

## The Role of Calories and Caloric Restriction in Carcinogenesis

*Richard Weindruch, PhD,\* Demetrius Albanes, MD,†  
and David Kritchevsky, PhD‡*

Caloric restriction (CR) without essential nutrient deficiency retards the rate of biologic aging and the development of cancer and other late-life diseases in mice and rats.<sup>20, 22, 36, 74</sup> The ability of CR to increase life span is not confined to rodents; it also occurs in fish, spiders, water fleas, rotifers, and other animals.<sup>74</sup> The mechanism(s) by which CR prolongs life and retards disease has, to date, eluded investigators.

This review begins with a historical overview of the CR paradigm. Summaries of CR's inhibitory effects on spontaneous and induced tumors in rodents are then provided, followed by commentary on potential underlying mechanisms. We conclude by reviewing the association between caloric intake and human cancer.

### HISTORICAL OVERVIEW

It was first reported in 1934 by McCay and Crowell<sup>37</sup> that CR increased the life span of rats. A full report of this study<sup>38</sup> showed that rats permitted to grow rapidly attained an average life span of about 480 days, whereas rats underfed in order to keep growth at a minimum (10 g every 2 to 3 months) lived to an average age of 800 to 900 days. The latter diet provided about 38% of calories as protein, 32% as fat, and 30% as carbohydrate. Underfeeding, as opposed to CR per se, may lead to deficiencies of minerals, vitamins, or other trace nutrients, but McCay recognized this possibility and added small amounts of cod liver oil and dried yeast to the diets of the food-restricted rats to prevent malnutrition. As discussed subsequently,

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\*Assistant Professor, Department of Medicine, and Associate Director, Institute on Aging, University of Wisconsin, Madison, Wisconsin

†Medical Epidemiologist, National Cancer Institute, Bethesda, Maryland

‡Associate Director, The Wistar Institute, Philadelphia, Pennsylvania

inquiry into CR's effects on spontaneous and induced tumors also dates back to the beginning of this century.

One can cite even earlier anecdotal literature linking low calorie diets to longevity and the prevention of cancer. Luigi Cornaro (The Venetian Centenarian [1464-1566]) lived a life of excess until age 40 and thereafter subsisted on 14 ounces of food daily, plus wine and exercise. Between the ages of 83 and 95 he wrote a series of monographs published under the title *The Art of Living Long*,<sup>15</sup> in which he stated, "Not to satiate oneself with food is the science of health." It is of additional interest to cite a published lecture by Frederick L. Hoffman,<sup>21</sup> which, six decades ago, attributed increased cancer risk to overnutrition.

### SPONTANEOUS TUMORS IN RODENTS

A complete survey of the literature on CR's inhibitory actions on spontaneous tumors in rodents is unnecessary in view of the subject's treatment in earlier reviews<sup>50, 67, 68</sup> and in more recent ones.<sup>1, 2, 44, 53, 72, 74</sup> Instead, an overview is provided followed by a discussion of selected recent findings.

In 1940, Tannenbaum<sup>63</sup> discovered that underfeeding retarded the appearance and reduced the incidence of spontaneous breast and lung tumors in mice from susceptible strains. These results were soon confirmed and extended to CR.<sup>58, 64, 71</sup> The impressive progress of the 1940s, however, was followed by a decade of nonactivity in this area.

In the 1960s and 1970s, Ross<sup>50</sup> characterized CR's effects on spontaneous tumors and life span in male Sprague-Dawley rats. The incidence of the most common neoplasms (pituitary and pancreatic adenomas and lung reticulum cell sarcomas) was reduced by CR, whereas the incidence of the much rarer tumors was either unaffected or increased by CR. Ross and Bras<sup>51</sup> tested both long-term CR and a short period of CR (7 weeks) initiated at weaning. Control rats were fed ad libitum and lived less than 1000 days; they exhibited about a 26% incidence of benign tumors and a 10% incidence of malignant tumors. Rats subjected to severe, long-term CR (one third of ad libitum) lived up to 1400 days and had 90% fewer tumors. Rats on CR for 7 weeks showed a decrease in risk for developing benign tumors but did not exhibit increased life span. The final incidence of benign tumors was markedly reduced by long-term CR, whereas malignant tumor incidence was diminished only slightly.

