# CHOLESTEROL (Group 3)

## A. Evidence for carcinogenicity to humans (*inadequate*)

Intake of dietary cholesterol was greater in premenopausal cases than controls in a case-control study of diet and breast cancer; however, this finding was not statistically significant, and the association was less strong than that with dietary fat[1]. In a reanalysis of the same data, dietary cholesterol did not have an effect independent of saturated fat intake[2]. Further, in a cohort study of 89 538 US nurses, there was no increased risk of breast cancer associated with dietary fat or dietary cholesterol[3]. Dietary cholesterol intake was greater in cases than in controls in a case-control study of colorectal cancer, but the risk ratios were lower than for saturated fat intake[4]. Risk ratios were also elevated for dietary cholesterol and colon cancer in a second case-control study, although they were lower for rectal cancer and risk ratios were elevated to a greater extent for dietary protein[5]. In a study in which cholesterol intake of Seventh-Day Adventists was compared with that of lacto-ovo-vegetarians and nonvegetarians, differences for colon cancer risk were not 'striking'[6]. However, a study using food disappearance data from 20 countries showed that, when dietary cholesterol was controlled for, the partial correlations of dietary fat and fibre with colon cancer mortality were no longer significant. Cross-classification showed a significant, main effect for cholesterol but not for fat or fibre[7].

Dietary cholesterol was associated with increased risk of lung cancer in a case-control study. The association was found in all subjects, in smoking subjects and in males, but not in females[8]. Dietary cholesterol was also found to be weakly associated with increased risk of bladder cancer in a further case-control study[9]. These studies involved the use of relatively restricted dietary questionnaires, and it was not possible to determine whether the association with dietary cholesterol was part of a stronger association with other dietary factors with which the intake of cholesterol is associated.

Dietary cholesterol was analysed in relation to cancer mortality in a ten-year follow-up of the Honolulu Heart Program in the USA. There was no significant association, but data for individual cancer sites were not reported[10].

The available data on serum cholesterol levels and cancer have been considered[11], and subsequently reported independently[12]. It was concluded that observational studies afford substantial evidence that preclinical cancer causes a lowering of blood cholesterol, and limited, but biologically plausible evidence that males with naturally low blood cholesterol levels are at increased risk of colon cancer. Since then, there have been reports of seven studies primarily related to follow-up of cohorts established for the study of cardiovascular disease[13-20]. A study of 4035 residents of California, USA, aged 40-89, showed no association between plasma cholesterol and cancer morbidity or mortality over a seven-year period for either men or women for any cancer site[13]. In a five-year follow-up of 10 940 participants in the Hypertension Detection and Follow-up Program in the USA, a small but statistically significant inverse relationship was found between baseline serum cholesterol level and cancer incidence. When cases diagnosed in the first two years were excluded, the association was similar in magnitude but no longer statistically significant. The numbers of

cases did not permit analysis by cancer site[14]. Up to six years of follow-up (mean, three years) were reported for 10 000 middle-aged men in the Malmö Preventive Program in Sweden[15]. Serum cholesterol was inversely related to cancer mortality (44 deaths) — a relationship seen also for the 25 cancer deaths that occurred more than 2.5 years after screening[15]. Serum urate levels at screening were correlated with early but not late (more than 2.5 years after screening) cancer mortality. As urate levels might indicate proliferation of cancer cells, the association of raised serum cholesterol with late deaths may be due to another mechanism than cancer present at the time of screening[16].

