Discussion

About half of the clinically important abnormalities wrongly interpreted by casualty officers were correctly interpreted by the radiographers at examination. Although we do not underestimate the hazards of overtreatment, we did not analyse the false positive interpretations made by the casualty officers or radiographers. In general, minor mistakes were responsible for these, such as attributing a fracture to an accessory ossicle that was often some distance from the site of the injury. We think that casualty officers are unlikely to treat patients on the basis of a radiographer's suspicion unless there is clear focal clinical evidence.

Swinburne proposed training radiographers in the recognition of patterns.[3] This has been introduced in obstetric and to a lesser extent non-obstetric ultrasonography. Aberdour suggested delegating certain categories of reporting and considered that "radiographers may prove able to report on some or all casualty patients."[4] Galasko and Monahan reported the value of double reading casualty radiographs, with a third reading uncovering an appreciable number of further abnormalities.[5] Not surprisingly, individual radiographers' performances correlated reasonably well with seniority, and this may increase the efficacy of this scheme in district hospitals with relatively more senior radiographers. Defence organisations have informed us that as long as casualty officers were aware that the radiographer's report was not legally binding they would not object to the radiographer's opinion being volunteered.

This scheme does not require any expense or paperwork. We emphasise that although marking radiographs is regarded as informal, only when it is introduced as a regular procedure will it reduce errors considerably and be regarded as clinically helpful by casualty officers, who need only to look at the packet to see the marking.

TABLE I—*Interpretations of radiographs by radiographer and casualty officer*

Interpretation of radiograph	Radiographer	Casualty officer
Correct	1307	1331
Incorrect:		
False positive	37	38
False negative	68	63
Uncertain	84	64
Total	1496	1496

TABLE II—*Casualty consultants' assessment of clinical importance of abnormalities detected in radiographs*

	False negative interpretations made by:		
	Radiographers	Casualty officers	Casualty officers but not radiographers
Important	43	34	16
Not important	25	29	12
Total	68	63	28

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Are low cholesterol values associated with excess mortality?

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Abstract

The relation between cholesterol concentration and mortality was studied prospectively over 17 years in 630 New Zealand Maoris aged 25-74. The dead or alive state of each person was determined in 1981. The causes of death were divided into three categories: cancer, cardiovascular disease, and "other." Using univariate and both linear and non-linear multivariate methods of analysis for survivorship data, significant inverse relations with serum cholesterol were found for total mortality in women, for mortality from cancer in men and women, and for other causes of mortality in both men and women. The inverse and non-linear association with total mortality in women remained significant when deaths in the first five years of follow up were excluded. This suggests that the association was not explained by undetected illness causing low cholesterol concentrations at the time of initial examination.

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Introduction

A review in 1981 of 17 epidemiological studies found in eight an inverse relation between blood cholesterol values and total cancer mortality, particularly in older men, while in the remaining nine studies there was no relation in men or women.[1] Three additional studies found that the inverse association gradually disappeared as the duration of follow up increased, suggesting that the lower cholesterol concentrations in people subsequently dying of cancer were due to the effect of undetected disease.[2-4] This explanation, however, has not been supported by other studies.[5 6]

A study of New Zealand Maoris followed up for 11 years

found a significant inverse relation between serum cholesterol concentration and total mortality in both men and women, and the association remained when deaths in the first two years of follow up were excluded from the analysis.[7] This paper examines the relation between serum cholesterol and mortality in New Zealand Maoris after a further period of follow up.

Subjects and methods

The study population of 630 people aged 25-74 years 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 and survey procedures have been described.[7 8] The population was followed up in 1968-9, 1974, and again in 1981. On each occasion the dead or alive state of every person was determined from necropsy reports, doctors' records, hospital records, death certificates, and relatives. The dead or alive state in 1981 was known for all but two of the original subjects, and the cause of death was determined using all available information.

Survival data were analysed with the Mantel-Haenszel method for survivorship data[9] and Cox's proportional hazards regression model[10] using SAS.[11] Significance was assessed at the 5% level of probability.

Results

Age specific baseline values of serum cholesterol concentration, systolic blood pressure, and the Quetelet index (weight/height^2) have been described.[7] The 17 year age specific mortality patterns were comparable to those observed after 11 years.[7] One third (33·9%) of the deaths were from cardiovascular disease and one fifth (20·7%) from cancer, similar to the national mortality patterns.[12]

Mantel-Haenszel analyses for survivorship data were used to relate grouped baseline cholesterol concentrations and all causes of death (table I). Within each 10 year age group except the oldest, and in both sexes, mortality was higher in the low cholesterol group than in the other two groups. As in the 11 year follow up, the age adjusted χ^2 tests showed a significantly higher mortality in the lowest cholesterol group for women ($\chi^2=11·19$; $p=0·004$) with an odds ratio (low cholesterol group to high cholesterol group) of 1·9. The odds ratio comparing the middle cholesterol group with the high cholesterol group was close to 1·0, suggesting the possibility of a non-linear relation between cholesterol and survival time.

