Experimental Evidence of Dietary Factors and Hormone-dependent Cancers

Kenneth K. Carroll

Department of Biochemistry, University of Western Ontario, London, Ontario, Canada N6A 5C1

Summary

Current awareness of the importance of environmental factors such as diet in the etiology of human cancer has stimulated renewed interest in animal models for studying effects of diet on tumorigenesis. Diet can influence cancer in animals by affecting the initiation or subsequent preneoplastic stage of tumorigenesis, but it has less effect on tumor growth. Caloric restriction has a general inhibitory influence on tumorigenesis. Dietary fat, on the other hand, tends to promote tumorigenesis, but only certain types of tumors, such as mammary tumors, are affected. Both caloric restriction and dietary fat appear to act primarily during the preneoplastic stage, and their effects on hormone-dependent tumors may be mediated through changes in the hormonal environment. Variations in other dietary factors, such as protein, vitamins, or minerals, above the levels required for normal maintenance seem to have little influence on the genesis or growth of tumors.

Introduction

The role of diet in tumorigenesis was a popular field of investigation during the 1940's and early 1950's. It is currently enjoying a revival of interest because of increasing awareness of the role of environmental influences on cancer mortality in human populations (33, 43) and the possibility that diet may be an important factor in this regard (15, 25, 55, 106). In discussing the experimental evidence obtained from work with animals, consideration will therefore be given to its possible relevance to carcinogenesis in humans.

Most of the experimental work on diet in relation to hormone-dependent cancers has been concerned with mammary tumors in mice or rats. Some investigators have used spontaneous tumors (2, 80, 81), and others have used tumors induced by various carcinogenic agents (27, 30, 38). The effects of different dietary components, such as protein, fat, vitamins, and minerals, have been investigated, as well as the overall caloric intake; and a number of reviews of this work have been published (12, 15, 17, 74, 86, 87, 92, 94, 99).

In discussing nutritional influences, one must distinguish clearly between the genesis and the growth of tumors (87). Although there is good evidence that diet can affect tumorigenesis, it has much less influence on the growth of established tumors. In general, overnutrition favors and undernutrition inhibits tumor growth (87), but underfeeding or caloric restriction are not practical methods of controlling the growth of tumors.

The process of tumorigenesis itself can be divided into at least 2 stages. This concept was derived originally from work with skin tumors (3, 35), but it probably applies to other tumors, such as mammary tumors, as well (6, 17, 22, 70). In the 1st or initiating stage, normal cells are converted into potentially neoplastic cells by interaction with a carcinogenic agent. This is followed by a developmental or preneoplastic stage during which these cells undergo further changes leading to tumor formation. This period may actually comprise more than 1 stage in the development of tumor cells (6).

There are various ways in which diet may affect the initiating stage of tumorigenesis. Some foods contain small amounts of substances such as polycyclic hydrocarbons, aflatoxin, aminoglucosides, and nitrosamines, which are potentially capable of causing cancer (33, 41, 59, 68, 104). Diet can also influence the metabolism of carcinogens in the body. In some cases this may lead to more rapid inactivation of carcinogens, and in other cases it may promote their formation from precursor molecules. Such effects might be mediated by the influence of dietary components on inducible enzymes (19, 96) or by altering the intestinal microflora (25, 44, 45).

After cells have been exposed to a carcinogenic stimulus, it usually takes some time before tumors begin to develop. During this preneoplastic stage the process seems to be relatively susceptible to external influences, and it is then that diet appears to exert the greatest effects on tumorigenesis. The following discussion will therefore be concerned primarily with this aspect of the role of diet in tumorigenesis and will refer mainly to mammary tumors, since they have been investigated much more thoroughly than any other hormone-dependent tumors in experimental animals.

Caloric Intake

Caloric restriction inhibits formation of spontaneous mammary tumors in mice (Table 1). Similar results have

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2 Medical Research Associate of the Medical Research Council of Canada.
been obtained with induced mammary tumors (27, 62) and spontaneous pituitary adenomas (69) in rats. A variety of other mouse tumors, including hepatoma, primary lung adenoma, leukemia, skin tumors, and sarcoma are also inhibited by reducing caloric intake. It therefore appears to be a general phenomenon, although some tumors seem to be affected more than others by caloric restriction (86, 87, 92, 94).