In the Busselton community study in Western Australia, 1564 subjects have been followed for 13 years. In men aged 60-74, but not in men aged 40-59 or in women, a negative association between serum cholesterol level and cancer mortality was found[17]. It was not indicated if the association persisted when early cancer deaths were excluded. In New Zealand, 630 Maoris aged 25-74 were followed for over 17 years. A significant inverse relationship between cancer mortality and serum cholesterol was found for men and women considered together. The relative risk in the pooled data, derived by comparing the approximate 10th and 90th percentiles of serum cholesterol concentration, decreased from 3.0 to 2.4 after excluding deaths in the first five years[18]. Fifteen years of follow-up of 11 325 healthy men aged 40-59 in the Seven Countries Study has also been reported. Among 477 cancer deaths five or more years after cholesterol measurement, there was a significant excess of deaths from lung cancer in the lower 20% of the cholesterol distribution in the populations. Nevertheless, regional comparisons of cancer mortality showed highest cancer rates in northern Europe, where the cholesterol levels were highest[19]. In contrast, in a cohort study in Sweden of 92 000 subjects less than 75 years old examined in 1963-1965 and followed by linkage to the Swedish Cancer Registry until 1979, there was a positive association between serum cholesterol level and risk of rectal cancer in men. When serum cholesterol and $\beta$-lipoprotein levels were considered together, the risk for men with elevated serum cholesterol ($\geqslant$ 2.5 g/l) and $\beta$-lipoprotein ($\geqslant$ 2.2 g/l), relative to those with lower levels, was 1.6 for colon cancer (95% confidence interval, 1.2-2.2) and 1.7 for rectal cancer (1.2-2.4)[20]. In the largest study so far reported, the incidence of cancer was determined in 160 135 male and female members of a prepaid health plan in California, USA, for whom serum cholesterol levels were determined as part of a multiphasic health examination. Follow-up was for eight to 16 years. No consistent association of low cholesterol with cancer incidence was found, although cancer incidence was highest in those in the lowest quintile of serum cholesterol levels in the first two years after the measurement[21].

Five case-control studies have been reported in which serum cholesterol was assessed[22-26]. A case-control study of 37 cases of primary brain tumours and two controls per case found elevated levels of serum cholesterol in the cases compared to the controls. The difference was not reduced by controlling for potential confounders (including weight)[22]. In the second study, serum cholesterol was measured in 244 patients with adenomatous polyps of the colon, 182 patients with Dukes' A or B colon cancer and 688 hospital controls. The mean serum cholesterol levels were lower for the Dukes' B cases, accounting for most of the difference. There was no difference in mean levels between those with adenomatous polyps

and their controls. After adjustment for nutritional status using serum albumin level, however, there was no difference between any of the groups[23]. In a nested case-control study within a cohort, 245 newly-diagnosed cases of large-bowel cancer in members of a prepaid health care plan and five matched controls for each case were compared, on the basis of serum cholesterol measurements performed as part of a multiphasic health examination prior to the diagnosis of the cases. No direct or inverse relationship between serum cholesterol and large-bowel cancer was found[24]. A fourth case-control study was based on a cohort of 18 995 people examined at a health centre between 1970-1973, where medical records were found for 100 of 176 cancer cases who had died by 1979, for 393 of 900 control subjects still alive in 1979, and for 69 of 153 people who had died of cardiovascular disease in the same period. Serum cholesterol levels in the cancer cases were significantly lower than those in controls only in the two-year period prior to death and were inconsistently depressed three to six or seven to 16 years prior to death[25]. In a fifth study, a positive association was found between serum cholesterol levels and the prevalence of adenomatous polyps at colonoscopy performed in 842 patients. The odds ratio for large-bowel adenoma between the highest and lowest quintiles of serum cholesterol was 1.9 (95% confidence interval, 1.1-3.5) after adjustment for age and 2.0 (1.1-3.6) after adjustment for body-mass index[26]. Serum cholesterol was assessed in relation to disease-free survival of 279 colon cancer patients. There was an 11% (nonsignificant) lower cumulative disease-free survival at five years in those with serum cholesterol levels below the median than in those with levels above the median[27]. In a further study, family history of cancer was found to be positively associated with serum cholesterol levels in young adults[28].

Thus, although studies of cohorts assembled to study cardiovascular disease risk continue to show associations of low serum cholesterol with cancer incidence and mortality, the studies designed specifically to assess the relationship do not in general confirm the association. When site-specific data are available, they are not consistent. Nevertheless, a plausible mechanism exists — namely, that those who maintain a low serum cholesterol in face of a possibly elevated fat intake increase the concentration of cholesterol metabolites (especially bile acids) in the intestine and thus increase their risk for colon cancer[29].

