INCIDENCE OF CANCER IN MEN ON A DIET HIGH IN POLYUNSATURATED FAT

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Summary   In an eight-year controlled clinical trial of a diet high in polyunsaturated vegetable oils and low in saturated fat and cholesterol in preventing complications of atherosclerosis, 846 men were assigned randomly to a conventional diet or to one similar in all respects except for a substitution of vegetable oils for saturated fat. Fatal atherosclerotic events were more common in the control group (70 *v.* 48; P < 0·05). However, total mortality was similar in the two groups: 178 controls *v.* 174 experimentals, demonstrating an excess of non-atherosclerotic deaths in the experimental group. This was accounted for by a greater incidence of fatal carcinomas in the experimental group. 31 of 174 deaths in the experimental group were due to cancer, as opposed to 17 of 178 deaths in the control group (P = 0·06).

Introduction

IN 1969 we presented the results of an eight-year clinical trial designed to determine whether a diet which lowers serum-cholesterol levels can also reduce clinical manifestations of atherosclerosis.[1] Fatal acute atherosclerotic events were significantly more common in the controls than in the experimental group. Despite this difference, total mortality was scarcely affected, indicating an excess of non-atheromatous deaths in the experimental group. We anticipated that these deaths would be due to a variety of competing causes in these elderly men. At first, we attempted to clarify this problem by examining non-atheromatous deaths in the last two years of the study. Our results were inconclusive, and when we published them, we left open the question of toxicity associated with feeding polyunsaturated fats in amounts larger than most populations consume. Subsequently we reviewed all our data with regard to deaths from causes other than atherosclerotic complications, especially when we read of experiments which associate unsaturated-fat feeding with an increased incidence of spontaneous and induced neoplasms in animals.[2] When we found a higher than expected incidence of carcinoma deaths in the experimental group, we did a detailed retrospective record search in an effort to identify all malignancies in the study population, fatal and non-fatal. We also added the experience of the two years which followed returning experimental and control groups to the standard institutional diet.

Methods

The experimental design and methods are given in detail in our 1969 report.[1] In 1959 we started a controlled trial of a diet high in polyunsaturated fat and low in saturated fat and cholesterol. The participants, men living in a veterans' home, were assigned randomly to the control group (422 men) or to the experimental group (424 men). The efficacy of randomisation was demonstrated by the comparability of the two groups in respect of nearly all baseline observations.[1] The efficacy of the randomisation in respect of cigarette smoking has been analysed in more detail elsewhere.[3] The study was done " double blind " in that both groups were fed diets differing from the regular institutional diet but simulating conventional food, and the doctors evaluating clinical events or deaths did not know what the diet assignment was. Meals were served cafeteria style, and adherence to the diet was monitored by means of individual attendance records.

Sample diets were analysed periodically throughout the study. Average values are presented in table I. The experimental diet simulated a conventional United States diet, and nearly quadrupled the intake of polyunsaturated

TABLE I—COMPOSITION OF DIETS

Component	Control	Experimental
Total calories/day	2496	2496
Protein (g./day)	96·3	97·4
Fat calories (% of total)	40·1	38·9
Iodine value of fat	53·5	102·4
Cholesterol (mg./day)	653	365
Polyunsaturates (% total fatty acid)	10	39·5

