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# RISK OF STOMACH CANCER IN ASSOCIATION WITH SERUM CHOLESTEROL AND BETA-LIPOPROTEIN

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**Abstract**

The relation between serum levels of cholesterol and beta-lipoprotein (BLP) and stomach cancer risk was studied in a Swedish cohort of 92710 individuals. The cohort was examined with a single measurement of cholesterol and BLP between 1963 and 1965 and followed up in the Swedish Cancer Registry until 1983. During the follow-up period 576 stomach cancers were reported. The risk of stomach cancer was negatively correlated to serum levels of cholesterol with a relative risk (RR) of 0.85 for every 40 mg/dl increase of cholesterol ($p<0.001$) and to BLP with an RR of 0.90 for every 3 units increase of BLP ($p<0.01$) when analysed one at a time. In a multiple regression analysis, however, only the relation to cholesterol remained statistically significant. The risk association seemed to be most pronounced between the third and fifth years of follow-up.

*Key words:* Stomach neoplasms; cancer, cholesterol, beta-lipoprotein, cohort study.

Globally, stomach cancer is the most frequent malignant tumour (19). In the Western world, however, the incidence of stomach cancer has declined over several decades. From having been one of the major cancer sites in the Swedish population it is now the fifth commonest cancer among men and the seventh among women (18).

There are geographical variations in stomach cancer rates e.g. with high rates in Japan and low rates in the United States (28). There are also variations among ethnic and racial groups, with blacks having a higher incidence than whites in the United States and Japanese immigrants having the highest rates (16). In Sweden, stomach cancer rate is higher in lower socioeconomic groups (27).

The etiology of stomach cancer is not known. Correlations have been reported between stomach cancer and nitrate–nitrite compounds, deficiency of vitamins A, C, or E, smoked and salted food (3, 20, 24). An association between stomach cancer risk and high carbohydrate intake could indirectly reflect the intake of other nutrients, e.g. protein, fat or vitamins (5, 17). The intake of carbohydrate has been shown to be inversely associated with protein and fat intake, and according to ARMSTRONG & DOLL (1) stomach cancer was negatively correlated to per capita fat intake. In a case–control study milk consumption was negatively correlated to stomach cancer risk (7), although no direct association between low fat intake and stomach cancer risk at an individual level has been reported (9). However, a low fat intake over a long time period decreases the serum levels of cholesterol (8), and KATO & SHIMIZU (12) found a tendency towards a negative correlation between serum levels of cholesterol and stomach cancer in a population of 14700 individuals followed for 17 years.

The purpose of the present study was to analyse the relation between stomach cancer incidence and serum levels of cholesterol and BLP in a large Swedish cohort followed up for 18–20 years.

## Material and Methods

Between 1963 and 1965, 97027 persons from 4 districts in the central part of Sweden took part in a general health screening (21). The present study was limited to the 92710 persons less than 75 years of age because of the high proportion of non-participants in the older group. The mean age at the time of examination was 48 years in both sexes (range 17–74 years).

Twelve serum variables including cholesterol and BLP were analysed for each individual with an automated laboratory in Stockholm (10). The blood samples were not

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taken during fasting conditions. The serum analyses were made spectrophotometrically according to a modified Liebermann-Burchard method of cholesterol measurements described by ZAK et coll. (29) and a method for BLP by BURSTEIN & SAMAILLE (2). BLP was recorded in units; one unit corresponds to 0.18 g/l when comparing with electrophoresis methods. No data on tobacco, alcohol consumption or diet were available.

The mean ± SD serum level of cholesterol was 252±41 mg/100 ml (6.5±1.1 mmol/l) in the total cohort, 249±39 mg/100 ml (6.4±1.0 mmol/l) in men, and 256±43 mg/100 ml (6.6±1.1 mmol/l) in women. The mean ± SD level of BLP was 12±3.3 units (2.2±0.6 g/l) in each sex. The correlation coefficient between serum cholesterol and BLP was 0.48.

