Cancer, Vitamins, and Plasma Lipids: Prospective Basel Study[1,2]

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ABSTRACT—In the Basel study (BS) (1960-73) on cardiovascular and peripheral arterial diseases, a mortality follow-up was completed for the period 1965-80. Of the 4,224 men at risk for these diseases, 531 died. The causes of death were established from the death certificates and classified into 8 groups. For each case 2 age- and sex-matched controls were selected and compared with the corresponding cases with regard to the various variables obtained at the three examinations (1960, 1965, 1971). This report dealt with cancer mortality, plasma lipids, plasma vitamins, alcohol and cigarette consumption, and intake of milk and citrus fruits. The results were all obtained at the second follow-up examination (BS III, 1971-73). Cancer of the lung, stomach, large bowel, and all other sites were treated separately. The average follow-up from BS III until death varied from 3.7 years (other sites) to 4.9 years (cancer of the lung). Of 129 cancer deaths, the highest incidence was found for cancer of the lung (38) followed by stomach (19) and large bowel, (15) and the remainder (57) was for other sites. Plasma lipids did not differ significantly among cases and controls. However, the lowest values were observed in colorectal cancer and gastric carcinoma (mean cholesterol, 213 mg/dl). β-Carotene was significantly lower in cancer cases of the lung than in controls (14.8 μg/dl vs. 23.7; $P<.05$). It was also low in gastric cancer cases (13.0 μg/dl). Vitamin A was below average only in cases with gastric cancer (difference due to the small number not significant). Vitamin C was consistently lower in cancer cases than in controls. The lowest value was found for cancer of the stomach and corresponded to a below-average consumption of citrus fruits. Vitamin E was low in cancer of the colon. Plasma lipids correlated strongly with vitamin E ($r=0.5$) and to a lesser extent with vitamin A ($r=0.25$). β-Carotene correlated poorly with β-lipoproteins (low-density and very low-density lipoproteins) but significantly with total cholesterol. Smoking was inversely related, as was alcohol consumption, to the β-carotene level. From these results, the conclusion was that vitamins influence carcinogenesis in humans.—JNCI 1984; 73:1463-1468.

The mortality from many diseases has changed profoundly during the past decades. This finding holds true not only for infectious diseases but also for chronic diseases, such as cardiovascular diseases (*1*) and some cancers. In particular, cancer of the stomach has declined whereas the incidence of cancer of the lung is still increasing in Switzerland (*2*), and a lesser increase in carcinoma of the large bowel still is observed in males. These changes are obviously related to environmental factors operating through mechanisms of atherogenesis or carcinogenesis, which are at best only partly known at present.

Epidemiologic research has clearly established the concept of cardiovascular risk factors. Modification of risk factors can subsequently change disease incidence (*3, 4*). Some risk factors for cardiovascular disease, such as cigarette smoking, correlate also with cancer. Others, such as hypertension, do not appear to contribute substantially to cancer risk. Intriguingly, plasma cholesterol is related in a complex way to cancer: A low cholesterol concentration appears to increase the risk of cancer of the colon (*5*), whereas eating habits that maintain high plasma cholesterol values correlate with the incidence of cancer of the large bowel (*6*).

It was shown recently that low vitamin A and β-carotene plasma concentrations predict certain cancers, and a correlation between low vitamin A levels and stomach cancer has been suspected for several years (*7, 8*).

The mortality follow-up of the BS (*9*) allows us to address these questions because in the last follow-up examination (1971-73) a survey was made of certain eating habits as the plasma vitamin concentrations were measured. The BS began in 1960 with particular emphasis on peripheral vascular disease. Healthy employees, 15-60 years of age, of the pharmaceutical and chemical companies in Basel were recruited. In the base-line examination (1960-62) 4,858 men and 1,471 women took part. The cohort was re-investigated in 1965 (BS II) and 1971 (BS III). A complete mortality follow-up from 1965-80 was completed recently (*10*).

For mortality follow-up, the decision was made to include only the cohort that participated in the second and/or third follow-up examination because of a substantial drop-out after the base-line examination and, more importantly, to exclude persons already afflicted by disease. Due to few cases among women, the analysis was restricted to the male cohort only. In this report the results pertinent to cancer, vitamins, and serum lipids are presented.

The BS is the only prospective Swiss study in which data on risk factors, vitamins, and mortality are available. Despite the selection introduced by voluntary participation, a comparison of causes of death shows that the

ABBREVIATIONS USED: BS=Basel study; HDL=high-density lipoprotein; OD=optical density.