In many of these experiments, food intake was restricted to between one-half and two-thirds of normal, but the effects on tumorigenesis do not seem to be due to inanition, since the restricted animals were generally healthy and active and had a longer life-span than unrestricted animals. Both underfeeding, in which the intake of all nutrients is reduced, and caloric restriction per se, in which only the carbohydrate or carbohydrate and fat intake are reduced, have been shown to inhibit tumorigenesis (Table 1). The greatest inhibition seems to result when the caloric intake is reduced to less than 80% of the normal intake (84, 86). Restriction to 50% of normal intake is about the maximum that can be tolerated for long-term experiments.

The experimental evidence suggests that the effects of caloric restriction are exerted not on the initiation of tumors but at some later stage of their development. Thus, Tannenbaum (80) found that spontaneous mammary carcinoma in mice were significantly inhibited by instituting caloric restriction at varying times before the tumors began to appear, when the mice were 2, 5, or 9 months old. According to the results of Tannenbaum (82), experiments with skin tumors induced by benzpyrene also showed that restriction during the period after treatment with carcinogen had the greatest inhibitory effect, although this conclusion was questioned by Clayson (17). Intermittent restriction, consisting of twice-weekly fasts of 24-hr duration, with feeding ad libitum between fasts, had no inhibitory effect on formation of spontaneous mammary carcinoma in mice (89).

Most of the experimental work has been concerned with effects of undernutrition, but Waxler et al. (98) used mice made obese by treatment with gold thioglucose and found that the mice developed spontaneous mammary carcinomas at a faster rate than did controls. However, if the obese mice were restricted in diet so that they weighed only as much as the controls, they developed fewer tumors than did the controls (97). In these experiments, there seemed to be a correlation between body weight and tumorigenesis, and some supporting evidence for this has been reported by Tannenbaum and Silverstone (92). On the other hand, these workers found no correlation between body weight and incidence or time of appearance of spontaneous mammary carcinomas in 250 mice fed ad libitum on adequate stock diet (92). The maximum weights attained by the mice ranged from 22 to 42 g. In the experiments of Moore and Tittle (62), rats in which mammary tumor formation was inhibited by caloric restriction or forced exercise were smaller and had less body fat than controls.

The diversity of tumors affected by caloric restriction suggests some common mechanism of action, such as inhibition of tumorigenesis due simply to lack of available energy or metabolites required for the process. There is still the possibility, however, that different mechanisms are involved for different types of tumors. Mice and rats on restricted rations show changes in ovaries, uteri, and mammary gland analogous to those seen in hypophysectomized animals; and inhibition of spontaneous mammary tumors might be a result of decreased estrogen production and/or diminished responsiveness of mammary tissue to estrogen (49). Alternatively, Boutwell et al. (7) suggested that adrenal hyperfunction in restricted animals might be responsible for the inhibitory effect on tumorigenesis. Bullough (10) observed that mitotic activity is inhibited by caloric restriction, and he concluded that cell division is limited by the availability of metabolites to provide energy for mitosis. The developmental stage of carcinogenesis could thus be influenced by an inhibitory effect on mitotic activity, including that of latent cancer cells.

The inhibitory effect of caloric restriction on induced tumors can be largely overcome by increasing the dose of carcinogen to the point at which nearly all animals in both control and restricted groups develop tumors (94). The experiments of White and White (100) and of King et al. (52) provide possible examples of this overriding effect of a strong carcinogenic stimulus on mammary tumorigenesis.