The cohort was matched with the Swedish Cancer Registry (SCR) between 1958 and 1983, to search for all reports of stomach cancer in the cohort. The SCR is nationwide and collects reports on newly diagnosed malignant tumours from physicians as well as from pathologists. Thus most cases are reported by at least 2 independent sources. Approximately 95% of all stomach cancers are reported to the SCR (15). Each person in Sweden is given a unique identification number which was the basis for the record-linkage. The identification number consists of 10 digits, i.e. year, month and day of birth, supplemented with digits indicating region and number sequence of birth, sex, and one control digit. The numbers are not affected by possible changes in names.

Deaths occurring during the follow-up period were identified by a record-linkage with the nationwide Swedish Cause of Death Register, which contains reports on all deaths in Sweden. In the analysis, each subject was considered to be at risk from the time of examination until diagnosis of stomach cancer, death, or December 31, 1983. Cases of stomach cancer reported to SCR before the date of the screening examination were not included in the analyses.

The proportional hazards regression method by Cox (4) was used to compute RR estimates, 95% confidence intervals (CI) and two-tailed tests of statistical significance of relationships between variables studied and stomach cancer incidence. All regression models were adjusted by sex, age at examination (five-year groups), and district using a stratified version of Cox' regression method (6).

## Results

During the follow-up period, 576 stomach cancers in the cohort were reported to the SCR. The person-years were 1 605 184 and the stomach cancer incidence was 0.36 per 1 000 person-years. The age and sex specific incidence rates are shown in Table 1. The mean age at cancer diagnosis was 69 years and the mean time period from screening examination to cancer diagnosis was 10 years.

**Table 1**

*Incidence of stomach cancer by age and sex in a cohort of 92 710 Swedish men and women followed for 20 years*

| Age, years | Men | | Women | |
|---|---|---|---|---|
| | No. of cases | Incidence per 1 000 person-years | No. of cases | Incidence per 1 000 person-years |
| −49 | 13 | 0.05 | 13 | 0.05 |
| 50–59 | 43 | 0.21 | 26 | 0.13 |
| 60–69 | 123 | 0.68 | 55 | 0.29 |
| 70–79 | 145 | 1.44 | 86 | 0.72 |
| ≥80 | 33 | 1.70 | 39 | 1.43 |
| Total | 357 | 0.46 | 219 | 0.26 |

**Table 2**

*Numbers of stomach cancer and stomach cancer incidence per 1 000 person-years of follow-up by serum cholesterol and BLP. Rates are standardized for age, sex and district*

| | No. of cancers | Person-year of follow-up | Standardized rate |
|---|---|---|---|
| Cholesterol, mg/100 ml | | | |
| <220 | 118 | 315 549 | 0.46 |
| 220–244 | 120 | 370 210 | 0.35 |
| 245–269 | 148 | 400 474 | 0.36 |
| 270–294 | 114 | 292 696 | 0.35 |
| >294 | 76 | 226 255 | 0.28 |
| BLP, units | | | |
| <10 | 119 | 353 223 | 0.42 |
| 10–11 | 138 | 440 831 | 0.34 |
| 12–13 | 132 | 350 475 | 0.37 |
| 14–15 | 114 | 237 186 | 0.41 |
| >15 | 73 | 223 469 | 0.26 |
| Total | 576 | 1 605 184 | 0.36 |

The age and sex standardized incidence rate decreased from 0.46 for those having a cholesterol level <220 mg/100 ml to 0.28 for those having >294 mg/100 ml (Table 2). The risk of stomach cancer in the present cohort was significantly negatively correlated to serum cholesterol (Table 3). For every 40 mg/100 ml (i.e. SD) increase in serum cholesterol level the cancer risk decreased by 15%. The correlation was statistically significant for both men and women when analysed separately.

Increased serum BLP levels were also linked with a decreased risk of stomach cancer (Tables 2 and 3). The relation to BLP was, however, not significant when controlling for serum cholesterol (Table 4).

The risk of stomach cancer associated with serum cholesterol level varied during the years of follow-up (Table 5). The risk was lowest between the third and the fifth year of follow-up. The difference in risk levels were statistically significant ($p<0.05$) when comparing year 3 to 5 of follow-up with the first 2 years.

