Cholesterol and mortality in New Zealand Maoris

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Summary and conclusions

The relation between serum cholesterol concentration and mortality was studied prospectively over 11 years in 630 New Zealand Maoris aged 25-74. Serum cholesterol concentration was measured at initial examination in 1962-3 in 94% of the subjects and whether each was dead or alive was determined in 1974. The causes of death were divided into three categories: cancer, cardiovascular disease, and "other." The Mantel-Haenszel method of analysis of survivorship data showed a significant inverse relation between serum cholesterol concentration and overall mortality in men ($\chi^2_2=11{\cdot}6$; $p=0{\cdot}003$) and women ($\chi^2_2=7{\cdot}6$; $p=0{\cdot}02$) with odds ratios of 2·3 and 1·9 respectively. Similar significant inverse relations were found for cancer and "other" causes of death. These relations remained significant when baseline age, systolic blood pressure, and the Quetelet index were controlled in Cox's proportional hazards regression model.

The results of this study provide evidence for a potentially deleterious effect of low serum cholesterol concentration. Hence, further research is needed before indiscriminate efforts are made to lower serum cholesterol concentrations in New Zealand Maoris.

Introduction

In Western industrial populations raised serum cholesterol concentrations constitute an important predictor of morbidity and mortality from coronary heart disease. Unlike blood pressure, however, serum cholesterol concentrations are not directly correlated with overall mortality, and evidence of an inverse relation has been reported.[1]

Compared with Polynesians following a more traditional life style in the South Pacific, New Zealand Maoris have a high incidence of cardiovascular disease. We have therefore conducted a prospective study over 11 years to assess the relation between serum cholesterol concentrations and deaths from all causes in a population of New Zealand Maoris.

Subjects and methods

The population was first examined in 1962-3 and consisted of two rural samples and one urban sample of people with at least half-Maori ancestry. The sampling procedures have been described.[2] Out of 670 people aged 25-74 years in the original samples, 630 (94%) were examined for baseline values. Serum cholesterol concentration was measured with a modified Abell-Kendall method in the laboratory of the Epidemiology Unit, Wellington Hospital, which has participated in the lipid standardisation programme of what is now the Centre for Disease Control, Atlanta, Georgia, since 1962. Blood pressure was measured once for each subject by one of two doctors using an ordinary mercury sphygmomanometer with a 14 cm cuff. Height and weight were measured by standard procedures.

The population was followed up in 1968-9 and 1974 and it was determined whether each and every patient was dead or alive. Information on cause of death was collected from necropsy reports, doctors' records, hospital records, death certificates, and relatives. The cause of death was categorised, without knowledge of the subject's baseline values, by RB as cardiovascular disease, cancer, or "other." Since the cause of death could not always be accurately determined, the analyses concentrated on total mortality though some analyses of more specific causes were also conducted.

Survival data were analysed with the Mantel-Haenszel method for survivorship data (log-rank method)[3] and Cox's proportional hazards regression model.[4] The Mantel-Haenszel method assumes no underlying distributions of data but does require categorisation of independent variables. Cox's method requires assumptions of regression analysis but permits estimation of relative risks adjusted for other variables.

Results

Table I shows the population studied at initial examination, the cause and number of deaths over the 11 years, and the age-specific "all-causes" death rates for both men and women. As expected, the death rates increased with age. About one-third of the deaths were from cardiovascular disease and one-sixth from cancer.

TABLE I—*Age distribution, number and causes of deaths, and mortality rates during 11-year follow-up of 630 Maori men and women*

Age (years)	No examined initially	Deaths over 11 years: Total	From cancer	From CVD*	From "other" causes	Overall mortality rates (%)
			Men			
25-34	92	5	0	1	4	5·4
35-44	66	7	1	1	5	10·6
45-54	90	28	6	10	12	31·1
55-64	53	28	4	15	9	52·8
65-74	18	13	1	5	7	72·2
Total	319	81	12	32	37	25·4
			Women			
25-34	81	4	2	0	2	4·9
35-44	84	10	5	3	2	11·9
45-54	73	11	4	3	4	15·1
55-64	48	24	3	10	11	50·0
65-74	25	20	4	8	8	80·0
Total	311	69	18	24	27	22·2
Grand total	630	150	30	56	64	23·8

CVD = Cardiovascular disease.

