CHOLESTEROL AS RISK FACTOR FOR MORTALITY IN ELDERLY WOMEN

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Summary 92 women aged 60 years and over (mean 82·2, SD 8·6) living in a nursing home and free from overt cancer were followed-up for 5 years. 53 died during this period; necropsy revealed cancer in only 1 patient. Serum total cholesterol at entry ranged from 4·0 to 8·8 mmol/l (mean 6·3, SD 1·1). Cox's proportional hazards analysis showed a J-shaped relation between serum cholesterol and mortality. Mortality was lowest at serum cholesterol 7·0 mmol/l, 5·2 times higher than the minimum at serum cholesterol 4·0 mmol/l, and only 1·8 times higher when cholesterol concentration was 8·8 mmol/l. This relation held true irrespective of age, even when blood pressure, body weight, history of myocardial infarction, creatinine clearance, and plasma proteins were taken into account. The relation between low cholesterol values and increased mortality was independent of the incidence of cancer.

Introduction

TOTAL serum cholesterol values tend to rise during life, but not beyond age 60 in men and 70 in women; concentrations then decrease slightly.[1,2,3] Total serum cholesterol is related positively to the incidence of coronary heart diseases in elderly people.[4,5] Yet an increased mortality rate has been demonstrated in septuagenarian men with low cholesterol values, and has been attributed to the large number of cancers in that group.[6] However, except for prostatic cancer, which seems to increase at an age-dependent rate in elderly men, cancer mortality declines from the age of 70, and is not important enough to account for the association of mortality with low cholesterol values in very old people, especially women.[7,8] We tried to eliminate the role of cancer as a confounding factor in a prospective study designed to assess the relation between mortality and total serum cholesterol in a group of elderly women.

Subjects and Methods

Subjects

The subjects were drawn from 111 women living in a home for elderly people. We excluded smokers, women who had been living in the home for less than 6 months, those known to have cancer, those with an acute illness or liver disease, and those taking drugs to lower serum cholesterol. The remaining 92 women (mean age 82·1 [SD 8·6], range 60–97 years) were followed-up for 5 years. Before entry to the study the following were recorded: a complete medical history, physical findings, electrocardiogram, chest X-ray, and laboratory tests (blood count, erythrocyte sedimentation rate, blood glucose, glycosylated haemoglobin, total cholesterol, proteins, protein electrophoresis, creatinine clearance).

Statistical Methods

For variables that could be quantified the following were calculated—minimum, maximum, first quartile, median, third quartile, mean, standard deviation. Pearson's correlation coefficient was used to measure the linear relation between two quantifiable variables. The Mann-Whitney test was used to compare the means between two groups. We used Cox's proportional hazards technique[9] for assessing the relation between serum total cholesterol level and mortality. We took into account age, body weight, blood pressure, history of myocardial infarction, creatinine clearance, and level of plasma proteins as possible interacting or confounding factors of mortality.

Data Analysis Strategy[10,11]

We started with Cox's model without interaction, using the following variables: cholesterol (C), squared value of cholesterol (C2), age (A), blood pressure (BP), body weight (BW), creatinine

TABLE I—DISTRIBUTION OF VARIABLES

Variable	Minimum	Maximum	First quartile	Median	Third quartile	Mean (SD)
Age (yr)	60·7	97·1	76·7	83·4	87·5	82·2 (8·6)
Diastolic BP (mm Hg)	67	110	76	81	88	82 (8)
Weight (kg)	34	90	45	53	68	57 (14)
Cholesterol (mmol/l)	4·0	8·8	5·5	6·0	7·1	6·3 (1·1)
Creatinine clearance (ml/min)	14	111	32	41	56	45 (21)
Plasma proteins (g/l)	60	80	67	70	73	70 (4)

PRIMI TRIAL STUDY GROUP: REFERENCES—*continued*

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TABLE II—CORRELATIONS BETWEEN CHOLESTEROL AND OTHER QUANTIFIABLE VARIABLES

—	Age	Creatinine clearance	Plasma proteins	Body weight	Diastolic BP
Correlation coefficient	−0·29	0·11	0·13	0·04	0·12
95% confidence interval	(−0·46, −0·10)	(−0·10, 0·30)	(−0·07, 0·33)	(−0·18, 0·25)	(−0·09, 0·31)

clearance (CC), history of myocardial infarction (MI), and plasma proteins (P).

In the first step we tested for interactions between A and C, and between A and C2. Then the test was repeated, with A being replaced, in succession, by BP, BW, CC, MI, and P. Since no such interaction was found, it was possible, in the second step to look for confounding factors for cholesterol among A, BP, BW, CC, MI, and P. In the third step, we tested the final relation obtained between cholesterol and mortality.