In a study by Weindruch et al,<sup>75</sup> female mice from a long-lived hybrid strain were fed either 40 kcal/week (restricted) or 85 kcal/week (control) diets from 3 weeks of age. Their longevity and tumor incidence are shown in Figure 1. It should be noted that the control group was fed 20% less than the normal ad libitum intake. CR increased life span (average and 10th decile) by about 35%. The overall incidence of tumors was 78% for the control group and 38% for mice on CR. Lymphoma (the most common neoplasm) was found in 46% of the control group and only 13% of the CR mice. The average life span for lymphoma-bearing mice in the control and CR groups was 31 and 42 months, respectively. Hepatoma, the next most

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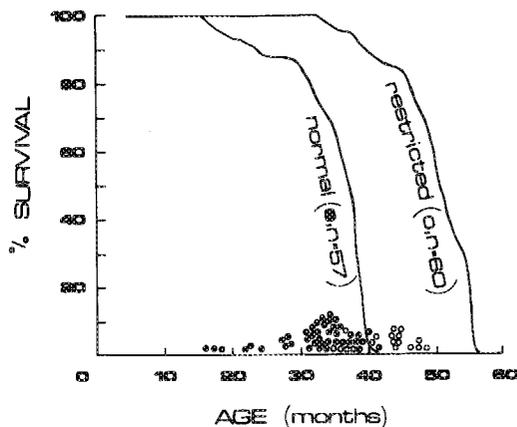
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Figure 1. Influence of caloric restriction on life span and tumor incidence in female mice from the long-lived C3B10RF<sub>1</sub> hybrid strain. The circles show the age of death for tumor-bearing mice. (Adapted from Weindruch R, Walford RL, Fligiel S, et al: The retardation of aging by dietary restriction: Longevity, cancer, immunity and lifetime energy intake. *J Nutr* 116:641, 1986; with permission.)



common tumor, was found in about 20% of mice from each cohort; however, hepatoma-bearing CR mice lived an average of 44 months, which was 10 months longer than for hepatoma-bearing controls.

With regard to possible human application, two findings are germane and encouraging. First, CR initiated in mid adulthood (12 months) in mice from long-lived strains retards the development of spontaneous tumors and extends life span by 10 to 20%.<sup>73</sup> A similar result was recently reported for the short-lived, mammary tumor-prone C3H/Bi mouse strain, first subjected to CR when 4 to 5 months old.<sup>60</sup> Second, moderate CR imposed at only 20 to 30% below the ad libitum intake level can reduce and retard late-life neoplasia in rodents.<sup>45, 49, 61, 66, 69</sup> The latter result is relevant because it is easier to adhere to a mild CR regimen than to a severe one.

Albanes<sup>1</sup> analyzed the relationships among caloric intake, body weight, and tumor incidence (spontaneous and induced) in mice, combining data from 14 reports and 82 experimental groups. For mice on CR, caloric intake averaged 29% less, and tumor incidence averaged 42% less than in the ad libitum groups. A nearly linear relationship between caloric intake and tumor incidence was observed among these studies (Fig. 2). Caloric intake appeared to be a more important factor than fat intake in reducing neoplasia.

### INDUCED TUMORS IN RODENTS

Research on the effects of underfeeding or CR on induced tumors has gone through three distinct periods. In 1909, Moreschi<sup>40</sup> was the first to report that growth of sarcomas transplanted into mice was directly related to total food intake. This finding elicited interest from many investigators, notably Rous,<sup>52</sup> who showed that underfeeding inhibited the growth of spontaneous as well as transplanted tumors in mice. During the next 25 years there was desultory interest in this area, with no organized investigation of the phenomenon.