DR. CATT AND OTHERS: REFERENCES—*continued*

10. Brown, J. J., Davies, D. L., Lever, A. F., McPherson, D., Robertson, J. I. S. *Clin. Sci.* 1966, **30**, 279.
11. Romero, J. C., Staneloni, R. J., Dufau, M. L., Dohmen, R., Binia, A., Kliman, B., Fasciolo, J. C. *Metabolism*, 1968, **17**, 10.
12. Boyd, G. W., Landon, J., Peart, W. S. *Proc. R. Soc. B*, 1969, **173**, 327.
13. Blair-West, J. R., Cain, M., Catt, K., Coghlan, J. P., Denton, D. A., Funder, J. W., Scoggins, B. A., Wright, R. D. *in* Progress in Endocrinology (edited by C. Gual); p. 276. Amsterdam, 1969.
14. Boyd, G. W., Adamson, A. R., James, V. H. T., Peart, W. S. *Proc. R. Soc. Med.* 1969, **62**, 1253.
15. Vander, A. J., Luciano, J. R. *Am. J. Physiol.* 1967, **212**, 651.
16. Fraser, R., James, V. H. T., Brown, J. J., Isaac, P., Lever, A. F., Robertson, J. I. S. *Lancet*, 1965, ii, 989.
17. Bourgoignie, J. J., Catanzaro, F. J., Perry, H. M. *Circulation*, 1968, **37**, 27.
18. Helmer, O. M., Griffith, R. S. *Endocrinology*, 1952, **51**, 421.
19. Helmer, O. M., Judson, W. E. *Am. J. Obstet. Gynec.* 1967, **99**, 9.
20. Skinner, S. L., Lumbers, E. R., Symonds, E. M. *Clin. Sci.* 1969, **36**, 67.
21. Menard, J., Malmejac, A., Milliez, P. *Endocrinology*, 1970, **86**, 774.
22. Laragh, J. H., Sealy, J. M., Ledingham, J. G. G., Newton, M. A. *J. Am. med. Ass.* 1967, **201**, 98.
23. Dickinson, C. J., Yu, R. *J. Physiol., Lond.* 1967, **190**, 91.
24. Mohammed, S., Fasola, A. F., Privitera, P. J., Lipicky, R. J., Martz, B. L., Gaffney, T. E. *Circulation Res.* 1969, **25**, 543.
25. Helmer, O. M. *Can. med. Ass. J.* 1964, **90**, 221.
26. del Greco, F., Simon, N. M., Goodman, S., Roguska, J. *Medicine, Baltimore*, 1967, **46**, 475.
27. Gunnells, J. C., Grim, C. E., Robinson, R. R., Wildermann, N. M. *Archs intern. Med.* 1967, **119**, 232.
28. Weinberger, M. H., Dowdy, A. J., Nokes, G. W., Luetscher, J. A. *J. clin. Endocr. Metab.* 1968, **28**, 359.
29. Kahn, J. R., Skeggs, L. T., Shumway, N. P., Wisenbaugh, P. E. *J. exp. Med.* 1952, **95**, 523.
30. Massani, Z. M., Finkielman, S., Worcel, M., Agrest, A., Paladini, A. C. *Clin. Sci.* 1966, **30**, 473.
31. Hollenberg, N. K., Epstein, M., Basch, R. I., Merrill, J. P., Hickler, R. B. *Circulation Res.* 1969, **24/25**, suppl. I, p. 113.
32. Brown, J. J., Davies, D. L., Lever, A. F., Robertson, J. I. S. *Br. med. J.* 1965, ii, 1215.
33. Bath, N. M., Gunnells, J. C., Robinson, R. R. *Am. J. Med.* 1968, **45**, 381.
34. Creditor, M. C., Losehky, V. K. *ibid.* 1967, **43**, 371.
35. Maebashi, M., Miura, Y., Yoshinaga, K. *Lancet*, 1968, i, 1408.
36. Stokes, G. S., Goldsmith, R. F., Starr, L. M., Gentle, J. L., Mani, M. K., Stewart, J. H. *Circulation Res.* 1970, **27**, suppl. II, p. 11.
37. Funder, J. W., Blair-West, J. R., Cain, M. D., Catt, K. J., Coghlan, J. P., Denton, D. A., Nelson, J. F., Scoggins, B. A., Wright, R. D. *ibid.* **27**, 249.
38. MacDonald, G. J., Louis, W. J., Renzini, V., Boyd, G. W., Peart, W. S. *ibid.* p. 197.
39. Catt, K. J., Cain, M. D., Coghlan, J. P., Zimmet, P. Z., Cran, E., Best, J. *ibid.* suppl. II, p. 177.