Finally, we tested the stability of the model by assessing 92 new models with only 91 patients each, according to Storer and Crowley.[12]

Results

Table I shows the distribution of the quantifiable variables at the time of entry into the study. A history of myocardial infarction had been documented in 7 patients, could be excluded in 78, and was uncertain in 7. Table II shows the correlations of cholesterol with the other quantifiable variables. In the patients who had antecedents of myocardial infarction, the mean cholesterol value was 5·9 mmol/l (SD = 1·2). It was 6·3 mmol/l (SD = 1·1) in those without an antecedent of myocardial infarction (Mann-Whitney test: p = 0·28).

During the 5 year follow-up, 53 of the 92 patients died. The causes of death were—hepatic carcinoma undetected at entry to the study, 2%; infection (bronchopneumonia, septicaemia), 38%; vascular diseases (stroke, myocardial infarction, pulmonary embolism, heart failure), 32%; miscellaneous (eg, renal insufficiency, dehydration, non-cancerous intestinal obstruction, trauma, cachexia), 24%; unknown, 4%.

In the patient who died from cancer, initial cholesterol value was 5·9 mmol/l. All 6 patients who died from stroke had initial cholesterol values above the median (6·0 mmol/l).

Cox Analysis

Step 1 showed no significant interaction between cholesterol and the other variables. Step 2 showed that the only confounder for cholesterol was age. The final proportional hazards model is:

$$\lambda(t; A, C) = h(t) \exp(0{\cdot}074\,A - 2{\cdot}543\,C + 0{\cdot}1815\,C2)$$

where $\lambda(t; A, C)$ is the hazard function and represents mortality; h is the variation of mortality during the 5 years when age and cholesterol are fixed; and t is the time since entry to the study. The likelihood ratio test gives a p value of 0·03 for the presence in the model of the variables C and C2. Details about the estimated coefficients are given in table III.

Fig 1 shows how the relative death rate varies with cholesterol when age is fixed. The death rate is lowest with

TABLE III—STATISTICS RELATED TO THE HAZARD FUNCTION

Variable	Estimated coefficient	Standard error	Estimated coefficient/ standard error	Exponential (estimated coefficient)
Age	0·074	0·020	3·72	1·077
Cholesterol	−2·543	1·183	−2·15	0·079
(Cholesterol)²	0·182	0·093	1·95	1 200

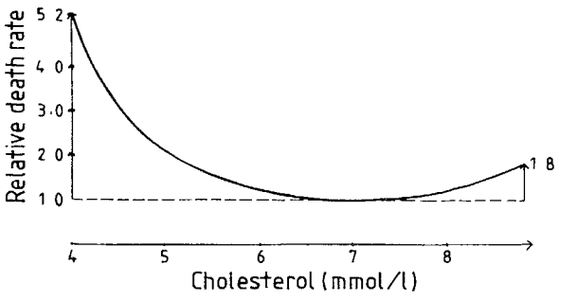

Fig 1—Relative death rate and total cholesterol.

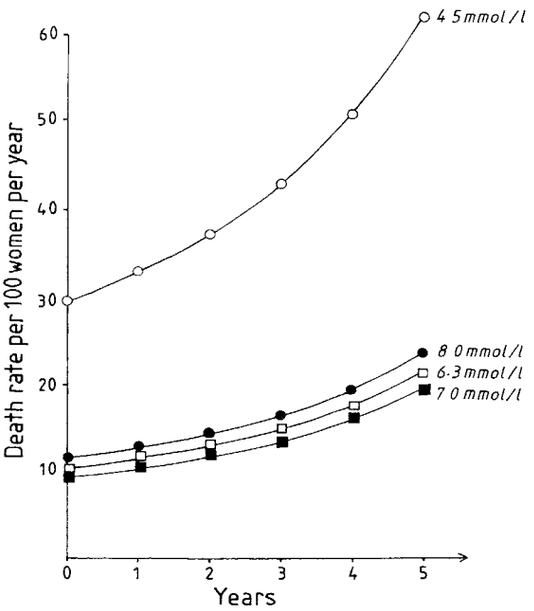

Fig 2—Death rate (hazard function) for women aged 82·2 at entry in the study, according to different levels of cholesterol.

serum cholesterol of 7·0 mmol/l (95% CI 5·4–8·6), 5·2 times (CI 1·1–23·9) greater than the lowest with 4·0 mmol/l, and 1·8 times (CI 0·4–7·7) greater with 8·8 mmol/l.

When we verified the stability of the model (step 4 of the strategy), the cholesterol value associated with the minimum death rate ranged from 6·8 to 7·3. The preceding 5·2 multiplier (associated with cholesterol value of 4·0 mmol/l) ranged from 4·2 to 6·5, and the 1·8 multiplier (associated with cholesterol value of 8·8 mmol/l) ranged from 1·4 to 2·3. We conclude that, despite the small number of subjects, the results obtained with the model are reliable. Fig 2 is an illustration of the final model.