[1] Presented at the Vitamin A and Cancer Prevention Conference sponsored by the Malnutrition Panel, U.S.-Japan Cooperative Medical Science Program of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, and the National Cancer Institute on February 28-29, 1984, at the National Institutes of Health, Bethesda, Md.

[2] Supported in part by a grant from the regional Krebsliga beider Basel.

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[6] We thank Dr. Salkeld, F. Hoffmann-La Roche & Co. Ltd., for his assistance in the preparation of the manuscript and Mrs. H. Nann for her secretarial work.

TABLE 1.—*BS mortality follow-up (men only)*

Investigation	Population at risk	Death	Autopsy
BS II: 1965	4,224	531	315
BS III: 1971	3,756	322	185

relative distribution of cancer and cardiovascular disease is comparable to that of the total Swiss population (*10*). Thus our findings are representative for a male Swiss urban industrialized population. However, the total mortality was one-third lower than that of the Swiss population of the same age.

METHODS

Mortality follow-up.—For analysis of the mortality among the BS cohort over the period 1965-80, the living status was established for all participants who took part in the second (1965-67, BS II) and/or the third investigation (1971-73, BS III). A complete follow-up was possible on all 4,224 men at risk for cardiovascular and peripheral arterial diseases. The causes of death were established according to the death certificates. The cancer registry[7] and autopsy data[7] (table 1) allowed an additional control of the death certificate. The death certificate was corrected according to the autopsy and cancer registry data. In instances where a tumor coexisted but death occurred due to a cardiovascular cause or other causes, these cases were classified with the cancer group. The grouping used for analysis of the data is shown in table 2.

Selection of controls.—For each case, 2 age- and sex-matched controls who were still living in 1980 were selected by a random procedure from the BS II file. The data of the controls were compared with those of the mortality group as shown in table 2. The number of cases with data in BS III was smaller since several were already deceased or did not take part in the follow-up examination. However, also in the control cohort a drop-out was noted. The numbers of cases and controls with data in BS III are given in table 2.

[7] We thank Professor Thorhorst, head of the tumor registry, and Professor Heitz, head of the Institute of Pathology, University of Basel, for their generous permission to use their material.

Grouping.—According to the cause of death, 4 cancer groups were formed: cancers of the lung, the stomach, the large bowel, and other sites. In the last group the incidence of the different tumors was too small to allow detailed analysis.

Clinical and laboratory data.—The variables used in this report are listed in table 3. With the exception of smoking, all reported data were obtained at BS III. Blood samples were drawn in the morning after an overnight fasting period. Lipids and vitamins were immediately measured. The laboratory methods used were detailed elsewhere (*9*). Venipuncture occurred on a voluntary basis. Thus not all participants had laboratory data. Comparison of the various data in the different groups and controls was done with standard statistical procedures. Statistical significance for differences between group means was assessed with the Bonferroni test, i.e., after adjustment for the multiple comparison of all pairs of means. The χ^2 test was used to examine significance between different frequencies, and correlations were analyzed with Kendall's coefficient of rank correlation.

RESULTS

Age and Frequency of Cancer Death

Here, only the participants at BS III were considered. The average age at death did not differ significantly among the 4 cancer groups (table 4). The colorectal cancer group was, on the average, the oldest. The shortest observation period was in the group for other cancer sites (table 4). Cancer of the lung was by far the most common carcinoma. Interestingly, 13 cases of carcinoma of the pancreas were found. This tumor thus was fourth in rank. Malignant disease at other sites was observed less frequently and was included with pancreatic carcinoma in group 4.

Cardiovascular Risk Factors

Mean blood pressure was consistently higher in the tumor groups than that in the corresponding controls. In group 4 (various cancer sites) the difference was reached in statistical significance for BS II by the Bonferroni test (significance level, 0.05; $P<.0009$). This observation held true for the BS III values; however, the difference was smaller.

TABLE 2.—*BS mortality follow-up*

Causes of death	ICD-8[a] No.	Total cases	With data in BS III	
			Cases	Controls
Cancer site				
1. Lung	162	62	38	108
2. Stomach	151	23	19	37
3. Colorectal	153-154	20	15	33
4. Other sites	140-239 (excluding 1-3)	91	57	143
All other death causes	0-999 (excluding 1-4)	335	193	579
Total		531 (12.57%)	322 (8.57%)	900 (21.3%)

[a] International Classification of Diseases, Eighth Revision.

