Oncology, University Hospital, S-581 85 Linköping, Sweden.
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Table 2. Age-adjusted cancer death rate ratio among breast cancer patients, according to preclinically determined serum cholesterol and age at diagnosis. 95% confidence limits are given within parentheses

	Serum cholesterol (mg/dl)					Test for trend (*P*)
	≤ 219	220–244	245–269	270–294	≥ 295	
Age at diagnosis (years)						
≤ 49	1.0	0.9	0.8	0.9	1.8	0.49
	—	(0.4–1.7)	(0.4–1.7)	(0.5–2.0)	(0.8–3.8)	
50–59	1.0	1.2	1.0	1.1	1.1	0.94
	—	(0.7–2.2)	(0.6–1.9)	(0.6–2.0)	(0.6–2.1)	
≥ 60	1.0	0.9	0.9	0.9	0.9	0.95
	—	(0.5–1.5)	(0.6–1.5)	(0.6–1.5)	(0.6–1.5)	
Total	1.0	1.0	0.9	1.0	1.1	0.50
	—	(0.7–1.4)	(0.7–1.3)	(0.7–1.4)	(0.8–1.5)	
No. of patients	199	200	289	245	237	
No. of cancer deaths	71	67	93	86	90	

Test for interaction between age and serum cholesterol level as risk factors, $P = 0.89$.

between serum BLP level and risk of death. Similar findings have not, to our knowledge, been described before. We also found that being overweight was positively associated with an increased risk of death among women having breast cancer diagnosed, which was in agreement with findings in other studies [5–10, 12–14].

In a study of a large cohort of middle-aged Norwegian women, Vatten and Foss found an inverse relationship between serum cholesterol level and risk of subsequent breast cancer [20]. In contrast, breast cancer survival was positively related to the base-line cholesterol level, i.e. measured before the occurrence of breast cancer [15]. Those latter findings were not influenced by stage of the disease. In our analyses, despite having a larger cohort, including a larger number of cancer cases and a longer follow-up period, we were not able to detect a significant relationship between breast cancer survival and serum cholesterol level in any of the studied age groups.

In the analysis of women, 50 years or older, decreased survival was found for those having low BLP levels and being obese. The latter findings have been shown in several studies [5–15] but the inverse relation between BLP level and breast cancer survival has not been demonstrated by others.

In a previous study of the present cohort [19], we found that the risk of developing breast cancer was positively correlated to

Table 3. Age-adjusted cancer death rate ratio among breast cancer patients, according to preclinically determined BLP and age at diagnosis. 95% confidence limits are given within parentheses

	Serum BLP (units)					Test for trend (*P*)
	≤ 9	10–11	12–13	14–15	≥ 16	
Age at diagnosis (years)						
≤ 49	1.0	1.1	1.6	1.5	2.4	0.0091
	—	(0.5–2.2)	(0.8–3.4)	(0.6–3.9)	(1.2–4.9)	
50–59	1.0	0.9	0.8	1.0	0.9	0.78
	—	(0.5–1.5)	(0.4–1.4)	(0.5–1.7)	(0.5–1.7)	
≥ 60	1.0	1.0	0.9	0.7	0.7	0.043
	—	(0.6–1.4)	(0.6–1.5)	(0.4–1.1)	(0.5–1.1)	
Total	1.0	1.0	1.0	0.9	1.0	0.66
	—	(0.7–1.3)	(0.7–1.4)	(0.6–1.2)	(0.7–1.3)	
No. of patients	214	280	233	205	238	
No. of cancer deaths	77	100	82	66	82	

Test for interaction between age and BLP, $P = 0.0058$.

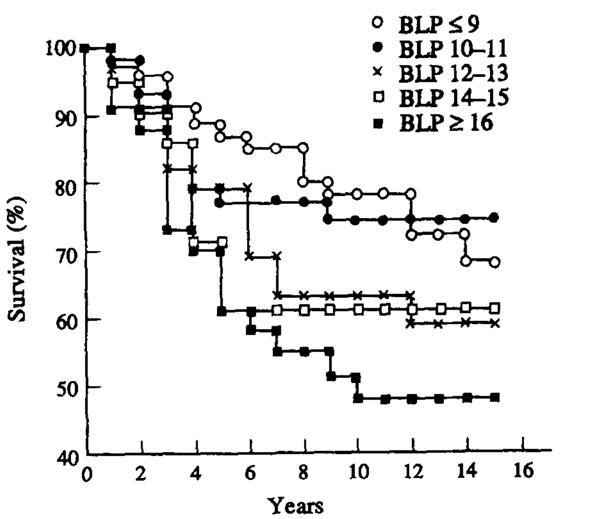

Fig. 1. Survival of breast cancer patients among women < 50 years of age at different levels of BLP.

BLP level, and negatively correlated to serum cholesterol level and Quetelet's index level among women < 50 years of age. The highest risk for breast cancer was actually found in women having both low cholesterol and high BLP levels. For women ≥ 50 years, being overweight was positively associated with breast cancer risk, whereas serum lipid levels were not. The risk of developing cancer seemed, therefore, to show the same pattern as the risk of death among breast cancer patients.