Table II shows the age-specific mean serum cholesterol concentrations, systolic blood pressure, and Quetelet index (weight/height²) at initial examination for both men and women. The mean serum cholesterol concentration increased until age 35-45 in men and age 55-64 in women and then decreased. The mean serum cholesterol concentration in each age group was lower than that in New Zealand Europeans studied with comparable methods.[2] Systolic blood pressure increased with age, particularly in women, the mean value being similar to that in New Zealand Europeans, though considerably higher than in atoll-dwelling Polynesians.[2] The Quetelet index showed the same relation with age in both sexes as the serum cholesterol concentration: the index was higher in Maoris than in either New Zealand Europeans or atoll-dwelling Polynesians.

Table III shows the results of the Mantel-Haenszel analyses for survivorship data, relating baseline cholesterol concentrations and all causes of death. Within each age group in both sexes mortality was

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higher in the low-cholesterol group than in the other two groups; the age-adjusted results showed the same effect, and the age-adjusted χ^2_2 test gave significant results for both men and women (11·6, p=0·003; and 7·6, p=0·02 respectively), with odds ratios (low-cholesterol-group result: high-cholesterol-group result) of 2·3 and 1·9 respectively. Since the inverse association may have been caused by initially low serum cholesterol concentrations in subjects with debilitating diseases, the analyses were repeated excluding all deaths in the first two years of follow-up. With the reduced number of subjects a similar excess mortality was found in the low-cholesterol group as compared with that in the other two groups and the results were of only borderline significance: for men $\chi^2_2=5·6$, p=0·06, odds ratio (as above)=1·9; and for women $\chi^2_2=6·1$, p=0·04, odds ratio =1·7.

The Mantel-Haenszel method was used to examine the relation between serum cholesterol concentration and mortality from cancer, but since there were only 30 deaths from cancer the data for men and women were pooled for this analysis (table IV). For all subjects except those aged 55-64, there was an excess mortality from cancer in the low-cholesterol group as compared with that in the other groups; the age-adjusted χ^2_2 value of this relation was significant (7·5; p=0·02), and the odds ratio was 3·2. Similar inverse relations in each age group were found with mortality from other causes as the end point: for men $\chi^2_2=7·8$, p=0·02, odds ratio=2·5; and for women $\chi^2_2=10·6$, p=0·005, odds ratio=3·8. No relations were found between serum cholesterol concentrations and mortality from cardiovascular disease.

Similar categorical analyses were performed for systolic blood pressure and the Quetelet index. A direct relation between systolic blood pressure and total mortality was found for Maori men, but not for women, with the adverse effect of blood pressure becoming apparent only when the baseline value exceeded 150 mm Hg. No relation was found between the Quetelet index and total mortality.

Cox's proportional hazards regression analysis was then used to examine the influence of cholesterol concentration on mortality when controlling for other variables. Table V shows the results of these analyses with total mortality and deaths from cancer, cardiovascular disease, and other causes as the dependent variables and age, serum cholesterol concentration, systolic blood pressure, and the Quetelet index as the independent variables. This technique has the advantage of modelling the whole survival curve, although it does require the usual regression assumptions. Age and systolic blood pressure were directly related to total mortality in men, whereas both the cholesterol concentration and the Quetelet index were inversely related to total mortality when controlling for other variables. For women, age and the Quetelet index were directly related and serum cholesterol concentration indirectly related to total mortality. The risk ratios of total mortality at a serum cholesterol concentration of 4·14 mmol/l (160 mg/100 ml) as compared with that at a concentration of 6·73 mmol/l (260 mg/100 ml) when adjusted for age, systolic blood pressure, and the Quetelet index were 1·7 for men and 1·4 for women.

The regression analyses were repeated after excluding all deaths in the first two years of follow-up, and the results were the same for serum cholesterol concentration and systolic blood pressure, although the coefficients for the Quetelet index were not significant in either sex. The cause of death-specific regression analyses confirmed the inverse relation of serum cholesterol concentration with mortality from cancer and other causes in both sexes. Serum cholesterol concentration was weakly related with mortality from cardiovascular disease in women (table V).