### Dietary Fat

Dietary fat intake has also been shown to influence tumor incidence, but in this case only certain types of tumors seem to be affected (15, 87, 92, 94). Numerous studies have shown

#### Table 1

<table>
<thead>
<tr>
<th>Kind of restriction*</th>
<th>Degree of restriction (as % of control diet)</th>
<th>Duration of study (mos.)</th>
<th>Strain of mouse</th>
<th>Tumor incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>U</td>
<td>50</td>
<td>18</td>
<td>DBA</td>
<td>20/50 (40)</td>
</tr>
<tr>
<td>C + F</td>
<td>75</td>
<td>16</td>
<td>C3H</td>
<td>30/44 (67)</td>
</tr>
<tr>
<td>C + F</td>
<td>50</td>
<td>22</td>
<td>C3H</td>
<td>32/32 (100)</td>
</tr>
<tr>
<td>C</td>
<td>67</td>
<td>23</td>
<td>DBA</td>
<td>27/50 (54)</td>
</tr>
<tr>
<td>C</td>
<td>75</td>
<td>15</td>
<td>C3H</td>
<td>17/30 (58)</td>
</tr>
</tbody>
</table>

* Adapted from Tannenbaum and Silverstone (94).

* U, underfeeding; C + F, carbohydrate and fat restricted; C, carbohydrate restricted.
that high-fat diets increase the incidence of skin tumors and mammary tumors in mice and rats. Some of the results obtained with mammary tumors are shown in Table 2. There are also isolated reports that dietary fat enhances the incidence of other tumors such as spontaneous hepatomas (76) and intracranial tumors (78). On the other hand, various other tumors, particularly sarcoma induced by injection of carcinogenic hydrocarbons, appear to be unaffected by dietary fat (15).

In the experiments with skin tumors and mammary tumors, a number of different fats and oils were used; Tannenbaum (87) concluded that the enhancement of tumor yields was related to amount rather than type of dietary fat. Our experiments with mammary tumors induced in rats by DMBAa showed that unsaturated fats generally gave higher tumor yields than did saturated fats (14), but this was due mainly to an increase in number of tumors per tumor-bearing rat (Chart I).

High-fat diets tend to be high in calories as well, but paired feeding experiments indicated that dietary fat has an effect that is independent of caloric intake (85). Lavik and Baumann (54), working with skin tumors in mice, obtained evidence that enhancement of tumorigenesis was related to the triglyceride component of dietary fat, rather than the nonsaponifiable fraction. This does not seem to have been investigated with mammary tumors, perhaps because of the effort and expense involved in carrying out such experiments.

Dietary fat, like caloric intake, appears to affect primarily the developmental stage of tumorigenesis (15). Our studies with mammary tumors indicated that dietary fat was more effective when fed after administration of the carcinogen (Table 3), and similar results were obtained in earlier experiments with skin tumors (83). Dietary fat may thus be considered to exert a promoting effect on these 2 types of tumors (15). It is difficult to rule out completely the

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### Table 2

<table>
<thead>
<tr>
<th>Type of fat</th>
<th>Level in diet (% by wt)</th>
<th>Carcinogenic agent</th>
<th>Duration of study (mos.)</th>
<th>Strain</th>
<th>Tumor incidence (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low fat</td>
<td>High fat</td>
</tr>
<tr>
<td>Mice</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kremitb</td>
<td>12</td>
<td>None</td>
<td>18</td>
<td>DBA</td>
<td>16/50 (32)</td>
<td>32/50 (64)</td>
</tr>
<tr>
<td>Kremaxb</td>
<td>16</td>
<td>None</td>
<td>21</td>
<td>C3H</td>
<td>40/54 (74)</td>
<td>48/54 (89)</td>
</tr>
<tr>
<td>Rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Criscob</td>
<td>46</td>
<td>Stilbestrol</td>
<td>13</td>
<td>A × C line 9935</td>
<td>9/12 (75)</td>
<td>11/12 (92)</td>
</tr>
<tr>
<td>Lard</td>
<td>16-30</td>
<td>2-Acetylaminofluorene</td>
<td>7</td>
<td>AES</td>
<td>2/31 (6)</td>
<td>55/71 (78)</td>
</tr>
<tr>
<td>Olive oil</td>
<td>20</td>
<td>None</td>
<td>10</td>
<td>Sprague-Dawley</td>
<td>3/25 (12)</td>
<td>5/13 (39)</td>
</tr>
<tr>
<td>Corn oil</td>
<td>20</td>
<td>DMBA</td>
<td>4</td>
<td>Sprague-Dawley</td>
<td>15/21 (71)</td>
<td>21/22 (96)</td>
</tr>
</tbody>
</table>

* The low-fat diets contained from 0.5 to 3% fat except in the experiments of Dunning et al., where the level was 6.5%.