The second manifestation of interest in CR and induced cancer began in the 1940s. Although many investigators contributed to the literature, the

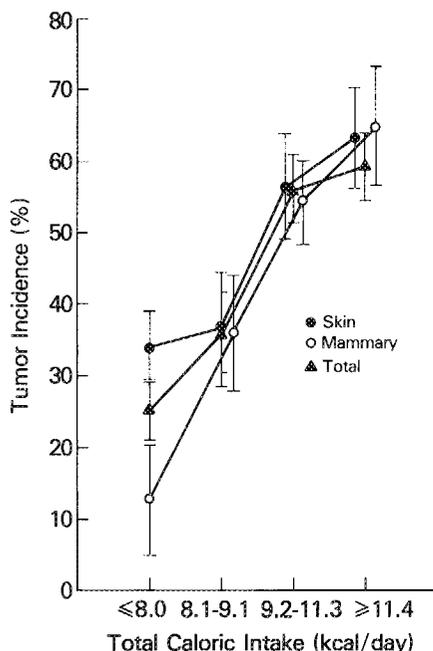


Figure 2. Relation between cumulative tumor incidence and caloric intake in mice from 82 experimental groups. Data are given for chemically induced skin tumors, spontaneous mammary tumors, and for all tumor sites. (From Albanes D: Total calories, body weight, and tumor incidence in mice. *Cancer Res* 47:1987, 1987; with permission.)

bulk of the findings came from Tannenbaum, who in his 1940 report<sup>63</sup> also described an inhibitory action of underfeeding on chemically induced tumors in mice. In later studies Tannenbaum began using a defined diet of sorts and looking into CR per se rather than underfeeding. The defined diet was crude by current standards, consisting of fox chow, skim milk powder, and cornstarch. Reduction of the level of cornstarch was Tannenbaum's means of restricting calories. Using this diet, he showed that CR inhibited both spontaneous and induced tumors in four different mouse strains,<sup>64</sup> and that CR acts during the promotion phase of carcinogenesis.<sup>65</sup> Other important investigations of this period were those of Lavik and Baumann<sup>33</sup> and Boutwell et al.,<sup>11</sup> who found that both the level of fat and calories affected chemically induced skin tumors in mice. Physical activity is another way of reducing caloric flux. Rusch and Kline<sup>57</sup> reported in 1944 that exercise reduced the growth of transplanted tumors in mice. Recently, Kritchevsky<sup>29</sup> reported that in rats treated with dimethylhydrazine (DMH), exercise reduced colon tumor incidence by 52% and tumor multiplicity by 38%. A 25% CR resulted in virtually identical reductions in incidence and multiplicity.

The latest period of interest in CR and induced cancer is less than a decade old. An important focus has been on the relative importance of calorie versus fat intake. Kritchevsky et al.<sup>30</sup> showed that rats whose caloric intake was restricted by 40% compared to ad libitum-fed controls exhibited significantly fewer DMBA-induced mammary tumors, even when their daily fat intake was double that of the control group. Such severe CR also inhibited growth of DMH-induced colon tumors.<sup>25</sup> Boissonneault et al.<sup>10</sup> found that rats fed a calorie-restricted high-fat diet exhibited a 90% lower

incidence of DMBA-induced mammary tumors than rats fed the same high-fat diet ad libitum and an 84% lower incidence of tumors than rats fed a low-fat diet ad libitum.

