

Letter to the Editors

PLASMA CHOLESTEROL AND *IN SITU* CERVICAL CANCER: AN AUSTRALIAN CASE-CONTROL STUDY

Dietary cholesterol has been hypothesized as a cocarcinogen for human colon cancer [1] but other studies have indicated an inverse association between plasma cholesterol and risk of lung, stomach, and colon cancer [2]. Whether this is a true aetiological link or the result of a preclinical metabolic change in a patient with cancer has been questioned [3]. Recently, the relationship between serum cholesterol and the incidence of cancer was examined in a cohort of 160,135 men and women in California [4]. Cancer incidence in the first 2 years after the cholesterol measurement was consistently higher among persons whose cholesterol levels were in the lowest quintile. Incidence after this 2 year period was generally unrelated to cholesterol level, thus supporting the impression that this association was reflecting a preclinical manifestation of cancer [5]. However there were two exceptions to this pattern. Lymphoma in men and cervical cancer in women had significantly elevated risks in the lowest quintile which persisted beyond the first 2 years of follow-up. In particular, for cervical cancer after exclusion of the first 2 years of follow-up, the RR's from lowest to highest quintile were: 1.8, 1.6, 1.4, 1.6, 1.0.

An hypothesis previously put forward to explain a possible etiologic relationship between low serum cholesterol and elevated cancer risks was that such an association could be secondary to a protective effect on cancer risk of either retinol or carotene. One report noted a correlation between retinol and cholesterol (partial correlation coefficient 0.32 in white females) [6] and another a similar correlation between beta-carotene and cholesterol (partial correlation coefficient 0.35) [7].

We had the opportunity to examine both the relationship between plasma cholesterol and

cervical cancer risk and the influence on this issue of plasma micronutrients in a case-control study of *in situ* cervical cancer in Sydney, Australia. The study was a matched community based case-control design with 117 cases and 196 controls matched on age and residential area. The methods have been described in detail elsewhere [8]. The general response rate was 70% for cases and 69% for controls and of these 76% of the cases ($n = 89$) and 69% of the controls ($n = 136$) had plasma cholesterol, retinol and beta-carotene measured. Both dietary and plasma retinol showed no effect on *in situ* cervical cancer risk but beta-carotene showed a marked protective effect (plasma beta-carotene reduced risk from top to bottom quartile by 80%) [8]. Cholesterol was measured in duplicate by a standardized automated method at Royal Prince Alfred Hospital biochemistry laboratories. Conditional logistic regression was used to compare cases and individually matched controls with respect to dietary and blood measures [9]. The dietary and plasma nutrient indices were categorized into quartiles for these analyses. Tests for trend were made by assigning each quartile a score and then treating the variable as continuous in the regression model.

Table 1 presents the RRs by quartile of plasma cholesterol. Although there was no evidence of a trend in risk across the measurement quartiles, those in the lowest quartile had a 60% increased risk of cervical cancer as compared to those with plasma cholesterol greater than 6 mmol/l. When adjusted for the standard risk factors (number of sexual partners, age at first intercourse, smoking and oral contraceptive use), this effect increased to a 2.2-fold increase in risk and was further increased when risks were adjusted for plasma retinol and beta-

Table 1. Crude and adjusted conditional maximum likelihood estimates of relative risk and 95% CI for plasma cholesterol

Cholesterol mM/litre	Cases <i>n</i> = 89	Controls <i>n</i> = 139	Crude RR	Adjusted RR*	Adjusted RR†	95% CI
Q ₁ ≥ 6	18	32	1.0	1.0	1.0	
Q ₂ 5 < 6	23	38	1.2	1.5	2.1	(0.6-7.9)
Q ₃ 4 < 5	22	36	0.8	0.6	0.6	(0.2-2.0)
Q ₄ 0 < 4	26	30	1.6	2.2	2.8	(0.7-11.5)
Test for trend <i>p</i> = 0.6 <i>p</i> = 0.6 <i>p</i> = 0.6						

*Adjusted for number of sexual partners, age at first intercourse, smoking and oral contraceptive use.

†Adjusted for plasma beta-carotene and retinol and established risk factors, i.e. number of sexual partners, age at first intercourse, smoking and oral contraceptive use.

Table 2. Crude and adjusted conditional maximum dietary likelihood estimates of relative risk and 95% CI for cholesterol

Cholesterol mg/day	Cases <i>n</i> = 116	Controls <i>n</i> = 192	Crude RR	Adjusted RR*	Adjusted RR†	95% CI
Q ₁ < 251	26	51	1.0	1.0	1.0	
Q ₂ 251-356	30	47	1.2	1.3	1.4	(0.6-3.3)
Q ₃ 357-495	28	29	1.1	1.8	0.8	(0.4-2.0)
Q ₄ ≥ 496	32	45	1.3	1.1	1.2	(0.5-2.9)
Test for trend <i>p</i> = 0.4 <i>p</i> = 0.9 <i>p</i> = 1.0						

*Adjusted for number of sexual partners, age at first intercourse, smoking, and oral contraceptive use.

†Adjusted for dietary beta-carotene, dietary vitamin C, and established risk factors, i.e. number of sexual partners, age at first intercourse, smoking and oral contraceptive use.

carotene (<4 mmol/l = RR 2.8). Again, the linear trend was not significant as the third quartile did not show an increased risk. There was little correlation between either plasma retinol:cholesterol (0.03) or plasma beta-carotene:cholesterol (0.07) in these data. When dietary cholesterol was examined, no effect was seen (Table 2).

The findings of this study provide some support for an elevated risk of cervical cancer among those with a low plasma cholesterol, with the data exhibiting an irregular trend similar to that in the California study. Our data do not support the explanation that the effect with low cholesterol is either a retinol or carotene effect, as adjustment for these variables strengthened the inverse association. The data from this study of *in situ* cancer coupled with the results of the California cohort using cholesterol measurements at least 2 years prior to cancer diagnosis, indicate that if the lowering of cholesterol levels is a pre-clinical manifestation of cancer, it must happen at a very early stage of cancer progression. Alternative explanations could include confounding by some currently unknown lifestyle characteristic of women with low cholesterol that might place them at el-

evated risk of cervical cancer, or biological relationships such as changes in immunologic function, which have been related to reduced cholesterol levels [10].

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