### B. Evidence for carcinogenicity to animals (*inadequate*)

Cholesterol was tested for carcinogenicity in mice by administration in the diet, by subcutaneous administration and by bladder implantation. These studies were all inadequate for evaluation. Cholesterol has also been tested in combination with various carcinogens, but the results were inadequate to assess the carcinogenesis-enhancing potential of the compound[11]. Feeding of cholesterol to rats exposed to a mammary carcinogen did not affect the incidence of mammary tumours[30], while feeding after administration of a colon carcinogen resulted in a lower incidence of colon tumours[31].

### C. Other relevant data

No data were available on the genetic and related effects of cholesterol in humans. It did not transform Syrian hamster embryo cells and was not mutagenic to bacteria[32].

## References

[1]Miller, A.B., Kelley, A., Choi, N.W., Matthews, V., Morgan, R.W., Munan, L., Burch, J.D., Feather, J., Howe, G.R. & Jain, M. (1978) A study of diet and breast cancer. *Am. J. Epidemiol., 107*, 499-509

[2]Howe, G.R. (1985) The use of polytomous dual response data to increase power in case-control studies: an application to the association between dietary fat and breast cancer. *J. chron. Dis., 38*, 663-670

[3]Willett, W.C., Stampfer, M.J., Colditz, G.A., Rosner, B.A., Hennekens, C.H. & Speizer, F.E. (1987) Dietary fat and the risk of breast cancer. *New Engl. J. Med., 316*, 22-28

[4]Jain, M., Cook, G.M., Davis, F.G., Grace, M.G., Howe, G.R. & Miller, A.B. (1980) A case-control study of diet and colo-rectal cancer. *Int. J. Cancer, 26*, 757-768

[5]Potter, J.D. & McMichael, A.J. (1986) Diet and cancer of the colon and rectum: a case-control study. *J. natl Cancer Inst., 76*, 557-569

[6]Turjman, N., Calkins, B., Phillips, R., Goodman, G.T. & Nair, P.P. (1984) Dietary intake of plant sterols and cholesterol among population groups at different risks for colon cancer (Abstract No. 3330). *Fed. Proc., 43*, 855

[7]Liu, K., Stamler, J., Moss, D., Garside, D., Persky, V. & Soltero, I. (1979) Dietary cholesterol, fat and fibre, and colon-cancer mortality. An analysis of international data. *Lancet, ii*, 782-785

[8]Hinds, M.W., Kolonel, L.N., Hankin, J.H. & Lee, J. (1983) Dietary cholesterol and lung cancer risk in a multiethnic population in Hawaii. *Int. J. Cancer, 32*, 727-732

[9]Risch, H.A., Burch, J.D., Miller, A.B., Hill, G.B., Steele, R. & Howe, G.R. (1987) Dietary factors and the incidence of cancer of the urinary bladder. *Am. J. Epidemiol.* (in press)

[10]McGee, D., Reed, D., Stemmerman, G., Rhoads, G., Yano, K. & Feinleib, M. (1985) The relationship of dietary fat and cholesterol to mortality in 10 years: the Honolulu Heart Program. *Int. J. Epidemiol., 14*, 97-105

[11]*IARC Monographs, 31*, 95-132, 1983

[12]McMichael, A.J., Jensen, O.M., Parkin, D.M. & Zaridze, D.G. (1984) Dietary and endogenous cholesterol and human cancer. *Epidemiol. Rev., 6*, 192-216

[13]Wingard, D.L., Criqui, M.H., Holdbook, M.J. & Barrett-Connor, E. (1984) Plasma cholesterol and cancer morbidity and mortality in an adult community. *J. chron. Dis., 37*, 401-406