Comparison of effects of graded levels of CR<sup>26</sup> on DMBA-induced mammary cancers showed that 10% CR did not lower tumor incidence but reduced tumor multiplicity by 36% and tumor burden (grams of tumor per animal) by 47%. When calories were restricted by 20%, tumor incidence was reduced by 33%, multiplicity by 40%, and burden by 53%. CR by 30% led to 42% reduction in incidence, 72% in multiplicity, and 91% in burden. Consistent with findings for spontaneous tumors, this study showed that less than drastic CR was effective in reducing tumorigenicity. Comparison of 25% CR in diets containing high levels of fat showed significant reductions in tumor incidence, multiplicity, and burden in rats treated with DMBA.<sup>27</sup> Variable CR tested in DMBA-treated rats showed tumor incidence to be associated significantly with weight gain, total caloric intake, and feed efficiency.<sup>31</sup>

### CALORIC RESTRICTION AND TUMORS IN RODENTS: POTENTIAL MECHANISMS

How does CR act to reduce tumor incidence and delay tumor onset? There are several plausible mechanisms, some of which are supported by experimental findings. CR might reduce initiation through one or more of the following: less activation of carcinogens, more efficient detoxification or removal of activated carcinogens,<sup>45</sup> fewer ingested dietary carcinogens, reduced expression of tumor virus genes or protooncogenes,<sup>14, 41</sup> and enhanced DNA repair.<sup>34, 76</sup> The anticancer actions of CR might also depend on a reduction in promotion and, again, several nonmutually exclusive possibilities exist: lowered basal rates of cell proliferation,<sup>5, 42</sup> perhaps due to reductions in plasma insulin and related growth factors<sup>55, 56</sup>; reduced production of free radicals (believed to be involved in promotion<sup>13</sup>); increased rate of free radical removal resulting from increased activities of the free radical scavenging enzymes catalase and superoxide dismutase<sup>28, 59, 78</sup>; more vigorous immune responses<sup>74</sup>; and less energy for tumor growth.<sup>54</sup> Which (if any) of these postulated mechanisms underlie the antineoplastic actions of CR is at present unknown.

### HUMAN CANCER

Caloric intake has been linked to human cancer risk, but to a far lesser extent than for cancer in experimental animals. In addition to studies of caloric intake per se, other investigations have shed light on this issue through the assessment of two factors closely related to caloric intake: (1) physical activity level (i.e., the second major source of energy expenditure after basal metabolism); and (2) relative body weight, which in adulthood generally reflects caloric intake relative to energy expenditure. Studies of

caloric intake are first described, followed by brief summaries of cancer and the latter energy-related factors.

Caloric intake is usually assessed via dietary questionnaires such as 24-hour recall surveys, food frequency questionnaires, and the more complete diet history methods.<sup>8</sup> Food frequency questionnaires are most commonly used in epidemiologic research<sup>9, 46</sup>; however, these can, at best, only estimate energy intake. More valid measures of caloric intake such as are provided by multiple-day dietary diaries are difficult and time-consuming and hence are utilized in relatively few epidemiologic or clinical studies. Advantages and shortcomings of several available methods for measuring individual caloric intake have been previously discussed.<sup>8</sup> In contrast, ecologic investigations of this area commonly use per capita food "disappearance" information or some other estimate of average population food consumption.

Four cross-sectional and seven case-control studies have described relationships between caloric intake and cancer in humans. Countries with higher total per capita food calories showed greater cancer incidence and mortality compared to those with low per capita caloric intake.<sup>6</sup> This report presented site- and sex-specific correlation coefficients ( $r$ ) for 33 countries. Significant positive associations were observed between total calories and cancer of the breast, colon, rectum, uterus, and kidney in women ( $r$  values of 0.56 to 0.66) and cancer of the colon, rectum, kidney, and nervous system in men ( $r = 0.55$  to 0.75). A major problem in most of such international comparisons of cancer as related to dietary factors (e.g., caloric or fat intake) is the relatively poor quality of the data concerning food availability. The very nature of data concerning fat availability on a national level, for example, renders them general rather than precise. A cross-sectional study of colorectal cancer mortality in Hong Kong<sup>19</sup> found more than a twofold increase for persons in the highest of three family income categories as compared to the lowest income group. The consumption of all foods was increased among high-income individuals. Estimated daily caloric intake for male adults was 3900 kcal in the highest income group and 2700 kcal in the low-income population. No correlation was found between caloric intake and breast or ovarian cancer mortality in a Japanese population.<sup>24</sup>

Only seven case-control studies have described the relationship between caloric intake and cancer. Five of these found a positive association between total caloric intake and cancer risk, and two found no clear relationship. The seven studies follow.