TABLE II—NUMBERS AND SITES OF FATAL AND NON-FATAL CARCINOMAS AND OTHER NEOPLASMS DIAGNOSED DURING THE DIET PHASE AND THE TWO-YEAR PERIOD AFTER TERMINATION OF THE DIET

Site	Diet phase		Post-diet phase	
	Control	Experimental	Control	Experimental
Buccal and pharynx	6	10	1	0
Digestive and peritoneum:	6	12	6	3
Stomach	1	6	2	0
Other	5	6	4	3
Respiratory:	13	18	3	1
Lung and bronchus	12	16	2	1
Other	1	2	1	0
Genitourinary:	10	16	2	3
Prostate	8	11	2	1
Other	2	5	0	2
Other carcinoma	0	1	0	0
Total carcinomas, excluding skin	35	57	12	7
Skin carcinomas	21	10	4	2
Other malignancies*	3	3	1	1
Fatal benign tumour	0	0	0	1
Total	59	70	17	11

* These include lymphosarcoma, reticulum-cell sarcoma, rhabdomyosarcoma, angiosarcoma, lymphocytic leukæmia, and astrocytoma.
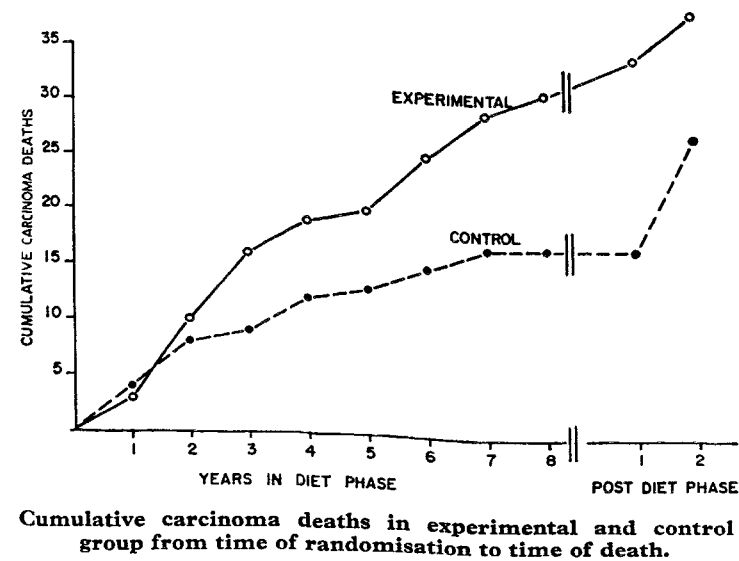
fat at the expense of saturated fat. Cholesterol intake was cut approximately in half. Beta-sitosterol content of the experimental diet was high, averaging 215 mg. per day in several analyses.

Definitions of atheromatous deaths and events are presented in detail in our original report.[1] Neoplasms were diagnosed on the basis of tissue reports, biopsy and/or necropsy. Information about neoplasms was retrieved by reviewing clinical records and cytology, surgical-pathology, and necropsy reports. Retrieval of records from within this institution was almost complete. Although cancer-morbidity data were undoubtedly incomplete, chances of failing to identify a non-fatal malignancy were equal in the two groups. Mortality data are about 99% complete.[1] Diagnoses were reviewed and recorded " blindfold " by M. L. P. and later reviewed by S. D. Death-certificate diagnoses were not accepted. (There was only one instance where a non-verified death-certificate diagnosis of cancer was found—a man in the experimental group with a death-certificate diagnosis of carcinoma of the larynx.) The various categories of neoplasms are shown in table II.

The experiment was divided into two phases—the 8⅓ years in which the control and experimental diets were fed (diet phase) and the period after the men had returned to the standard institutional diet (post-diet phase).