It is not clear why high BLP levels among younger women were inversely correlated to breast cancer survival. Breast cancer tumour cells have LDL receptors and high levels of BLP may, therefore, have a promoting effect on breast carcinogenesis [28, 29] with an increased risk for relapse. The breast is an endocrine target organ and it is a reasonable assumption that BLP levels could have an influence on the sex hormone levels [30–39]. Furthermore, oestrogen supplementation has been shown to increase the LDL level [40], and the association between decreased breast cancer survival and high BLP levels may in part be an oestrogenic effect. This association does not, however, explain the findings of decreased survival for older women with low BLP levels.

Table 4. Age-adjusted cancer death rate ratio among breast cancer patients, according to preclinically determined Quetelet's index and age at diagnosis. 95% confidence limits are given within parenthese

	Quetelet's index					Test for trend (P)
	≤ 22	22–23	24–25	26–27	≥ 28	
Age at diagnosis (years)						
≤ 49	1.0	1.5	1.9	1.2	2.4	0.10
	—	(0.8–2.8)	(1.0–3.7)	(0.5–2.9)	(0.9–6.5)	
50–59	1.0	0.7	1.3	1.5	2.1	0.0009
	—	(0.3–1.3)	(0.7–2.3)	(0.9–2.7)	(1.2–3.7)	
≥ 60	1.0	1.1	1.2	1.1	1.2	0.39
	—	(0.6–1.8)	(0.7–1.9)	(0.7–1.8)	(0.8–2.0)	
Total	1.0	1.1	1.4	1.4	1.7	0.0006
	—	(0.8–1.5)	(1.0–1.9)	(1.0–1.9)	(1.2–2.3)	
No. of patients	230	213	229	231	267	
No. of cancer deaths	69	64	83	83	108	

Test for interaction between age and Quetelet's, $P = 0.19$.

Table 5. Stage distribution and mean levels of serum cholesterol, serum BLP and Quetelet's index among 195 women with breast cancer < 50 years of age

Stage	No. of patients	Serum cholesterol Mean	Serum cholesterol S.E.	BLP Mean	BLP S.E.	Quetelet's index Mean	Quetelet's index S.E.
I	67	237	4	11.2	0.4	22.6	0.4
II	108	238	4	12.0	0.3	23.2	0.3
III	14	235	10	12.2	1.1	23.4	0.9
IV	6	241	30	13.0	2.3	24.9	1.1
Test for trend		$P = 0.96$		$P = 0.091$		$P = 0.055$	

Table 6. Age and stage-adjusted cancer death rate ratio in cancer patients < 50 years of age at diagnosis according to serum cholesterol, serum BLP and Quetelet's index. 95% confidence limits are given within parentheses

	Quintiles					
	1	2	3	4	5	
Serum cholesterol	1.0	0.9	1.1	0.9	1.5	$P = 0.56$
	—	(0.5–1.9)	(0.5–2.5)	(0.4–1.9)	(0.7–3.3)	
BLP	1.0	1.0	1.5	1.5	1.7	$P = 0.088$
	—	(0.5–2.2)	(0.7–3.2)	(0.6–3.9)	(0.8–3.5)	
Quetelet's index	1.0	1.2	1.4	0.9	2.3	$P = 0.38$
	—	(0.7–2.4)	(0.7–2.7)	(0.4–2.1)	(0.8–2.7)	

Plausible explanations for the relationship between obesity and breast cancer development and prognosis among postmenopausal women have been described. Since adipose tissue is the location for transformation of androstendione to oestrone and the level of sex hormone binding globulin is lower among postmenopausal women [36, 41, 42], the target tissue contains higher levels of oestrone and hormone-dependent tumours may be stimulated to grow. Prentice *et al.* [43] have shown that dietary fat reduction and weight reduction decrease the serum oestradiol concentration. A higher oestrogen level may, therefore, be the explanation for a lower survival rate among postmenopausal, obese women.

Obese women aged less than 50 years, had, in the previous study of the present cohort [19], a lower risk of developing breast cancer. Why there was a positive relationship, even if it was not significant, between being overweight and breast cancer survival among the younger women in the present study is not fully understood. One hypothesis could be that obese premenopausal women have breast cancer in higher stages due to difficulties in the diagnostic procedures of obese women. The findings are, however, in accordance with those in the study by Greenberg *et al.* [11].

In the present study we were able to show that BLP level, but not total cholesterol level, was correlated to breast cancer survival. As total cholesterol level reflects a sum of different lipid fractions, e.g. VLDL, LDL and HDL, the risk relationships depend on which lipid fraction one has studied. This may explain why, in many studies, total cholesterol level has not been correlated to breast cancer incidence, mortality or survival.

In spite of the fact that international correlational studies [44], have shown positive relationships between high per capita fat intake and breast cancer death, high dietary fat intake at an individual level has not been significantly correlated to breast cancer development or prognosis [13, 45–50]. In a recent study, however, Holm and co-workers found that patients with oestrogen receptor-rich breast cancers, stages 1 and 2, having a high consumption of fat, had a shorter relapse-free survival than women with a lower fat intake [51]. The underlying cause for high BLP level is believed to be genetic in its origin [52], and it has also been shown that serum lipids are bad indicators of dietary intake of fat [52].

The present investigation has shown different relationships: decreased survival with increasing BLP levels among younger women, while an opposite risk relation was found for older women, and decreased survival with increasing obesity, irrespective of age. The stage of breast cancer was, however, the most important prognostic factor. Why serum cholesterol levels were not correlated to breast cancer survival, as found in the Norwegian study [15], is not clear.

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