*a Partially hydrogenated cottonseed or cottonseed-soybean oil.

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3 The abbreviation used is: DMBA, 7,12-dimethylbenz(a)anthracene.

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**Note:**

- The text discusses the effects of dietary fats on tumor incidence in mice and rats, highlighting the role of high-fat diets and their impact on skin and mammary tumors. It also touches on the relationship between dietary fat and caloric intake, suggesting that high-fat diets increase tumorigenesis independently of caloric intake. The text references various experiments and studies to support these claims, including the use of different fatty acids and oils in feeding trials.

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**Chart 1.** Effect of different dietary fats on incidence of mammary tumors induced in female Sprague-Dawley rats by a single 5-mg dose of DMBA p.o. The fats were fed as 20% by weight of a semisynthetic diet. The low-fat control diet contained 0.5% corn oil. Data are taken from Carroll and Khor (14).

**Table 3**

<table>
<thead>
<tr>
<th>Level of dietary fat</th>
<th>Before DMBA</th>
<th>After DMBA</th>
<th>Tumor incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>20</td>
<td>29/30 (97)</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>20</td>
<td>28/30 (93)</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0.5</td>
<td>22/30 (73)</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>0.5</td>
<td>22/30 (73)</td>
<td></td>
</tr>
</tbody>
</table>

* Data from Carroll and Khor (13).
possibility that dietary fat exerts some effect on the carcinogenic agent (39), but it seems more probable that the fat acts by providing a more favorable environment for development of latent tumor cells (15).

With hormone-dependent tumors, this leads one to think about possible effects on the hormonal environment. Mammary tumors and the normal development of the mammary gland are both influenced strongly by hormones, particularly estrogens and prolactin (23, 60, 61, 77). Dunning et al. (27) observed a stimulatory effect of dietary fat on mammary glands of rats implanted with pellets containing stilbestrol. Rats on high-fat diet showed histological evidence of more hypertrophy and secretory activity than did rats on diets containing lower levels of fat. However, a stimulated gland may actually be more refractory to mammary tumor induction, since tumorigenesis can be inhibited by treatment with hormones (48) or by pregnancy ensuing soon after treatment with a carcinogenic hydrocarbon (22). On the other hand, pregnancy occurring at a later stage causes a marked stimulation of tumor growth (21). Age is also a factor. Female rats 50 to 60 days old are more prone to develop tumors after treatment with a carcinogenic hydrocarbon than are either younger or older rats (20, 47).

Recently, Nagasawa and Yanai (65) reported a correlation between mammary cell division, as measured by incorporation of [3H]thymidine into the DNA of mammary gland, and age-related variation in sensitivity to tumor development.

Preliminary studies in our laboratory to investigate possible effects of dietary fat on distribution and metabolism of injected [3H]estradiol showed a tendency toward higher tissue levels in rats on low-fat diet. This somewhat unexpected result could be interpreted to mean that a larger proportion of the tissue receptors are already occupied by endogenous hormone in rats on high-fat diet (15). Competition for tissue receptors between noncarcinogenic (estriol) and carcinogenic estrogens (estrone, estradiol) may play a role in breast cancer. Cole and MacMahon (18) proposed that low ratios of estriol to estrone and estradiol in the decade or so after puberty are associated with high risk of breast cancer, and studies of urine and estrogen profiles in Asian and North American women have provided evidence in support of this concept (57, 58).