Results

The unrestricted consumption of the two diets had no significant effect on average body-weight.

Cumulative carcinoma deaths in experimental and control group from time of randomisation to time of death.

Serum-cholesterol levels fell promptly in the experimental group and the mean stayed 12·7% below that of the control group. Fatal acute atherosclerotic events during the diet phase were more numerous in the control group (70) than in the experimental group (48), and the same was true of the combined definite clinical events.[1] However, total mortality during the diet phase was not significantly different —178/422 controls compared with 174/424 in the experimental group.

TABLE III—INCIDENCE OF SELECTED BASELINE VARIABLES IN PATIENTS WHO DIED OF CARCINOMA DURING THE DIET PHASE

—	Control group (17 carcinoma deaths)	Experimental group (31 carcinoma deaths)
Myocardial infarction, definite	2	5
Cardiac decompensation	2	5
History of angina pectoris	5	6
Cerebral infarction, definite	3	6
Age (yr.)	68·4	65·5
Serum-cholesterol (mg./100 ml.)	224·5	221·2

During the diet phase (see figure) there were 31 carcinoma deaths in the experimental group and 17 in the control group ($\chi^2 = 3.668$, P = 0·06). The carcinoma deaths are plotted from the time of randomisation to the time of death. In the post-diet phase the excess continued for a year (3 experimentals, 0 controls), but in the second year the controls exceeded the experimentals (4 experimentals, 10 controls). Cancers, both fatal and non-fatal, counted from the time of randomisation to the time of diagnosis are summarised in table II. There was a higher incidence of the more commonly occurring visceral carcinomas in the experimental group. The contrary observation in regard to basal and squamous-cell skin cancers (none fatal) is largely due to 2 controls who had multiple lesions of this sort.

We examined the relationship of carcinoma deaths with a number of other variables (table III). The percentage of pre-existing definite cerebral infarcts was higher, and the baseline serum-cholesterol values were lower, than in men not dying of

TABLE IV—DEATHS FROM CARCINOMA IN DIET PHASE ADJUSTED FOR CIGARETTE SMOKING

Cigarette smoking	Control			Experimental		
	No. of men	Carcinoma observed	Carcinoma adjusted	No. of men	Carcinoma observed	Carcinoma adjusted
Unknown	57	2	1·74	42	1	1·15
> 2 packs/day	13	0	0	7	0	0
1–2 packs/day	57	2	1·66	38	4	5·00
1/2–1 pack/day	129	6	7·02	173	19	16·53
< 1/2 pack/day	62	3	2·61	46	4	4·68
Occasional	18	1	1·03	19	0	0
None	86	3	3·24	99	3	2·79
..	422	17	17·30	424	31	30·15

Deaths are adjusted by multiplying the number of men affected in a given cigarette-smoking stratum of the control group by $(C+E)/2C$, in which C = number of controls in the stratum and E = number of experimental subjects. A corresponding calculation is made for the experimental group.[3]

carcinoma, but neither difference was statistically significant. Cigarette smoking is analysed in detail in table IV. There is no apparent non-dietary explanation for the higher frequency of carcinoma deaths in the experimental group.

There were more low adherers to diet in the experimental group with fatal carcinomas than in the controls (table V). This distribution is not significant by chi square, but the number in each cell is small. The number of low adherers in the experimental group with fatal carcinoma is (at least in part) a reflection of the adherence pattern of the total experimental group, which is significantly lower than in the controls (table VI). We also analysed the data in this table by chi square for regression to take into account the ordered character of the percent adherence.

TABLE V—ADHERENCE TO DIET IN PATIENTS WITH FATAL CARCINOMA DURING THE DIET PHASE*

Adherence (%)	Control group	Experimental group
0–10	2	10
10–20	1	2
20–30	1	3
30–40	0	0
40–50	3	3
50–60	3	3
60–70	0	4
70–80	2	2
80–90	4	1
90–100	1	3
..	17	31

* Adherence, calculated from attendance records, is expressed as a percentage of the maximum number of meals which could have been taken in the study dining-hall.
$\chi^2 = 10\cdot26$; $P > 0\cdot3$.