TABLE 3.—*Variables considered*

Primary cause of death (death certificate + autopsy)
Age
Blood pressure (mmHg)
Cholesterol (mg/dl)
Triglycerides (mg/dl)
Total β-lipoproteins (estimation of LDL + VLDL in OD)[a]
Vitamin C (mg/dl)
β-carotene (μg/dl)
Vitamin A (IU)
Vitamin E (mg/dl)
Alcohol consumption (daily, weekly, or less)
Smoking (number of smokers/cigarettes/day)
Milk consumption
Citrus fruits intake

[a] LDL=low-density lipoproteins; VLDL=very low-density lipoproteins.

TABLE 4.—*Age at death, age at BS III, and average follow-up period*

Cancer site	Average age, yr,[a] at:		Average No. of yr for follow-up
	Death	BS III	
Lung	67.5±5.9	62.6±5.9	4.9
Stomach	65.1±7.6	60.9±7.5	4.2
Colon and/or rectum	68.6±5.8	64.5±5.4	4.1
Other sites	65.9±7.7	62.2±6.9	3.7

[a] Values are means ± SD.

For plasma cholesterol, triglycerides, and β-lipoproteins, only the BS III values were considered. Stomach cancer and colorectal cancer groups had the lowest cholesterol and β-lipoproteins. The control group matched to the cancer of the stomach group happened to have rather similar plasma lipid values. Lung cancer and controls also did not differ with regard to their lipid values (table 5).

Smoking (less than or equal to five cigarettes/day; data from BS II) was significantly more prevalent in cases with cancer of the lung, as well as in cases with cancers of the stomach and large bowel. A trend for cancer was observed more in smokers in the group for other cancer sites than in the control groups. Thus the difference became again highly significant (table 6). However, if the cohort that participated in BS III is considered, the differences would become too small between controls and cancer groups and the statistical significance would be lost.

Plasma Vitamins

Vitamins B_1, B_2, and B_6 were comparable in all cancer groups and controls. The most striking difference in the β-carotene level occurred in the lung cancer group compared to controls (significance level, $P<.05$; P-value, .0006). An even lower concentration was found in the gastric cancer group. Due to the small number, statistical significance was not reached. Again, the control group had higher β-carotene values (table 5).

Surprisingly, the vitamin A level was comparable in lung cancer cases and controls. The lowest value was observed in the gastric cancer group; despite the fact that the corresponding controls had similarly low lipid levels, their vitamin A concentration (and β-carotene) was distinctly higher (table 5).

Vitamin E was low in carcinoma cases of the stomach and large bowel. The values were concordant to the plasma lipid concentration in the different groups. Vitamin C was consistently lower in the tumor groups than in the corresponding controls. The lowest concentration was observed with gastric carcinoma. At the time of the BS III, for which vitamin concentrations were measured, smoking did not differ significantly between cases with gastric cancer and controls.

Kendall's coefficient of rank correlation between lipids and vitamins (table 7) demonstrated the importance of considering the lipid concentration in evaluating the vitamin status. More than a quarter of the observed variances of vitamin E were explained by differences in β-lipoproteins. For vitamin A, cholesterol and β-lipoproteins contributed about 5% each to the observed variability. An interesting discordant behavior was detected for β-carotene, which apparently correlated significantly with total cholesterol but only poorly with β-lipoproteins.

To assess whether additional variables influence the vitamin status, we analyzed alcohol, milk, coffee, and citrus fruit consumption and cigarette smoking in correlation to vitamins and plasma lipids. High ethanol

TABLE 5.—*Plasma lipids and vitamins in cancer cases and controls*[a]

Subjects (*n*)	Cholesterol, mg/dl	Triglycerides, mg/dl	β-lipoproteins, OD	Vitamin C, mg/dl	Vitamin A, IU	β-carotene, μg/dl	Vitamin E, mg/dl
Lung cancer cases (35)	230±52	157±149	710±233	0.79±0.44	286±77	14.8±9	1.5±0.46
Controls (102)	232±41	142±85	720±222	0.90±0.43	280±62	23.7±15.6[b]	1.7±0.52
Stomach cancer cases (19)	213±42	124±67	640±251	0.72±0.42	246±54	13.0±8.8	1.5±0.58
Controls (37)	215±36	132±68	650±188	0.93±0.35	274±48	19.4±9.4	1.5±0.31
Colon and/or rectum cancer cases (14)	213±38	126±62	615±226	0.77±0.43	284±57	20.1±20	1.4±0.36
Controls (33)	236±35	141±70	720±221	0.78±0.40	277±43	25.6±17	1.6±0.48
All other cancer site cases (47)	218±43	137±114	643±174	0.84±0.40	271±74	18.3±11.2	1.6±0.43
Controls (136)	220±38	133±103	670±224	0.90±0.39	273±61	20.7±12	1.6±0.41

[a] Values are means ± SD.
[b] Significance level, <.05; Bonferroni test.