TABLE II—*Mean (±SE of mean) baseline serum cholesterol concentration, systolic blood pressure, and Quetelet index at various ages in 630 Maori men and women*

Age (years)	No studied	Serum cholesterol concentration (mmol/l)	Systolic blood pressure (mm Hg)	Quetelet index ($kg/m^2 \times 10^3$)
		Men		
25-34	92	5·7±0·1	127·0±1·3	2·8±0·04
35-44	66	6·0±0·2	133·8±2·5	2·9±0·06
45-54	90	5·9±0·1	142·5±2·6	2·9±0·06
55-64	53	5·8±0·2	144·6±3·3	2·8±0·07
65-74	18	5·4±0·2	143·8±6·6	2·7±0·10
		Women		
25-34	81	5·3±0·1	123·7±2·3	2·8±0·08
35-44	84	5·3±0·1	138·0±3·1	3·0±0·07
45-54	73	5·7±0·1	153·2±3·4	3·1±0·09
55-64	48	5·8±0·2	160·4±4·7	3·0±0·09
65-74	25	5·7±0·3	171·1±6·4	2·7±0·11

Conversion: SI to traditional units—Serum cholesterol: 1 mmol/l≈38·6 mg/100 ml.

TABLE III—*Observed (O) and expected (E) number of deaths from all causes in Maori men and women with low, medium, and high baseline serum cholesterol concentrations (Mantel-Haenszel method of analysis)*

	Serum cholesterol concentration (mmol/l)											
	Low (2·6-5·1)				Medium (5·1-5·8)				High (5·8-11·9)			
Age (years)	No studied	O	E	O:E	No studied	O	E	O:E	No studied	O	E	O:E
					Men							
25-34	25	2	1·4	1·4	24	2	1·3	1·5	42	1	2·3	0·4
35-44	13	2	1·3	1·5	21	1	2·2	0·5	32	4	3·5	1·1
45-54	18	9	4·9	1·8	28	9	9·0	1·0	42	10	14·1	0·7
55-64	11	8	3·7	2·2	17	7	10·0	0·7	23	11	12·3	0·9
65-74	5	4	2·5	1·6	7	4	5·5	0·7	5	4	3·9	1·0
Age-adjusted	72	25	13·9	1·8	97	23	28·0	0·8	144	30	36·1	0·8
					Women							
25-34	30	4	1·4	2·9	27	0	1·4		24	0	1·2	
35-44	34	5	4·0	1·3	29	2	3·6	0·6	21	3	2·4	1·3
45-54	20	6	2·9	2·1	29	2	4·2	0·5	24	3	3·9	0·8
55-64	14	8	5·8	1·4	12	7	5·6	1·3	22	9	12·6	0·7
65-74	9	8	6·9	1·2	6	5	4·5	1·1	10	7	8·6	0·8
Age-adjusted	107	31	21·0	1·5	103	16	19·3	0·8	101	22	28·7	0·8

Conversion: SI to traditional units—Serum cholesterol: 1 mmol/l≈38·6 mg/100 ml.

TABLE IV—*Observed (O) and expected (E) numbers of deaths from cancer in 507 Maori men and women combined with low, medium, and high serum cholesterol concentrations*

	Serum cholesterol concentration (mmol/l)											
	Low (2·6-5·1)				Medium (5·1-5·8)				High (5·8-11·9)			
Age (years)	No studied	O	E	O:E	No studied	O	E	O:E	No studied	O	E	O:E
25-34	51	2	0·6	3·3	49	0	0·6		65	0	0·8	
35-44	43	3	1·8	1·7	48	1	2·1	0·5	48	2	2·1	1·0
45-54	27	4	1·9	2·1	49	3	3·7	0·8	56	3	4·4	0·7
55-64	10	1	1·3	0·8	19	4	2·3	1·7	27	2	3·4	0·6
65-74	5	3	1·5	2·0	6	2	2·0	1·0	4	0	1·5	
Age-adjusted	136	13	7·0	1·9	171	10	10·8	0·9	200	7	12·2	0·6

Conversion: SI to traditional units—Serum cholesterol: 1 mmol/l≈38·6 mg/100 ml.