Prolactin has also been implicated in mammary cancer (36, 66). Boyns et al. (8) observed a positive correlation between the basal blood level of prolactin in 3 strains of rats and their susceptibility to development of mammary tumors after treatment with a carcinogenic hydrocarbon. Pituitary prolactin levels were found to be elevated in a small series of female dogs bearing spontaneous mammary tumors (71), and there is some evidence that serum prolactin levels are elevated in women with breast cancer (4, 64); but Boyns et al. found no such difference (9). High levels of prolactin may inhibit induction of mammary tumors in the rat (37).

Recent studies of Chan and Cohen (16) suggest that the effects of dietary fat on mammary cancer incidence may be mediated through prolactin. Treatment with the antiprolactin drug, CB-154, reduced the incidence of mammary tumors induced in rats by DMBA and abolished the differential between animals on low-fat and high-fat diets. Treatment with the antiestrogen drug, U11,100A, also reduced the tumor incidence, but it failed to abolish the differential due to different levels of dietary fat. This latter result tends to argue against the suggestion of Hill et al. (46) that dietary fat affects breast cancer by altering estrogen levels as a result of changes in gut bacteria.

**Dietary Protein**

Tannenbaum and Silverstone (88) found that varying the casein content of semipurified rations from 9 to 45% had no particular effect on the formation of spontaneous mammary carcinoma in mice. Similar results were obtained with skin tumors and sarcoma (87). On the other hand, White and Andervont (103) found that severe restriction to 4% casein prevented formation of spontaneous mammary tumors in C3H mice. Feeding a diet containing 18% gliadin, which is low in lysine, reduced the tumor yield to 25% of normal (101). These effects are similar to the reductions in tumor yield that can be obtained by caloric restriction to give comparable reductions in body weight. However, Tannenbaum and Silverstone (93) were able to demonstrate an effect of dietary protein independent of body weight by regulating food intake to equalize body weights in mice on low- and high-protein diets. Ross et al. (69) reported that the incidence of pituitary adenomas was directly related to the protein content of the diet when rats were fed restricted but equal amounts of the different rations.

Although restriction of dietary protein inhibits tumorigenesis, it is still possible to obtain a relatively high tumor yield under such circumstances. White and White (100) obtained a tumor incidence of 45% by s.c. implantation of pellets containing diethylstilbestrol in mice on 4% casein diet.

Dunning et al. (28) investigated the effect of dietary tryptophan on the occurrence of diethylstilbestrol-induced mammary cancer in rats. They used semisynthetic diets in which the protein requirement was supplied by either casein or a tryptophan-free casein hydrolysate. Addition of 1.4% tryptophan to the latter diet gave a higher tumor yield and addition of 4.3% tryptophan a lower tumor yield than did the control casein diet. An inhibitory effect on body growth may explain the latter result.

Increasing the level of casein in the diet reduced the incidence of mammary carcinoma induced in rats by 2-acetylaminofluorene, provided dietary intake was restricted to the amount eaten when the diet contained less protein (32). In these experiments the carcinogen was added to the diet, and the increased food intake in unrestricted animals on high-protein diet therefore resulted in exposure to larger amounts of carcinogen, which apparently masked the inhibitory effect of casein. Gilbert et al. (40) observed that Wistar-type rats fed a diet containing 77% casein and less than 4% carbohydrate had a significantly lower incidence of spontaneous tumors than did rats on other diets containing from 12 to 15% protein. The rats on high-protein diet gained less weight than the other 3 groups, and the reduced tumor yield may have been partly due to caloric...
reduction. However, a group of rats on restricted amounts of a ration containing 15% protein gained less weight but developed more tumors than did those on the high-protein diet. Tumors observed in this study included pheochromocytoma, fibroadenoma of the breast, and pituitary adenoma.

Shay et al. (73) reported that rats on a semipurified diet containing casein at levels of 27 or 64% developed more mammary tumors than rats on stock diet, following treatment with 3-methylcholanthrene. When ovalbumin (64%) was used as source of protein, the rats did not grow well and the tumor yield was lower than in rats on stock diet. A diet containing 64% lactalbumin had little or no effect on tumor yield.