TABLE I—*Observed and age adjusted expected numbers of deaths from all causes in Maori men and women with low, medium, and high baseline serum cholesterol concentrations*

Serum cholesterol concentration		Men	Women
Low (3·0-5·1 mmol/l)	No of subjects	71	106
	Observed deaths	31	44
	Expected deaths	20·8	28·4
	Observed/expected	1·5	1·5
Medium (5·1-5·8 mmol/l)	No of subjects	99	103
	Observed deaths	41	25
	Expected deaths	43·2	31·5
	Observed/expected	0·9	0·8
High (5·8-11·9 mmol/l)	No of subjects	144	101
	Observed deaths	49	35
	Expected deaths	56·9	44·1
	Observed/expected	0·9	0·8

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

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 still found in women in the lowest cholesterol group, as was also reported in the 11 year follow up. This excess remained significant after excluding deaths in the first five years of follow up. For men, however, the current analyses differed from the earlier ones, since there was only a marginally significant relation between serum cholesterol group and mortality in men ($\chi^2=5·72$; $p=0·057$; low to high odds ratio 1·7), which disappeared when deaths in the first two years of follow up were excluded.

Cox's proportional hazards regression analysis was used to examine the influence of cholesterol concentration on mortality when controlling for other variables. Table II shows the results of analyses with all causes of mortality and also deaths from cancer, cardiovascular disease, and "other" causes as the dependent variables and age, serum cholesterol concentration, systolic blood pressure, and Quetelet's index as the linear independent variables in the hazard function.

Age and systolic blood pressure were directly related to total mortality in men. For women, only age was directly related to total mortality, although serum cholesterol concentration was marginally inversely related ($p=0·051$). Risk ratios were estimated comparing the approximate 10th and 90th percentiles of serum cholesterol concentrations, as in the earlier report.[7] The non-significant risk ratios of total mortality at serum cholesterol concentrations of 4·14 to 6·73 mmol/l (160 to 260 mg/100 ml) when adjusted for age, systolic blood pressure, and Quetelet's index were 1·4 for men and 1·6 for women, which compared with 1·7 for men and 1·4 for women in the 11 year follow up. While the current regression coefficients and relative risks were comparable to those given in the earlier report, the now larger probability values were due to a calculation error in the earlier report.

The regression analyses were repeated after excluding all the deaths in the first two years of follow up, and the results were similar to those in table II, although the previously marginally significant association with cholesterol in women became unimportant ($p=0·160$). Regression analyses, specific to cause of death and whether excluding deaths in the first two years of follow up or not, showed a significant inverse relation between serum cholesterol concentration and mortality from cancer and also a significant inverse relation in women when considering mortality from "other" causes.

Since the Mantel-Haenszel analyses suggested a non-linear relation between serum cholesterol concentration and total mortality, simple non-linear proportional hazards regression models were investigated by including a squared cholesterol term (table III), a procedure adopted by other workers in logistic analyses of this relation.[5] Inclusion of a squared cholesterol term significantly improved predictive ability in the models for total mortality in women and "other" causes of mortality in both men and women.

Total mortality was significantly and non-linearly related to serum cholesterol concentration for women, with a similar but non-significant trend for men. For women the risk ratio of total mortality at serum cholesterol concentrations of 4·14 and 6·73 mmol/l, controlling for covariates as before, became 2·2. The inverse relation remained when deaths in the first two years, and five years, of follow up were excluded. The risk ratio dropped to 1·6 at five years. When considering cause specific mortality serum cholesterol concentration was found to be non-linearly related to mortality from "other" causes in both men

TABLE II—*Prediction of mortality in 630 Maori men and women (Cox's proportional hazards regression coefficients): linear models*

Variable	Cause of death						
	All causes		Cancer	Cardiovascular disease		"Other" causes	
	Men	Women	Men and women	Men	Women	Men	Women
Age	7·56***	8·15***	8·68***	10·01***	10·67***	8·45***	12·05***
Serum cholesterol concentration	−0·32	−0·48	−1·09*	−0·04	0·19	−0·40	−1·67***
Systolic blood pressure	1·22**	0·31	0·20	2·62***	0·61	0·56	0·83
Quetelet index	0·03	0·05	0·02	0·03	0·07	0·10	0·09
Relative risk†	1·4	1·6	3·0	1·0	0·8	1·5	5·3
Relative risk at 11 year follow up[7]	1·7	1·4	3·4	1·2	0·7	1·8	3·2

*p < 0·05; **p < 0·01; ***p < 0·001.
†Relative risk of serum cholesterol concentrations of 4·14:6·73 mmol/l (160:260 mg/100 ml) after controlling for all other variables in model.

and women, an association which remained when deaths in the first two years of follow up were excluded. In all the non-linear models a low cholesterol concentration implied an increased hazard.

