

APOLIPOPROTEIN E ISOFORMS, SERUM CHOLESTEROL, AND CANCER

SIR,—It is unclear whether the relation between low serum cholesterol levels and cancer¹ is causal. In many studies occult tumour may have depressed cholesterol levels though in others the relation was found when serum cholesterol had been measured many years before the cancer was diagnosed. The relation is probably not explained by diet, because in the Seven Countries Study cohorts with widely different diets and corresponding differences in mean cholesterol levels experienced similar mean cancer rates.^{2,3} On the other hand, within each region cancer incidence was higher in men with a serum cholesterol in the lowest part of the cholesterol distribution for that country.³ Thus, naturally low cholesterol levels are sometimes associated with increased cancer risk.^{1,3}

Differences in the aminoacid sequence of apolipoprotein E (apo E) are major determinants of differences in plasma cholesterol levels within a population. Apo E has a key role in the clearance of cholesterol from plasma.⁴ The synthesis of apo E is under the control of three independent alleles, located at a single gene locus, coding for the major isoforms E-2, E-3, and E-4 with respective population frequencies of about 8, 77, and 15%.⁵ The homozygous E-3/E-3 is the most common phenotype encountered and E-2/E-2 is the least common. From apo E-2 to apo E-3, one cysteine residue is replaced by arginine, and from apo E-3 to apo E-4 another cysteine residue is replaced. As a result the avidity of apo E containing lipoproteins for lipoprotein receptors increases from apo E-2 to apo E-3 to apo E-4. In several populations,⁶⁻⁸ including the Finns and the Japanese (Dr G. Utermann, personal communication), the gradient in serum cholesterol levels in the population is associated with a gradient in apo E phenotype, E-2 being associated with lower serum low-density lipoprotein and total cholesterol levels than E-3 and E-4. Thus, if a naturally low cholesterol favours tumour growth, then subjects with the E-2/E-2 or E-2/E-3 phenotype should have an increased risk of cancer.

Unlike most other indices of lipid metabolism, apolipoprotein aminoacid sequences are not disturbed by disease, and the apo E phenotype found in a patient will have been present since birth. A comparison of apo E phenotypes in cancer patients with those in matched controls might thus shed light on the relation between low cholesterol and cancer. If it is causal then the E-2 allele should be more common among patients and E-3 and E-4 more common among controls. On the other hand, equal distribution of apo E phenotypes among cases and controls would suggest that the association between low cholesterol and cancer is spurious. Measurement of apo E phenotype by isoelectric focusing of plasma is a routine determination in lipid laboratories; epidemiologists interested in cholesterol and cancer should include it in their studies.

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1. McMichael AJ, Jensen OM, Parkin DM, Zaridze DG. Dietary and endogenous cholesterol and human cancer. *Epidemiol Rev* 1984; **6**: 192-216.
2. Keys A, Aravanis C, Blackburn H, et al. Serum cholesterol and cancer mortality in the seven countries study. *Am J Epidemiol* 1985; **121**: 870-83.
3. Katan MB. Effects of cholesterol-lowering diets on the risk for cancer and other non-cardiovascular diseases. In: Nestel PJ, et al, eds. *Atherosclerosis VII: Proceedings of the Seventh International Atherosclerosis Symposium*. Amsterdam: Elsevier, 1986.
4. Brown MS, Kovnanen PT, Goldstein JL. Regulation of plasma cholesterol by lipoprotein receptors. *Science* 1981; **212**: 628-35.
5. Utermann G, Steinmetz A, Weber W. Genetic control of human apolipoprotein E polymorphism: comparison of one- and two-dimensional techniques of isoprotein analysis. *Hum Genet* 1982; **60**: 344-51.
6. Utermann G, Kindermann I, Kaffarnik H, Steinmetz A. Apolipoprotein E phenotypes and hyperlipidemia. *Hum Genet* 1984; **65**: 232-36.
7. Robertson FW, Cumming AM. Effects of Apoprotein E Polymorphism on Serum Lipoprotein Concentration. *Arteriosclerosis* 1985; **5**: 283-92.
8. Utermann G. Genetic polymorphism of apolipoprotein E: impact on plasma lipoprotein metabolism. In: Crepaldi G, et al, eds. *Diabetes, obesity and hyperlipidemias III*. Amsterdam: Elsevier, 1985: 1-28.