TABLE VI—ADHERENCE TO DIET IN THE TOTAL STUDY POPULATION

Adherence (%)	Control group	Experimental group
0–10	82	120
10–20	47	46
20–30	31	42
30–40	21	30
40–50	42	23
50–60	40	33
60–70	32	32
70–80	42	37
80–90	50	31
90–100	35	30
..	422	424

$\chi^2 = 21\cdot78$; $P < 0\cdot01$.

The difference in adherence remains significant at the 1% level.

Discussion

The experience of other investigators using similar diets has not been the same. In an eleven-year report on the Oslo diet-heart study Leren noted 7 cancer deaths in his experimental group and 5 in the control group.[4] His criteria for a diagnosis of cancer are not given, and diets were not supervised after the fifth year. The six-year London trial of a diet high in soya-bean oil noted 6 cancer deaths in the control group and 1 in the experimental group. Again, cancer criteria are not given.[5] The Helsinki group has not yet published cancer data.[6] These differences in cancer experience may have been due to differences in patient population and in trial design. Our trial involved the longest period of dietary control of the studies cited. The high incidence of neoplasms which we report in both experimental and control subjects is due to factors not operative in the other studies—our subjects were much older than those in the other series, and we obtained a high necropsy-rate (80% of the men dying in the centre and 65% of all deaths in the study during the diet phase).

Many of the cancer deaths in the experimental group were among those who did not adhere closely to the diet. This reduces the possibility that the feeding of polyunsaturated oils was responsible for the excess carcinoma mortality observed in the experimental group. However, there were significantly more low adherers in the entire experimental group than in the controls (table VI). In both groups, the numbers of cancer deaths among the various adherence strata are compatible with random distribution (table V). A high incidence among high adherers would be expected if some constituent of the experimental diet were contributing to cancer fatality.

These observations present a dilemma. On the one hand, it is tempting to ignore the low-adherence segment of the study population. On the other hand, conclusions based on the better-adhering strata may be misleading because of bias. We cannot resolve this dilemma, and feel that the results must be examined in both ways.

Other trials of the effect of polyunsaturated-fat diets on the incidence of atherosclerotic complications have been negative in regard to an increased incidence of fatal cancer, and our own results are of borderline significance. However, our results must be

viewed in the light of animal experiments which suggest that fat intake (especially unsaturated-fat intake) affects the incidence of certain types of neoplasm.

Overweight has been associated with a higher incidence of cancer than the incidence observed in normal or underweight people,[7,8] and fat consumption is strongly correlated with death from neoplasms of the breast, ovaries, and rectum, and from leukæmia.[9] Earlier work suggested that animals on fat-rich diets had an increased incidence of spontaneous and carcinogen-induced carcinomas.[10,11] Carroll et al. have investigated carcinogen-induced mammary carcinomas in rats,[2,12] and found that increasing the level of dietary fat enhances the yield of these neoplasms. 20% corn-oil diets had a greater effect than 0·5% corn oil, and a greater effect than 20% coconut oil, which is largely saturated. In another experiment they fed 20% corn oil after the administration of the carcinogen to half the animals and up to the time of carcinogen administration in the other half. There was a higher incidence in the animals which were given the corn-oil diet after the carcinogen administration than in the group which was switched from the corn-oil diet to a low-fat diet at the time of carcinogen administration. These observations suggest a promoting rather than an initiating process. Their metabolic significance remains speculative.