[14]Morris, D.L., Borhani, N.O., Fitzsimons, E., Hardy, R.J., Hawkins, C.M., Kraus, J.F., Labarthe, D.R., Mastbaum, L. & Payne, G.H. (1983) Serum cholesterol and cancer in the hypertension detection and follow-up program. *Cancer, 52*, 1754-1759

[15]Petersson, B. & Trell, E. (1983) Premature mortality in middle-aged men: serum cholesterol as risk factor. *Klin. Wochenschr., 63*, 795-801

[16]Petersson, B. & Trell, E. (1983) Raised serum urate concentration as risk factor for premature mortality in middle aged men: relation to death from cancer. *Br. med. J., 287*, 7-9

[17]Cullen, K., Stenhouse, N.S., Wearne, K.L. & Welborn, T.A. (1983) Multiple regression analysis of risk factors for cardiovascular disease and cancer mortality in Busselton, Western Australia — 13-year study. *J. chron. Dis., 36*, 371-377

[18]Salmond, C.E., Beaglehole, R. & Prior, I.A.M. (1985) Are low cholesterol values associated with excess mortality? *Br. med. J., 290*, 422-424

[19]Keys, A., Aravanis, C., Blackburn, H., Buzina, R., Dontas, A.S., Fidanza, F., Karvonen, M.J., Menotti, A., Nedeljkovič, S., Punsar, S. & Toshima, H. (1985) Serum cholesterol and cancer mortality in the Seven Countries Study. *Am. J. Epidemiol., 121*, 870-883

[20]Törnberg, S.A., Holm, L.-E., Cartensen, J.M. & Eklund, G.A. (1986) Risks of cancer of the colon and rectum in relation to serum cholesterol and beta-lipoprotein. *New Engl. J. Med., 315*, 1629-1633

[21]Hiatt, R.A. & Fireman, B.H. (1986) Serum cholesterol and the incidence of cancer in a large cohort. *J. chron. Dis., 39*, 861-870

[22]Abramson, Z.H. & Kark, J.D. (1985) Serum cholesterol and primary brain tumours: a case-control study. *Br. J. Cancer, 52*, 93-98

[23]Neugut, A.I., Johnsen, C.M. & Fink, D.J. (1986) Serum cholesterol levels in adenomatous polyps and cancer of the colon. A case-control study. *J. Am. med. Assoc., 255*, 365-367

[24]Sidney, S., Friedman, G.D. & Hiatt, R.A. (1986) Serum cholesterol and large bowel cancer. A case-control study. *Am. J. Epidemiol., 124*, 33-38

[25]Gerhardsson, M., Rosenqvist, U., Ahlbom, A. & Carlson, L.A. (1986) Serum cholesterol and cancer — a retrospective case-control study. *Int. J. Epidemiol., 15*, 155-159

[26]Mannes, G.A., Maier, A., Thieme, C., Wiebecke, B. & Paumgartner, G. (1986) Relation between the frequency of colorectal adenoma and the serum cholesterol level. *New Engl. J. Med., 315*, 1634-1638

[27]Tartter, P.I., Slater, G., Papatestas, A.E. & Aufses, A.H., Jr (1984) Cholesterol, weight, height, Quetelet's index, and colon cancer recurrence. *J. surg. Oncol., 27*, 232-235

[28]Reed, T., Wagener, D.K., Donahue, R.P. & Kuller, L.H. (1986) Family history of cancer related to cholesterol level in young adults. *Genet. Epidemiol., 3*, 63-71

[29]Broitman, S.A. (1981) Cholesterol excretion and colon cancer. *Cancer Res., 41*, 3738-3740

[30]Cohen, L.A. & Chan, P.-C. (1982) Dietary cholesterol and experimental mammary cancer development. *Nutr. Cancer, 4*, 99-106

[31]Cohen, B.I., Raicht, R.F. & Fazzini, E. (1982) Reduction of *N*-methyl-*N*-nitrosourea-induced colon tumors in the rat by cholesterol. *Cancer Res., 42*, 5050-5052

[32]*IARC Monographs, Suppl. 6*, 166-167, 1987