Review

Caloric Restriction and Cancer

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Summary In 1909 Moreschi observed that tumors transplanted into underfed mice did not grow as well as those transplanted into mice fed ad libitum. His finding stimulated a decade of research which showed that caloric restriction also affected negatively the growth of spontaneous tumors. Between 1920 and 1940 little work was done in this area, possibly because of limiting methodology. In the 1940s the laboratories of Tannenbaum (Chicago) and Baumann (Wisconsin) were able to design studies using defined diets and showed that the observed effect was due to caloric content of the diet independently of the source of calories. After another active decade research activity in the calorie-cancer area declined until it was reborn in the 1980s. By the 1980s knowledge of physiology and molecular biology had advanced enough to allow investigators to probe mechanisms underlying the calorie-cancer phenomenon. We now know that caloric expenditure (as work or exercise) will lead to reduced risk. Energy restriction enhances DNA repair and moderates oxidative damage to DNA. Energy restriction reduces oncogene expression as well. Over a half century ago, Boutwell noted that energy restriction in female rats resulted in adrenal hypertrophy and reduced weight of ovaries and uterus. He suggested that energy restriction resulted in "pseudohypophysectomy." We now know that adrenalectomy can negate the effects of caloric restriction. Caloric restriction also affects insulin metabolism and may influence gene expression. These recent observations should help us understand some of the basic mechanisms involved in establishment and proliferation of tumors.

Key Words caloric restriction, exercise, insulin, metabolism

In 1935 McCay et al. (1) showed that underfed rats lived almost twice as long as ad libum fed controls. The diet contained 40% casein, 22% starch, 10% lard, 10% sucrose, 6% mineral mix, 5% yeast, 5% cod liver oil, and 2% cellulose (37.8 en% protein, 30.3 en% carbohydrate, 31.9 en% fat) and was fed at a level which limited weight gain to 10 g every 2–3 mo. The average life span of male rats was increased by 70%. That of female rats was not increased but the upper range of their life span rose from 1,189 to 1,421 d. The underfed rats showed evidence of a lower incidence of tumors (2). Thirty years earlier Moreschi (3) showed that the growth of transplanted tumors in mice was reduced significantly by underfeeding. The total weight of tumors in freely fed mice was 7.6±0.8 g whereas it was only 1.3±0.2 g in mice fed 1 g diet daily. A few years later Rous (4) reported that underfeeding inhibited growth of both spontaneous and transplanted tumors in mice. Sugiu and Benedict (5) found that recurrence of tumors after excision in mice was 82% in fully fed mice, but only 27% in underfed mice. Most of the early (1940–1950) work on caloric effects in tumorigenesis was carried out in the laboratories of Tannenbaum, at the Michael Reese Hospital in Chicago, and Baumann at the University of Wisconsin.

Originally Tannenbaum underfed mice in order to achieve caloric restriction and underfeeding did indeed inhibit spontaneous and chemically-induced tumors in several strains of mouse (6) (Table 1). However, realizing that simple underfeeding could lead to trace nutrient (minerals, vitamins) deficiencies Tannenbaum began using a formula diet consisting of commercial dog or fox chow, skim milk powder, and corn starch. The level of corn starch was manipulated in order to achieve the desired reduction in calories. Boutwell et al. (7), using a scientifically designed semi-purified diet, confirmed the tumor inhibiting effects of caloric restriction. Two basic studies carried out in the 1940s were by Lavik and Baumann (8) who showed that a high-fat, low calorie diet was about half as carcinogenic as a low-fat, high calorie diet (Table 2), and by Tannenbaum (9) who showed caloric restriction was effective only when imposed during the promotion phase of tumor growth (Table 3).

Visscher et al. (10) studied the effect of about 33% caloric restriction on spontaneous mammary tumors in virgin C3H mice. After 16 mo the calorie restricted mice exhibited no tumors whereas the freely-fed mice showed a 72% incidence of tumors. Histological examination of the ovaries, uteri, and mammae of the restricted mice suggested pseudohypophysectomy as the result of lower energy intake and the mechanism of action of caloric restriction was suggested to be a reduction in the level of ovarian secretion (11). The overall inhibitory effects of caloric restriction on the growth of spontaneous, transplanted or induced tumors in rats...
Table 1. Effects of underfeeding on carcinogenesis.  