Discussion

Several studies done in younger populations, mostly middle-aged men, have shown an excess of deaths at both extremities of the cholesterol distribution curve.[3,13–18] The mortality peak at the higher end of the curve is widely ascribed to cardiovascular diseases. As in our study, the peak is often more pronounced at the lower end.[13,15,19] The excess of mortality in subjects with low cholesterol is generally attributed to cancer.[3,13,20–23] In the Whitehall study,[18] the inverse association between cancer mortality and cholesterol values was confined to the first 2 years of follow-up, and the authors suggested that this phenomenon resulted from the metabolic consequences of cancer that was present but unsuspected at the time of examination. However, in a 17-year prospective study, Salmond et al[22] found, in New Zealand Maoris aged 25–74, an inverse and non-linear

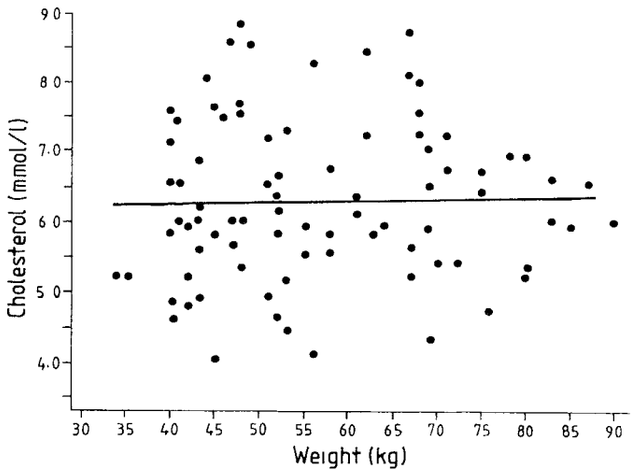

Fig 3—Relation between body weight and cholesterol.

r = 0·04; p = 0·69.

association of cholesterol with total mortality in women. This association remained significant when deaths in the first 5 years of follow-up were excluded, and could not be explained by undetected illness causing low cholesterol concentrations at the time of examination. The results of three Chicago epidemiological studies do not generally support the hypothesis of an inverse association between serum cholesterol and cancer in urban middle-aged white American males and females.[24] In a 7-year follow-up study of men aged 35 to 62 years, Kozarevic et al[25] found an inverse relation between serum total cholesterol and overall mortality without significant association between cholesterol and cancer mortality.

Anderson et al[26] state that, after age 50, there is no increased overall mortality with either high or low cholesterol levels, the association of mortality with low cholesterol being confounded by people whose cholesterol levels are falling, perhaps because of diseases predisposing to death. However, in a 7-year prospective study of 10 000 men aged 40–65, Yaari et al[14] found a J shaped relation between cholesterol and total mortality which persisted after removing data on early mortality (first two years).

In our elderly female population, there was a J-shaped relation between serum cholesterol and overall mortality (fig 1). In a group of elderly men living in a nursing home, Rudman et al[27,28] found, instead of a J-shaped curve, a linear inverse relation between serum total cholesterol and overall mortality, but the follow-up duration was only 14 months. A pattern similar to ours was found in a 10-year follow-up of septuagenarians by Agner and Hansen,[6] but only in men. In the Honolulu heart study[16] the ideal range of cholesterol values corresponding to minimum death risk in men aged 50 to 71 was 200–220 mg/dl (5·16–5·68 mmol/l). The optimum value found in our population (7 mmol/l) is distinctly above that range, and this discrepancy could be explained by differences in age and sex, since our patients were older females.

The raised mortality rate related to low cholesterol values in elderly people is commonly attributed to cancer, as in younger people. From Australian age and cause specific mortality rates Dugdale[29] estimated that lowering the serum cholesterol of the whole population by 10% should lengthen median life by 1 year, but the percentage of deaths from cancer should rise from 26·8 to 29·6. Our results clearly suggest that cancer mortality alone does not account for the excess of deaths in elderly women with low cholesterol. Nevertheless, the mortality peak is much higher in women with lowest initial cholesterol values than in those with highest values. In the group of 11 patients with cholesterol less than 5 mmol/l, 9 died during the study, and in 6 cases the death was due to infection. It is not likely that low cholesterol was only a marker of poor nutritional status, since the relation between cholesterol and mortality was independent of plasma protein level. There was either no correlation between body weight and cholesterol (r = 0·04, fig 3). According to Oliver[30] an increase in plasma cholesterol might be an adaptive process during ageing, necessary to maintaining the physical or chemical characteristics of the cell membrane. If this hypothesis is true, a reduction of cholesterol, either by drugs or by a high intake of polyunsaturated fats, should not be advisable in the elderly, at least when total cholesterol value is not over 7 mmol/l.

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