Aflatoxins contaminating cottonseed meal have been implicated in hepatic carcinoma in trout.[13] It is most unlikely that they were present in our experimental diet since the commercial production of edible oils in the United States removes these substances.[14]

Other explanations of our data should be considered. If elderly men are protected from atherosclerotic complications, they will die of something else, and cancer is the next most common cause of death in this population. Also it is theoretically conceivable that a diet high in saturated fat protects against cancer, but both epidemiological data and animal experiments suggest otherwise. At any rate, if the experimental diet is cocarcinogenic, the responsible component still needs to be identified.

Our results and those from the literature are uncertain and confusing in respect of the role of polyunsaturated fats in an increased incidence of malignancies. The high incidence of fatal carcinomas in our experimental group is of borderline significance. A retrospective review of any large collection of data will suggest causal relationships which are chance occurrences. Tests of significance such as chi square have been formulated to evaluate pre-stated hypotheses, and their application to hypotheses which were made after scrutiny of data will tend to overstate the significance of observed differences. Furthermore, it is important to remember that no population under study has been consuming a diet high in polyunsaturated fats over long periods of time.

What is the practical application of our data ? Certainly they should be considered in the design and performance of any new diet trial. A diet similar to our experimental one, but slightly lower in total fat and with polyunsaturates largely replaced by monounsaturates, would have a similar serum-cholesterol-lowering effect. We think it premature to make a blanket prescription of a diet high in polyunsaturated fat for the entire population. However, the risks involved seem small compared with the high incidence of atherosclerotic complications in patients with certain hyperlipidæmias,[15] and the use of diets high in polyunsaturated fat is certainly justifiable in selected patients. A trial of a diet low in fat, and very low in unsaturated fat, would be of interest in selected human carcinomas, especially breast cancer.

REFERENCES

1. Dayton, S., Pearce, M. L., Hashimoto, S., Dixon, W. J., Tomiyasu, U. Circulation, 1969, 40, suppl. no. II.
2. Gammal, E. B., Carroll, K. K., Plunkett, E. R. Cancer Res. 1967, 27, 1737.
3. Dayton, S., Pearce, M. L. Lancet, 1970, i, 473.
4. Leren, P. Circulation, 1970, 42, 935.
5. Research Committee to the Medical Research Council, Lancet, 1968, ii, 693.
6. Turpeinen, O., Miettinen, N., Karvonen, M. J., Roine, P., Pekkarinen, M., Lehtosuo, E. J., Alivirta, P. Am. J. clin. Nutr. 1968, 21, 255.
7. Tannenbaum, A. Archs Path. 1940, 30, 509.
8. Tannenbaum, A., Silverstone, H. in Cancer (edited by R. W. Raven); vol. I, p. 306. London, 1957.
9. Lea, A. J. Lancet, 1966, ii, 332.
10. Tannenbaum, A. Cancer Res. 1942, 2, 468.
11. Watson, A. F., Mellanby, E. Br. J. exp. Path. 1930, 11, 311.
12. Carroll, K. K., Khor, H. T. Cancer Res. 1970, 30, 2260.
13. Sinnhuber, R. O., Lee, D. V., Wales, J. H., Ayres, J. L. J. natn. Cancer Inst. 1968, 41, 1293.
14. Parker, W. A., Melnick, D. J. Am. Oil Chem. Soc. 1966, 43, 635.
15. Slack, J. Lancet, 1969, ii, 1380.

BLOOD-PRESSURE IN WOMEN AFTER ONE YEAR OF ORAL CONTRACEPTION

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Summary   In a prospective study of 66 women taking oral contraceptives, systolic blood-pressure increased in 50 cases after a year, the mean systolic pressure rising significantly by 6·6 mm. Hg. Mean diastolic pressure did not change significantly and in no case did the blood-pressure rise to 140/90 mm. Hg or more. A control group of 21 women using cervical diaphragms or intrauterine contraceptive devices showed no significant change in either systolic or diastolic blood-pressure during the same period.

Introduction

ORAL contraceptives may lead to an increase of blood-pressure in women whose blood-pressure has