| Mouse strain | Carcinogen | Site  | Duration (wk) | No. of tumors |
|--------------|------------|-------|---------------|---------------|
|              |            |       |               | Full fed | Underfed |
| ABC          | BP         | Skin  | 67            | 22       | 7        |
| Swiss        | BP         | Skin  | 26            | 24       | 6        |
| C57          | BP         | Subq. | 34            | 36       | 22       |
| DBA<sup>2</sup> | Spont. | Breast | 64            | 13       | 3        |
| DBA<sup>3</sup> | Spont. | Breast | 56            | 20       | 1        |

1 Adapted from Tannenbaum (6).  
2 Twelve virgin, 32 parous females.  
3 Fifty virgin females.

Table 2. Influence of calories and fat on methylcholanthrene-induced skin tumors in mice.  

| Regimen | Tumor incidence (%) |
|---------|---------------------|
| Calories | Fat       |              |
| Low      | Low       | 0            |
| Low      | High      | 28           |
| High     | Low       | 54           |
| High     | High      | 66           |

1 Adapted from Lavik and Baumann (8).

Table 3. Period of caloric restriction as related to tumor incidence.  

| Regimen | Tumor incidence (%) |
|---------|---------------------|
| Initiation | Promotion       |
| Ad libitum | Ad libitum   | 69          |
| Ad libitum | Restricted   | 34          |
| Restricted | Ad libitum   | 55          |
| Restricted | Restricted   | 24          |

1 Adapted from Tannenbaum (9). Skin tumors induced in mice by benzpyrene.

Table 4. Mammary and colon tumors in rats calorie restricted by 40%.

| Regimen | Fat | Type<sup>1</sup> | Amount (%) | Incidence (%) |
|---------|-----|------------------|------------|---------------|
| Mammary tumors<sup>2</sup> | CNO | 4.0             | 14/24 (58) |
| Ad libitum | CNO | 7.9             | 0/23 (0)   | 16           |
| Restricted | Ad libitum | CO | 4.0             | 16/20 (80)  |
| Restricted | Restricted | CO | 7.9             | 4/20 (20)   |
| Colon tumors<sup>3</sup> | BO | 4.0             | 17/20 (85) |
| Ad libitum | BO | 7.9             | 7/20 (35)  | 18           |
| Restricted | Ad libitum | CO | 4.0             | 19/19 (100) |
| Restricted | Restricted | CO | 7.9             | 10/19 (53)  |

1 CNO, coconut oil plus 1% CO; CO, corn oil; BO, butter oil plus 1% CO.  
2 Induced in female Sprague-Dawley rats by DMBA.  
3 Induced in male F344 rats by DMH.

and mice have been reviewed (12–14).

We studied effects of amount and type of fat in caloric restriction. In view of the earlier study by Carroll and Khor (15) which reported unsaturated fat to be more co-carcinogenic than saturated fat we compared corn oil effects with those of coconut or butter oils. As Table 4 shows, caloric restriction reduces the incidence of 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumors or 1,2-dimethylhydrazine (DMH)-induced colon tumors. The restriction is more effective in the presence of saturated fat. Boissonneault et al. (19) studied effects of DMBA on mammary tumor development in rats fed high or low fat diets or a high fat, restricted diet (Table 5). The high fat, restricted diet provided almost four times as much fat, but 19% fewer calories and led to 84% lower tumor incidence.

We (20) set about to determine the lowest level of restriction which began to effect carcinogenesis. As Table 6 shows as little as 10% restriction leads to reductions of 36, 10, and 47% in tumor multiplicity, weight, and burden, respectively.

In a further study of fat effects, rats were fed DMBA...
and then placed on ad libitum diets containing 5, 15 or 20% fat or 25% energy restricted diets containing 20 or 26.7% fat (21). The rats ingesting 15 or 20% fat ad libitum or 20 or 26.7% fat in the restricted diets ate exactly the same amount of fat daily. Among the ad libitum fed rats tumor incidence rose sharply between intake of 5 or 15% fat. Tumor multiplicity rose by 58 and 116% in comparing rats fed 15 or 20% fat with those fed 5% fat. Tumor weight increased by 15 and 45% with increasing fat load and tumor burden by 57 and 181%. In the rats fed the 25% restricted diet tumor incidence was lower than in those fed 5% corn oil ad libitum. Going from 20 to 26.7% corn oil in the restricted rats led to increases in tumor weight and tumor burden of 75 and 53%, respectively (Table 7). It would appear that increasing dietary fat leads to increases in tumor size.