In our experiments with mammary cancer induced in rats with DMBA, it was found that fewer tumors developed in animals on commerical feed compared to others fed semisynthetic diet containing approximately the same level of dietary fat (Chart 2). The semisynthetic diet contained animal protein (casein) as opposed to the commercial feed, in which much of the protein is derived from plant sources. Since mortality from breast cancer in humans shows a strong positive correlation with animal protein intake as well as with dietary fat (15), preliminary experiments were carried out to compare the effects on tumor yield of animal and plant protein fed in a semisynthetic diet. Rats given a diet in which the protein was supplied by soy protein isolate (Promine-R) grew more slowly than rats on a comparable diet with casein as source of protein, but they developed at least as many tumors (Table 4). These experiments therefore did not provide any indication that the lower incidence of tumors in rats on commercial feed is related to the protein component of the diet.

Effects of Other Dietary Components

Some studies have been carried out to test effects of different levels of vitamins and minerals in the diet on tumorigenesis in animals (87, 94). Varying the level of B vitamins from amounts just adequate for growth to from 3 to 9 times these amounts had little effect on incidence of spontaneous carcinoma in mice (90). A lower incidence of spontaneous carcinoma was reported by Morris (63) in mice deficient in riboflavin, but body weight and food consumption were also reduced and the effect may have been due to inanition.

Varying the level of a standard salt mix from 2 to 8% in a semisynthetic diet had no apparent effect on incidence of spontaneous mammary tumors in mice (91). A specific instance of tumorigenesis being influenced by deficiency of an inorganic dietary constituent is provided, however, by the report of Axelrad and Leblond (1). They observed that prolonged iodine deficiency leads to production of thyroid tumors in the rat. There is also some evidence that iodine deficiency may increase incidence of thyroid cancer in humans (87, 94).

Relevance of Animal Experiments to Human Cancer

Within the past 10 years, a number of authors have called attention to the positive correlation between dietary fat intake and mortality from certain types of cancer in different countries of the world (12, 15, 24–26, 46, 55, 56, 105–107). The correlation is strongest with breast cancer, intestinal cancer, and cancer of the prostate, but it is not seen with other types such as stomach cancer (15).

Correlations of this sort must be regarded with caution because of the difficulties of collecting reliable epidemiological data and because associations between variables may be coincidental. However, when a correlation such as that between fat intake and breast cancer mortality is supported by experimental evidence from animal models, it seems worthy of more serious consideration. Dietary fat has also been reported recently to enhance the yield of induced colon tumors in rats (67). It is thus of interest to consider the possible relevance of results obtained with animal models to the role of diet in human cancer.

In the animal model used for our experiments, the incidence of mammary tumors induced in rats by a single 5-mg dose of DMBA was increased from about 70 to 95% by raising the level of dietary fat from 0.5 to 20% by weight (14). Attempts to increase this differential in tumor incidence by lowering the dose of carcinogen were unsuccessful (13). These results appear to be representative of those obtained with other animal models (Table 2), although a greater differential has been reported in some studies. On the other hand, the age-adjusted mortality from breast cancer in humans shows a 5- to 10-fold difference between countries with a per capita fat intake of 50 g/day or less and countries with an intake of 140 to 150 g/day (Chart 3).

As pointed out earlier, our experiments suggest that unsaturated fats have a greater effect on tumor yield than do saturated fats (see Chart 1). This may not be true for other animal models, but systematic studies have not been carried out. The epidemiological data for humans indicate that...
Table 4
Yields of mammary tumors induced by DMBA in rats on semisynthetic diets containing casein or soy protein isolate

Groups of 10 female Sprague-Dawley rats were placed on the diets at weaning. The diets contained 5% corn oil and had the same basal composition as in previous experiments (14) except that a different vitamin mix (42) and salt mix (5) were used.