**Table 3**

*Risk of stomach cancer in relation to serum cholesterol and BLP in 92 710 Swedish men and women. All estimates were adjusted for age, sex and district (*p<0.05; **p<0.01; ***p<0.001)*

| Sex | No. of cancer cases | RR associated with 40 mg/100 ml increase in serum cholesterol | 95 % CI | RR associated with 3 units increase in serum BLP | 95 % CI |
|---|---|---|---|---|---|
| Men | 357 | 0.87* | 0.78–0.97 | 0.90* | 0.81–1.00 |
| Women | 219 | 0.83* | 0.73–0.94 | 0.90 | 0.79–1.02 |
| Total | 576 | 0.85*** | 0.78–0.93 | 0.90** | 0.83–0.97 |

**Table 4**

*Results of Cox's multiple regression analysis of the relation between stomach cancer risk and serum levels of cholesterol and BLP in 92 710 Swedish men and women (**p<0.01)*

| Variable | RR | 95 % CI | RR associated with |
|---|---|---|---|
| Cholesterol | 0.87** | 0.79–0.96 | 40 mg/100 ml increase |
| BLP | 0.95 | 0.87–1.04 | 3 units increase |

**Table 5**

*Risk of stomach cancer in relation to serum cholesterol in different periods of follow-up (*p<0.05; ***p<0.001)*

| Years of follow-up | No. of cases | RR associated with 40 mg/100 ml increase in serum cholesterol | 95 % CI |
|---|---|---|---|
| 1–2 | 53 | 1.04 | 0.80–1.35 |
| 3–5 | 92 | 0.70*** | 0.57–0.87 |
| 6–10 | 134 | 0.83* | 0.69–0.99 |
| 11–15 | 144 | 0.84* | 0.71–0.99 |
| ≥16 | 153 | 0.91 | 0.78–1.08 |

## Discussion

A negative correlation between serum cholesterol level and stomach cancer risk was observed in the present cohort. The risk was the lowest from the third to the fifth year of follow-up. The samples were not taken during fasting conditions, which, according to KATAN & BEYNEN (11), does not affect the serum cholesterol values.

The negative correlation between stomach cancer and serum levels of cholesterol in this cohort is in agreement with the results from the study of KATO & SHIMIZU (12). These findings do not necessarily imply a causal relationship but rather other mechanisms. A high intake of carbohydrate is known to correlate to low intake of proteins and fat. A low fat intake over a long time period decreases the serum levels of cholesterol (9). The high stomach cancer risk among persons with low cholesterol levels could reflect a low intake of fat or other nutrients, e.g. vitamin A or beta-karoten (22). MARENAH et coll. (14) suggested that an association between low serum cholesterol and cancer may be secondary to a relation between low retinoid concentrations and cancer.

In the present cohort the correlation between serum cholesterol level and the RR of colorectal cancer was positive, i.e. the risk of stomach cancer and colorectal cancer were correlated to cholesterol in inverse manners (25, 26). This is in agreement with record-linkage studies of stomach cancer patients in Denmark and Finland showing decreased risk of cancer of the colon and the rectum (13, 23). There was no statistically significant correlation between BLP and stomach cancer risk when controlling for cholesterol level. However, as the lower limit of the CI equals 0.87, the data do not contradict a possible relation also to BLP. The study is based on only one measurement of the variables studied and do not include data on stability over time and measurement errors. Non-differential misclassification would, however, tend to reduce any associations between the studied variables and cancer risks.

Why the correlation between serum cholesterol level and stomach cancer risk tended to be most pronounced between year 3 to 5 of the follow-up period is not clear. A cholesterol lowering effect of an undiagnosed cancer could be expected to result in a negative correlation already within the first 2 years of follow-up. There were no differences between men and women in RR of stomach cancer, neither in relation to serum cholesterol nor BLP levels.

The incidence of stomach cancer has declined in Sweden as a whole whereas the incidence of colorectal cancer is almost stable or slowly increasing. The annual decline of stomach cancer was about 3 % from 1958 to 1983 (18), a trend that is more likely to be explained by other factors rather than an increment of serum cholesterol alone.

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