The experiments described above involved institution of caloric restriction at the beginning of each particular study. How early in the course of the experiment must restriction be instituted to be effective? Tannenbaum (22), studying the incidence of spontaneous mammary tumors, placed mice on a restricted regimen at 2, 5 or 9 mo of life. After 20 mo the level of tumor inhibition was 100% in mice placed on the restricted diet at 2 mo, 95% when restriction was begun at 5 mo, and 80% when begun at 9 mo. Weindruch and Walford (23) studied tumor incidence and survival in 1 y old mice placed on 28% caloric restriction for 1 mo and on 44% restriction thereafter. As can be seen from Table 8, life span was increased by 23% in tumor-free mice and by about 10% in tumor-bearing mice. Incidence of multiple tumors, lung tumors, lymphomas, and hepatomas were reduced by 63, 50, 34, and 7%, respectively. When rats were placed on varying patterns of ad libitum feeding or caloric restriction incidence of DMBA-induced mammary tumors was correlated with weight gain, caloric intake, and feed efficiency (24) (Table 9).

Ross and Bras (25) studied tumorigenesis in three groups of male rats-those fed ad libitum over their life span, those whose calories were restricted by 70% over their life span, and those who were calorie-restricted for 7 wk after weaning then placed on an ad libitum diet. Restriction from weaning extended life span by about

| Food intake | Group | High fat | Low fat | High fat restricted |
|-------------|-------|----------|---------|---------------------|
| g/d         | 8.0±0.3 | 11.0±0.7 | 6.7±0.2 |
| kcal/d      | 40.8±1.5 | 42.2±2.7 | 34.1±1.0 |
| g fat/d     | 2.7±0.10 | 0.6±0.04 | 2.2±0.07 |
| Tumor incidence (%) | 11/15 (73) | 6/14 (43) | 1/14 (7) |

1 Adapted from Boissonneault et al. (19).

| Regimen | Tumor incidence (%) | Multiplicity2 | Average tumor weight (g) | Tumor burden (g) |
|---------|---------------------|---------------|--------------------------|------------------|
| Ad libitum | 12/20 (60%) | 4.7±1.3 | 2.0±0.8 | 10.1±3.3 |
| 10% Restriction | 12/20 (60%) | 3.0±0.8 | 1.8±0.5 | 5.4±3.0 |
| 20% Restriction | 8/20 (40%) | 2.8±0.7 | 1.9±0.7 | 4.7±1.9 |
| 39% Restriction | 7/20 (35%) | 1.3±0.3 | 0.7±0.6 | 0.9±0.8 |
| 40% Restriction | 1/20 (5%) | 1.0 | | |
| Probability | <0.005 | NS | ≤0.10 | ≤0.05 |

1 Adapted from Klurfeld et al. (20).
2 Tumors/tumor-bearing rat.
3 NS-not significant.

All diets contained 5% corn oil.

| Regimen | Incidence (%) | Multiplicity2 | Tumor weight (g) | Tumor burden (g) |
|---------|---------------|---------------|------------------|------------------|
| Ad libitum | 13/20 (65) | 1.9±0.3 | 2.0±0.7 | 4.2±1.9 |
| 5% Corn oil | 17/20 (85) | 3.0±0.6 | 2.3±0.7 | 6.6±2.7 |
| 20% Corn oil | 16/29 (80) | 4.1±0.6 | 2.9±0.5 | 11.8±3.2 |
| Restricted | 12/20 (60) | 1.9±0.4 | 0.8±0.2 | 1.5±0.5 |
| 26.7% Corn oil | 6/20 (30) | 1.5±0.3 | 1.4±1.0 | 2.3±1.6 |
| Probability | ≤0.005 | ≤0.0001 | ≤0.0001 | ≤0.0001 |

1 Adapted from Klurfeld et al. (21).
2 Tumors/tumor-bearing rat.
Table 8. Life span and spontaneous cancer incidence in mice calorie restricted beginning at 1 y of age.1

| Tumor type | Incidence (%) | Mean age at death (mo) |
|------------|---------------|------------------------|
|            | Control | Restricted | Control | Restricted |
| No tumor   | 13     | 25         | 33.7±2.4 | 41.3±0.9 |
| Multiple   | 16     | 6          | 34.1±0.8 | 40.3±1.9 |
| Lung       | 12     | 6          | 34.4±1.7 | 38.6±2.2 |
| Lymphoma   | 47     | 31         | 31.9±0.9 | 36.2±1.2 |
| Hepatoma   | 43     | 40         | 33.9±0.8 | 35.1±1.0 |

1 Adapted from Weindruch and Walford (23).
2 Sixty-seven restricted mice, 68 control mice. Controls fed 160 kcal/wk; restricted fed 115 kcal/wk for 1 mo and 90 kcal/wk thereafter.