<table>
<thead>
<tr>
<th>Age when DMBA given (days)</th>
<th>Dietary protein</th>
<th>Body wt</th>
<th>Tumor yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Initial</td>
<td>At DMBA treatment</td>
</tr>
<tr>
<td>50</td>
<td>Casein</td>
<td>49</td>
<td>157</td>
</tr>
<tr>
<td></td>
<td>Soy protein*</td>
<td>49</td>
<td>142</td>
</tr>
<tr>
<td>60</td>
<td>Casein</td>
<td>47</td>
<td>189</td>
</tr>
<tr>
<td></td>
<td>Soy protein</td>
<td>48</td>
<td>165</td>
</tr>
<tr>
<td>75</td>
<td>Casein</td>
<td>47</td>
<td>207</td>
</tr>
<tr>
<td></td>
<td>Soy protein</td>
<td>47</td>
<td>190</td>
</tr>
</tbody>
</table>

* Includes tumors found when the rats were autopsied 4 months after treatment with DMBA.

Soy protein isolate (Promine-R) kindly supplied by Dr. E. W. Meyer of Central Soya, Chicago, Ill.

Chart 3. Correlation between per capita consumption of dietary fat (34) and age-adjusted mortality from breast cancer in different countries (72). The values for dietary fat are averages for 1964 to 1966 and those for cancer mortality are for 1964 to 1965, except in a few cases where data were available only for 1960 to 1961 or 1962 to 1963.

animal fat intake does not correlate as well as total dietary fat with breast cancer mortality, and intake of vegetal fat shows little, if any, correlation (Chart 4). Vegetal fat may be expected to be, if anything, more unsaturated than animal fat, although some plant fats such as coconut oil are relatively saturated and others may be partially hydrogenated for edible use. This classification, therefore, does not provide a reliable guide to possible differences between effects of saturated and unsaturated fats on human breast cancer. However, death rates from breast cancer, prostatic cancer, and intestinal cancer are much higher in Americans than in Japanese, although both have similar dietary intakes of unsaturated fat in the form of linoleic acid. Analysis of adipose tissue also showed that Japanese have a higher proportion of linoleate than do Americans (50).

Perhaps it is too much to expect quantitative as well as qualitative agreement between the results of animal experimentation and epidemiological data from human population studies. However, it appears somewhat doubtful that the 5- to 10-fold difference in death rates from breast cancer, prostatic cancer, and intestinal cancer in different countries can be explained on the basis of differences in fat intake alone. It is therefore of interest to consider possible effects of other dietary constituents on carcinogenesis.

Analysis of data from FAO Food Balance Sheets for 132 different countries showed that total fat intake was strongly...
correlated with animal fat, animal protein, and total caloric intake and, to a lesser extent, with total protein and vegetal fat (Table 5). Since mortality from breast cancer shows a strong positive correlation with total fat intake, it is to be expected that it will also show positive correlations with other dietary variables such as animal protein and total calories, and this in fact observed (15).

In the animal experiments discussed earlier, restriction of caloric intake had an inhibiting effect on tumorigenesis, but rather severe restriction was required in most instances to produce a marked reduction in tumor yield, and the effect did not appear to be specific for any particular type of tumor. It seems reasonable to expect that caloric restriction may also have an inhibitory effect on human carcinogenesis in countries where large segments of the population are undernourished, but the data from animal experiments would lead one to expect a relatively unselective effect with regard to different cancer sites. Although caloric intake may be a factor in human carcinogenesis, it does not appear to offer a practical approach to the problem.

A positive correlation between animal protein intake and breast cancer mortality has been noted by Drasar and Irving (26) as well as by ourselves (15), but the results of animal experiments indicate that the protein content of the diet can be varied over a wide range without much effect on tumor yield. Preliminary studies also failed to show differences in tumor yield as a result of feeding different types of dietary protein (Table 4)

There is little evidence that vitamins or minerals play a significant role in tumorigenesis, and effects of other normal ingredients of the diet have not been investigated experimentally to any extent. There has been much speculation recently about the possible beneficial effects of dietary fiber (11, 29, 53). High-residue diets accelerate passage of material through the digestive tract and may reduce tumor incidence in humans. Drasar and Irving (26) were unable to find any correlation between dietary fiber and cancers of the breast and colon, but a more detailed subsequent analysis showed a small negative correlation between cereal fiber and cancer of the colon (51). Natural diets fed to animals normally give a much higher residue than do purified diets, and tumor yields tend to be lower on the former type of diet (31, 94). Our own experience is in agreement with this (Chart 2).