TABLE 6.—*Smoking and cancer: Data from BS II*

Subjects	Smoker	Nonsmoker	χ^2
Lung cancer cases	44	18	P=.0001
Controls	40	73	
Stomach cancer cases	15	8	P=.005
Controls	12	30	
Colorectal cancer cases	10	5	P=.005
Controls	8	26	
Other cancer site cases	43	48	Not significant
Controls	80	81	
Total cases	112	79	P=.0001
Total controls	140	210	

TABLE 8.—*Correlation between lipids, vitamins, and life style*[a]

Nutrients	Consumption of:				
	Alcohol	Milk	Coffee	Citrus	Smoking of cigarettes/day
Vitamin C	−0.03	−0.05	−0.09	0.27	−0.03
β-Carotene	−0.11	0.00	−0.06	0.11	−0.09
Vitamin A	0.12	−0.19	0.03	−0.04	0.02
Vitamin E	0.02	−0.12	0.00	−0.06	−0.04
Cholesterol	0.02	−0.10	0.02	−0.11	0.02
β-Lipoproteins	0.02	−0.15	0.08	−0.08	−0.01

[a] Kendall's coefficient of rank correlation.

consumption correlated weakly with vitamin A (table 8). In any case, alcohol seemed to influence β-carotene and vitamin A in opposite ways. Surprisingly, we observed an inverse (albeit weak) correlation among milk consumption, plasma lipids, and fat-soluble vitamins. However, we found a strong direct correlation between the consumption of citrus fruits and plasma vitamin C. The inverse correlation between number of cigarettes per day and β-carotene might have importance. No consistent differences were reported for consumption of coffee and vegetables.

With the exception of colorectal cancer, more cancer cases drank ethanol daily than did controls. The difference was most pronounced in cancer of the lung (χ^2, P=.07) and was significant for all cancer cases together (P=.02). If we compare the consumption of citrus fruits in the different cancer groups and controls, we find in the gastric cancer group with the lowest vitamin C concentration no individual with high citrus fruit intake. Citrus fruits were eaten less than three times weekly by 79% of the cases and by 54% of the controls.

DISCUSSION

Of all deaths observed in the male cohort of the BS, 40% had cancer and in 35.2% the primary cause of death was considered to be cancer. The total mortality was lower than that of the Swiss population of similar age, but the relative contribution of the main causes did not differ (*10*). Thus our cohort seems to be representative for a Swiss urban working population. The single most important cause was cancer of the lung followed by cancer of the stomach and large bowel. In Switzerland, as in most industrialized Western countries, cancer of the lung increased from 20 to 200/100,000 between 1921 and 1974 in the age groups 50-69 years (*2*). During the same period, cancer of the stomach declined from over 200 to approximately 40/100,000 in the same age group. In the higher age group the decrease is slightly less. As shown by Doll and Peto (*6*) these changes occurred in a similar fashion between the years 1950 and 1976 in many different industrialized countries.

In view of the long, silent period of cancer development, mortality changes reflect changes in carcinogenesis dating far back before the actual event recorded as cancer death takes place. Furthermore, the epidemiologic study period 1965-80 covers the time in which dynamic changes of incidence did occur. Thus observations in the latter part of our study probably mean something different in regard to future events than to events rather close to the recording period. This possibility was observed by the International Collaborative Group on cholesterol level and risk of death from cancer (*11*). Age itself will lower differences, as observed with our results on smoking. At BS II the difference between the cancer groups compared to the controls was significant. At BS III (in an albeit smaller number) the difference is less impressive and loses statistical significance.

Accurate death certificates have crucial importance. The availability of a cancer registry and the autopsy rate of over 60% allowed a careful assessment. In the non-autopsied cases, a 5% cancer rate seems likely if we extrapolate from our autopsy material (Stähelin HB, Hüsser A, Buess E: Manuscript in preparation). Thus the true incidence of malignant diseases remains slightly higher than the incidence reported in this study. Since we are mainly interested in cancer, it seems justified to consider as cancer cases also those subjects who died from another disease but had cancer in addition.