Table 9. DMBA-induced mammary tumor incidence in rats subjected to variable caloric restriction.1

| Regimen | Incidence (%) | Weight gain (g) | Caloric intake | FE×10², ³ |
|---------|---------------|-----------------|----------------|-----------|
| A-A-A-A | 50            | 156             | 7,508          | 2.08      |
| R-R-R-R | 20            | 76              | 5,624          | 1.35      |
| R-A-A-A | 60            | 152             | 7,401          | 2.05      |
| R-R-A-A | 40            | 126             | 6,746          | 1.87      |
| A-R-R-A | 45            | 126             | 6,691          | 1.88      |
| A-R-R   | 30            | 99              | 6,958          | 1.42      |
| Correlation with incidence, r | 0.96 | 0.83 | | 0.94 |

1 Adapted from Kritchevsky et al. (24).
2 A=ad libitum; R=restricted. Each letter=1 mo.
3 FE=feed efficiency (weight gain/caloric intake).

50% and reduced the incidence of both benign and malignant tumors by 94%. The short (7 wk) period of restriction did not influence life span, but reduced the incidence of benign tumors by 49% and of malignant tumors by 16%.

Exercise will also reduce the incidence of transplanted (26) or chemically induced (27, 28) tumors. Treadmill exercise lowers incidence of DMH-induced colon tumors in rats to about the same extent as 25% caloric restriction (29) (Table 10).

What is the relevance of these animal studies to man? Hoffman suggested in 1913 (30) that “erroneous diet” was an important factor in carcinogenesis and later (31) proposed that energy excess was that factor. Berg (32) also proposed a relationship between high energy intake and carcinogenesis. Epidemiological data (33, 34) point to a relationship between cancer mortality and overweight. Miller et al. (35) reported that the daily caloric intake of women with breast cancer was significantly higher than that of controls and Jain et al. (36), and Bristol et al. (37) found caloric intake to be positively and significantly correlated with colon cancer incidence. Lyon et al. (38) showed that risk of colon cancer in both men and women increased with increasing caloric intake (Table 11). There are now a number of studies which show that cancer risk is inversely proportional to the degree of muscular activity required in various occupations (39–42) (Table 12).

Table 10. Influence of caloric restriction ± treadmill exercise on DMH-induced colon tumors in male F344 rats.1

| Regimen | Tumor incidence (%) | Multiplicity ³ |
|---------|---------------------|---------------|
| Diet    | Exercise⁴           |               |
| AL      | –                   | 75            | 2.1±0.4 |
| AL      | +                   | 36            | 1.3±0.2 |
| CR (25%)| –                   | 35            | 1.3±0.2 |
| CR (25%)| +                   | 29            | 1.1±0.1 |
| CR (40%)| –                   | 21            | 1.2±0.2 |

1 Adapted from Klurfeld et al. (29).
2 AL=ad libitum; CR=calorie restricted.
3 Tumors/tumor-bearing rat.
4 Treadmill 20 meters/min at 7° incline. 60 min/d. 5 d/wk.

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Table 11. Energy intake and colon cancer risk.¹

| Energy intake | Odds ratio as a function of kcal/d |
|---------------|---------------------------------|
| Males         | Energy intake                  |
| <1.900        | 1.900–2.600                   | 2.600   |
| Odds ratio    | 1.0                            | 2.5     |
| Females       | Energy intake                  |
| <1.300        | 1.300–1.800                   | >1.800  |
| Odds ratio    | 1.0                            | 2.0     |
| Total energy  | Intake must be evaluated before |
| Total energy  | attempting to assign a causal   |
| Intake        | role to any food or nutrient    |
| that may      | that may be postulated to play a |
| be postulated | role in colon cancer.           |
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The mechanism(s) by which caloric restriction affects carcinogenesis are moot. Insulin deprivation will inhibit tumor growth (43) and cell division (44). When tumor-bearing rats are rendered diabetic their tumors cease to grow (45). Plasma insulin levels of rats fall upon the institution of caloric restriction (Table 13). Levels of IGF-I fall at first, but rebound to normal and IGF-II levels are unaffected (47). Insulin receptors increase in calorie-restricted mice (48) and rats (49).

Energy restriction increases the activity of superoxide diamutase, catalase, and glutathione peroxidase in the livers of aging rats (50). Energy restriction also modulates oxidative DNA damage (51) and enhances DNA repair (52). It also reduces oncogene expression in rats (53) and mice (54), and inhibits expression of c-fos and c-ki-ras (55). A recent publication devoted to effects of
Caloric restriction (56) carries descriptions of the number of effects on antioxidant systems, oncogene expression, and genome expression exerted by this nutritional modality.