TABLE V—*Prediction of mortality in 630 Maori men and women (Cox's proportional hazards regression analysis)*

Variable	Cause of death						
	Total		Cancer	CVD		"Other"	
	Men	Women	Men and Women	Men	Women	Men	Women
Age	6·68**	9·16***	8·25***	8·74**	12·42*	6·63***	11·30**
Serum cholesterol concentration	−0·52***	−0·33***	−1·22***	−0·18	0·30*	−0·56**	−1·17***
Systolic blood pressure	1·09***	−0·08	−0·70	2·48***	0·21	0·07	−1·33
Quetelet index	−0·13**	0·09*	0·19*	−0·08	0·10	−0·30*	0·15
Relative risk (at SC† = 4·14: at SC = 6·73)	1·7	1·4	3·4	1·2	0·7	1·8	3·2

CVD = Cardiovascular disease. *P<0·5. **P<0·01. ***P<0·001. †SC = Serum cholesterol concentration in mmol/l.
Conversion: SI to traditional units—Serum cholesterol: 1 mmol/l ≈ 38·6 mg/100 ml.

Discussion

Our findings disclose a consistent inverse relation between baseline serum cholesterol concentrations and total mortality over 11 years in a sample of New Zealand Maoris. This relation remained at a lower level of significance, after all deaths in the first two years of follow-up had been removed to reduce the possibility of bias from early mortality in subjects already sick and with low serum cholesterol concentrations initially. The relation also remained when age, systolic blood pressure, and the Quetelet index were controlled in a life-table regression analysis. When mortality from specific causes was studied an inverse relation was found between serum cholesterol concentration and mortality from cancer in men and women aged under 55 and also between serum cholesterol concentration and mortality from the other causes in both sexes.

Maoris are Polynesians who have lived in New Zealand for centuries, and their life styles have changed dramatically as compared with Polynesians who have remained in more isolated South Pacific environments. Perhaps as a consequence of these changes Maoris have high rates of morbidity and mortality from cardiovascular disease. Other analyses show that systolic blood pressure is the only risk factor associated with the prevalence and incidence of coronary heart disease in this group; no relation has been found between coronary heart disease and serum cholesterol concentrations, so risk factors related to this disease apparently have a different significance in Maoris from those in other Western industrial populations,[5] which also implies that the results of our study may not be found in other populations.

The relation between low cholesterol concentration and mortality may reflect poor nutrition, which would be a more direct cause of the excess mortality noted in the low-cholesterol group. Results of family studies in 1962-3, however, suggested that the nutritional state of New Zealand Maoris was adequate, with an average daily intake of 10 711 kJ (2560 kcal).[6] No direct evidence is available of their nutritional state in earlier times, although gross malnutrition has not been noticeable in New Zealand this century. This relation was found in all age groups, which makes a cohort effect of the depression of the 1930s an untenable explanation for the trends found.

Results of other studies support our findings. The Framingham study investigated the probability of dying within two years after examination and noted an inverse relation between serum cholesterol concentration and mortality in men but not in women, although this was not significant.[1] An inverse relation between serum cholesterol concentration and mortality from stroke, based on ecological data, was found in Japan.[7] A collaborative, prospective, international study[8] found serum cholesterol concentrations to be 0·13-0·18 mmol/l (5·0-7·0 mg/100 ml) lower in cases of cancer of the colon than in controls, and a significant inverse relation between serum cholesterol concentration and incidence of cancer has also been described.[9] Finally, in a co-operative trial of clofibrate as primary prophylaxis against ischaemic heart disease an excess of deaths from cancer and "other medical causes" was found in the placebo group with low serum cholesterol concentrations as compared with the placebo group with high serum cholesterol concentrations, although chance was proposed as the explanation.[10]

The relation between low serum cholesterol concentrations and excess mortality may be spurious; there may be many other important, undetected differences between the cholesterol groups, and serum cholesterol concentration is only a crude measure of lipid metabolism. Hypocholesterolaemia alone, however, may be causally associated with a higher risk of cancer.[9] Cholesterol may have a regulatory function in cell membranes,[11] which might explain the relation between low serum cholesterol concentrations and the incidence of cancer. Dietary cholesterol, however, has been proposed as a cocarcinogen for cancer of the colon.[12] Hence much remains to be learnt about the biological effects of cholesterol.

Our study shows the need for further research before indiscriminate attempts are made to lower serum cholesterol concentrations in Maoris to reduce their risk of coronary heart disease. The results emphasise the importance both of studying risk factors on a population-specific basis and of using total mortality as an end point for community-based intervention studies.

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