The total number of cancer cases considered in our study seems large. Most individual cancers occurred, however, so infrequently that treating them as separate groups seemed meaningless. Therefore, only cancers of the lung and of the stomach and large bowel were treated separately. In the comparison of small groups and numerous variables, the selection of controls becomes a central issue. In an initial analysis of some of our results, we compared cases to the total living cohort of similar age (*12*). Due to the large number of subjects, statistical significance at the 5% level was reached for numerous variables. That this procedure has the danger of the highest error becomes evident when one considers the

TABLE 7.—*Correlation between plasma lipids and vitamins*[a]

Lipids	Vitamin C	β-carotene	Vitamin A	Vitamin E
Cholesterol	0.01	0.21	0.21	0.45
β-Lipoproteins	0.01	0.07	0.25	0.51

[a] Kendall's coefficient of rank correlation.

results of the control groups drawn at random. The random selection of controls matched by age and sex to cancer cases of the stomach surprisingly yields subjects with below-average lipid levels.

The observed significantly lower β-carotene concentration after adjustment for all other tested variables in cancer of the lung is in agreement with reports of Shekelle et al. (*13*) and in other studies reviewed elsewhere (*5–7*). Vitamin A, which was found by Wald et al. (*14*) to be lower in cancer cases of the lung, did not differ among cases and controls in the BS findings that were similar to the findings reported by Willet et al. (*15*). Cancer of the stomach was associated with lower vitamin A levels, again in keeping with other studies (*8, 16, 17*). In contrast to most other studies in this field, we emphasize that vitamin analysis was performed immediately after blood sampling, which eliminated problems of storage and degradation.

As pointed out above, the cholesterol and β-lipoprotein levels were comparable in the cancer cases and controls. The different levels among the subject groups probably reflect different nutrient intake or the influence of other variables. In this context, the influence of smoking has to be considered. Smoking correlates with low vitamin C. Furthermore, smoking, especially the number of cigarettes smoked, correlates inversely with the β-carotene concentration. An influence of smoking on carotene was also observed by Davies et al. (*18*). However, β-carotene correlates significantly with total cholesterol but not with β-lipoproteins. This finding suggests a correlation with HDL-cholesterol not measured in our population. Smoking too is known to decrease HDL concentration. Investigators in other studies observed a significant correlation with HDL-cholesterol and carotene levels (*19, 20*). The weak inverse correlation between alcohol consumption and β-carotene blood levels may be due to the alcohol-cancer association observed in our study and recently in Japanese men in Hawaii (*21*).

The relatively short follow-up period in our cohort suggests that an effect of β-carotene might still be operating at a late stage of carcinogenesis (*6*). The discordant findings of low carotene and normal vitamin A in cancer of the lung are somewhat contradictory and not easily explained. Probably, the differences in alcohol consumption and smoking contribute to the discordant findings, since vitamin A correlates more strongly with β-lipoproteins than does β-carotene, as discussed above.

The consistently lower vitamin C concentration in all cancer groups is intriguing. The lowest values were observed in the gastric cancer group. In this group, intake of citrus fruits, which correlates strongly with plasma vitamin C, was markedly lower. In 1964 Meinsma (*22*) already found a low intake of citrus fruits in cases of gastric cancer. Thus one finds a tempting speculation to be that vitamin C prevents development of gastric cancer by its inhibiting the formation of N-nitroso compounds (*23*). On the basis of our results and the small number of events, we are not able to differentiate diffuse carcinoma and the so-called intestinal type carcinoma, which differ in many respects (*24*). Nevertheless, epidemiologic and experimental evidence points to the fact that adequate vitamin C ingestion may diminish the risk of cancer of the stomach and large bowel (*25, 26*).

Cancer cases of the large bowel had vitamin A and β-carotene levels comparable to the levels for controls, despite the low blood lipids. The correlation among lipids and vitamin E explains the low vitamin E concentration in the large bowel cancer group. Several other studies reviewed in detail elsewhere (*2, 27*) showed average cholesterol levels in cancer patients, with the notable exception of those for cases with subsequent cancer of the colon who had significantly lower lipid levels. The association of lipid-soluble vitamins with plasma cholesterol and β-lipoproteins still could yield a clue to the observation that societies with high meat and fat intake and low plasma lipids might be less well protected from a variety of mutagenic compounds compared to subjects with higher lipid levels under a similar nutrition and high lipid and vitamin levels as suggested by Dion et al. (*26*).

The findings of the BS clearly demonstrate the influence of several factors on carcinogenesis. Nevertheless, our results and the consistency of the epidemiologic and experimental evidence support the concept that carotenes, vitamin E, and vitamin C affect the development of certain cancers.

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