TABLE III—*Prediction of mortality in 630 Maori men and women (Cox's proportional hazards regression coefficients): non-linear models*

Variable	Cause of death			
	All causes		"Other" causes	
	Men	Women	Men	Women
Age	7·62***	8·01***	8·64***	12·07***
Serum cholesterol concentration	−2·10*	−2·93**	−3·62**	−5·85**
Squared cholesterol value	0·35	0·51**	0·64**	0·94**
Systolic blood pressure	1·19**	0·38	0·47	0·92
Quetelet index	−0·02	0·11	0·00	0·14
Relative risk†	1·9	2·2	2·5	6·7

*$p<0.05$; **$p<0.01$; ***$p<0.001$.
†Relative risk of serum cholesterol concentrations of 4·14:6·73 mmol/l (160:260 mg/100 ml) after controlling for all other variables in model.

Discussion

This analysis of a 17 year follow up of New Zealand Maoris shows a strong inverse and non-linear relation between total mortality and serum cholesterol concentration in women but not in men. The association in women remained when all deaths in the first five years of follow up were removed to reduce the possibility of bias from early mortality in subjects already sick and with low initial serum cholesterol concentrations. The relation also remained when age, systolic blood pressure, and the Quetelet index were controlled in a life table regression analysis. When studying mortality from specific causes—cancer, cardiovascular disease, and all "other" causes—an inverse relation was found between serum cholesterol concentration and mortality from cancer in the pooled data and also between serum cholesterol concentration and mortality from "other" causes in both sexes, although the association in men was apparent only in the non-linear regression model.

The non-linear inverse relation in women between serum cholesterol concentration and total mortality was suggested by the Mantel-Haenszel analyses and confirmed by the proportional hazards regression analyses. Furthermore, non-linear models were appropriate for both men and women when analysing mortality from causes other than cancer or cardiovascular disease. In these three settings the relative risks between low and high serum cholesterol concentrations are appreciably larger than the estimates of relative risk obtained with the linear models. The form of the non-linear Cox models reported here was chosen for simplicity and the models were found to fit the data reasonably well when investigated graphically.[11] The models in table III show that inclusion of the squared cholesterol term serves to highlight the increasing severity of the hazard as serum cholesterol concentrations become low. Suggestive evidence of such a non-linear effect has been found in several other studies, not only for all causes of mortality[2 5 13] but also for mortality from cancer.[3 5 14–16] That a non-linear association between cholesterol and cancer mortality is not supported in this study may be due to the small numbers of deaths from cancer and, perhaps, to the relative mix of neoplasms.[6]

The non-linearity of some of the observed inverse relations between serum cholesterol concentration and mortality in the New Zealand Maori study population suggests that part of the apparent lack of consistency in this association in other published reports may be due to the use of only linear models in some studies. Inconsistency in other reports may also be partly due to the use of differing types of statistical models. We used the proportional hazards approach to survival data, which focuses on both the fact of survival or death and the actual or censored survival time. Logistic regression has been a favoured analysis tool in many studies but this underutilises the survival information when it focuses only on the fact of survival or death. In this study comparison of the logistic and proportional hazards analyses of all causes of mortality gave broadly similar results, but the probability values associated with the various regression coefficients were larger for the logistic models.

Several possible explanations of the inverse relation between cholesterol and all causes of mortality and mortality from cancer may be excluded by this study. The relation is not due to confounding by other variables such as blood pressure or body mass index. The role of competing risks may be excluded as an explanation of our results since a life table model, which considers only subjects alive during a given period, was used in the analysis.

It appears unlikely that the association with cancer found in this study can be explained by cancer causing a low cholesterol value shortly before diagnosis because the magnitudes of the relative risk estimates were not reduced when deaths in the first two years were excluded, supporting the findings of several other studies.[6 15 16] Nevertheless, the relative risk in the pooled data decreased from 3·0 to 2·4 after excluding deaths in the first five years. While this decrease is not substantial, the possible effect of cancer causing low cholesterol concentrations many years before diagnosis cannot be excluded. This has been suggested for some cancers in the Framingham study.[14]

Hence the relations shown for mortality appear to be real. The associations may be causal with hypocholesterolaemic plasma having a deleterious influence on plasma membrane fluidity, or the relations may be secondary to the association between retinol and cholesterol. Recent studies support the second explanation.[17 18]

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