Caloric restriction by 40% increases slightly hexokinase activity in mammary tissue of normal female Sprague-Dawley rats, but inhibits activity of malic enzyme by 79% and of glucose-6-phosphate dehydrogenase by 70% (57). Female Sprague-Dawley rats were given DMBA and maintained on ad libitum or restricted diets. The ratio of large, palpable to small, non-palpable tumors was 4.9 in the controls and dropped to 3.8, 3.3, and 0.7, in rats subjected to 10, 20 or 30% caloric restriction, respectively (57) (Table 14). The data suggest that caloric restriction preferentially deprives tumors of nutrition.

Huseby et al. (11), Boutwell et al. (58), and their colleagues showed that caloric restriction in female rats resulted in adrenal hypertrophy and reduction in size of uterus and ovaries. They suggested that caloric restriction might be thought of as "pseudohypophysectomy." Pashko and Schwartz (59, 60) have shown that adrenalectomy can reverse the effects of caloric restriction on papilloma formation (Table 15) or lung tumor levels in mice. Plasma corticosterone levels are increased from 8.6±2.5mg/dL in normal mice to 15.0±3.2mg/dL in energy-restricted mice. These findings offer another av-

### Table 12. Colon cancer as related to lifetime work exercise.

| Proportion of life spent in sedentary or light work | Age 30–65 | Groups | Age 66–79 |
|-----------------------------------------------|--------|--------|--------|
|                                               | Cases | Controls | Odds ratio | Cases | Controls | Odds ratio |
| None                                          | 32    | 380     | 1.00     | 32    | 209     | 1.00     |
| 1–40%                                         | 49    | 365     | 1.59     | 20    | 85      | 1.54     |
| 41–100%                                       | 44    | 269     | 1.94²    | 33    | 123     | 1.75¹    |

¹ Adapted from Vena et al. (40).
² p≤0.01.
³ p≤0.05.

### Table 14. Mammary tumors in ad libitum-fed and calorically restricted female Sprague-Dawley rats.*

| Dietary regimen | Tumor incidence | Tumors/ tumor-bearing rat | Total tumor yield | Percent of LP¹ | Percent of SNP¹ | Ratio LP/SNP |
|-----------------|-----------------|---------------------------|-------------------|---------------|----------------|-------------|
| Ad libitum      | 60%             | 4.7±1.3²                 | 59                | 83            | 17             | 4.88        |
| 10% restriction | 60%             | 3.0±0.8                  | 36                | 79            | 21             | 3.76        |
| 20% restriction | 40%             | 2.8±0.7                  | 22                | 77            | 23             | 3.35        |
| 30% restriction | 35%             | 1.3±0.3                  | 10                | 40            | 60             | 0.67        |
| 40% restriction | 5%              | 1.0²                     | 1                 | —             | —              | —           |

* Adapted from Ruggeri et al. (57).
¹ LP, large, palpable; SNP, small, nonpalpable.
² Mean ± SE.
³ This single tumor was necrotic and not used for subsequent enzymatic studies.

### Table 13. Effect of caloric restriction on plasma insulin levels in rats.

| Experimental groups | Insulin (mU/mL) | Reference |
|---------------------|-----------------|-----------|
| Ad libitum (5% fat) | 122±16          | 20        |
| 30% restricted      | 42±5            |           |
| 40% restricted      | 41±8            |           |
| Ad libitum (5% fat) | 143±16          | 21        |
| 15% fat             | 164±15          |           |
| 20% fat             | 158±15          |           |
| Restricted (25%)    | 100±12          |           |
| 20% fat             | 117±13          |           |
| 26.7% fat           | 117±13          |           |
| Ad libitum (obese)  | 1003±193        | 46        |
| 40% restricted (obese) | 328±41 |           |

### Table 15. Papilloma development (TPA-induced) in adrenalectomized, food restricted mice.

| Group               | Regimen¹ | Papillomas/mouse |
|---------------------|----------|------------------|
| Sham operated       | AL       | 5.4              |
| Adrenalectomized    | AL       | 7.7              |
| Sham operated       | FR       | 1.0              |
| Adrenalectomized    | FR       | 6.2              |

¹ AL = ad libitum. FR = food restricted.

Note: Papillomas measured at 82 d. Adapted from Pashko and Schwartz (59).

The data suggest that caloric restriction preferentially deprives tumors of nutrition.
ene of investigation into the mechanisms of tumor growth and its control by caloric restriction. In 1945 Potter suggested that we might reduce cancer risk by eating less and exercising more (61). The simplest dietary advice would appear to be moderation, balance and variety (62).

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