In human diets, variations in one component are almost always associated with variations in others, and this makes it difficult to assess the effect of any one dietary component. For example, low-residue diets frequently contain higher levels of refined carbohydrate, and dietary fat is correlated with animal protein intake. This problem also extends to animal studies. Thus, the fat content of the diet cannot be increased without decreasing either the carbohydrate or protein, and it is often difficult to be certain which change is responsible for observed effects.

Environmental factors are considered to have a much greater influence on cancer incidence than do genetic traits (43), and diet may be one of the more important environmental variables. The large geographic differences in human cancer mortality give a measure of the potential for altering cancer incidence if these environmental factors can be identified and their mechanism of action determined. Because of the magnitude of the cancer problem in terms of human suffering and economic loss (33), it seems very desirable to explore such leads as rapidly as possible. This can be done by collecting more and better information on relationships between environmental variables and cancer incidence or mortality in human populations, by continuing to study effects of diet and other environmental variables on cancer incidence in animal models, and by comparing results obtained in these models with the epidemiological data on humans.

References


Table 5

Correlation coefficients between dietary variables

<table>
<thead>
<tr>
<th>Total fat</th>
<th>Animal fat</th>
<th>Animal protein</th>
<th>Total calories</th>
<th>Total protein</th>
<th>Vegetal fat</th>
<th>Carbohydrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal fat</td>
<td>0.951 (p &lt; 0.01)</td>
<td>0.931 (p &lt; 0.01)</td>
<td>0.878 (p &lt; 0.01)</td>
<td>0.801 (p &lt; 0.01)</td>
<td>-0.078 (NS)</td>
<td>-0.070 (NS)</td>
</tr>
<tr>
<td>Animal protein</td>
<td>0.931 (p &lt; 0.01)</td>
<td>0.841 (p &lt; 0.01)</td>
<td>0.777 (p &lt; 0.01)</td>
<td>0.224 (p &lt; 0.01)</td>
<td>+0.099 (p &lt; 0.01)</td>
<td>-0.075 (NS)</td>
</tr>
<tr>
<td>Total calories</td>
<td>0.878 (p &lt; 0.01)</td>
<td>0.841 (p &lt; 0.01)</td>
<td>0.777 (p &lt; 0.01)</td>
<td>0.224 (p &lt; 0.01)</td>
<td>+0.099 (p &lt; 0.01)</td>
<td>-0.075 (NS)</td>
</tr>
<tr>
<td>Total protein</td>
<td>0.801 (p &lt; 0.01)</td>
<td>0.777 (p &lt; 0.01)</td>
<td>0.784 (p &lt; 0.01)</td>
<td>0.235 (p &lt; 0.01)</td>
<td>+0.335 (p &lt; 0.01)</td>
<td>+0.286 (p &lt; 0.01)</td>
</tr>
<tr>
<td>Vegetal fat</td>
<td>-0.078 (NS)</td>
<td>-0.070 (NS)</td>
<td>-0.075 (NS)</td>
<td>+0.071 (NS)</td>
<td>+0.182 (NS)</td>
<td>-0.044 (NS)</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>(NS)</td>
<td>(NS)</td>
<td>(NS)</td>
<td>(NS)</td>
<td>(NS)</td>
<td>(NS)</td>
</tr>
<tr>
<td>Vegetal protein</td>
<td>-0.268 (p &lt; 0.01)</td>
<td>-0.300 (p &lt; 0.01)</td>
<td>-0.360 (p &lt; 0.01)</td>
<td>+0.018 (NS)</td>
<td>+0.264 (NS)</td>
<td>+0.069 (NS)</td>
</tr>
</tbody>
</table>

* Based on Food Balance Sheets for 132 countries (34).

NS, not significant.
Diet and Hormone-dependent Cancers


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Experimental Evidence of Dietary Factors and Hormone-dependent Cancers

Kenneth K. Carroll


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