(1) Miller et al<sup>39</sup> reported an association between dietary fat and breast cancer based on a 24-hour recall. The average daily caloric intake of breast cancer cases was slightly (but significantly) higher than that of controls. Caloric intake estimated from a dietary history questionnaire and 4-day diary records showed somewhat reduced case-to-control differences. The association was stronger among postmenopausal women than among premenopausal women. No clear dose-response relationship was present for caloric intake, however.

(2) In contrast, Jain et al<sup>23</sup> described a significant, positive dose-risk relationship for total calories among both men and women and the incidence

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(3) A study of large bowel cancer by Bristol et al<sup>12</sup> found greater caloric intakes for cancer patients (mean = 2370 kcal) than for controls (2046 kcal), with relative risk increasing from 1.0 (less than 1936 kcal) to 2.2 and 2.3 (more than 2486 kcal).

(4) Lyon et al<sup>35</sup> also observed higher caloric intake among colon cancer patients as compared to controls. Relative risk ratios of 1.0, 2.5, and 2.5 were observed for below 1900 kcal, 1900 to 2600 kcal, and above 2600 kcal in men, and 1.0, 2.0, and 3.6 for below 1300 kcal, 1300 to 1800 kcal, and above 1800 kcal in women. When adjustment was made for differences in body mass index, there was no alteration of the effect of energy intake.

(5) and (6) In contrast, two other studies<sup>32, 62</sup> of colorectal cancer reported negligible case-control differences in caloric intake. Stemmermann's group<sup>62</sup> observed slightly lower and higher mean caloric intake among colon and rectum cancer patients, respectively, as compared to controls. Likewise, only small case-control differences, inconsistent across sexes, were described for energy intake by Kune et al,<sup>32</sup> in an in-depth evaluation of dietary factors and large bowel cancer.

(7) A recent study<sup>18</sup> of the nutritional epidemiology of gastric cancer showed that men and women reporting high caloric intake had significantly elevated risk of disease. Among men, risk increased significantly from 1.0 to 1.7, 4.1, and 2.4 for the four increasing calorie quartiles (less than 1567, 1567 to 2043, 2044 to 2657, and greater than 2657 kcal/day). In women, the risk ratios were 1.0, 3.1 and 2.6 for three intake levels of less than 1440, 1440 to 1883, and greater than 1883 kcal/day.

These studies therefore provide evidence for a positive relationship between caloric intake and cancer of the breast and possibly colorectum and stomach.

Research generally also supports the notion that higher levels of physical activity protect against the development of cancer.<sup>3</sup> Data are primarily available for colon, lung, and total cancer in men, and there is some evidence for a protective role in breast and endometrial carcinoma as well. Studies addressing this question have usually examined either occupational histories or involvement in athletics. Several studies demonstrate an inverse relationship between occupational physical activity, based on job classification, and the development of malignancy. For example, in three recent studies, the risk of colon cancer was increased by between 30 and 100% among men employed in sedentary occupations.<sup>16, 17, 70</sup> Although other recent studies support a protective role for activity or fitness level,<sup>4, 7, 43</sup> there are conflicting reports, such as Polednak's.<sup>47</sup>

The relationship between body weight, body mass indices, or relative body weight and site-specific cancer has been investigated in more than 90 epidemiologic studies.<sup>3</sup> In most of these investigations, a positive association has been demonstrated between body mass index or relative body weight and cancer of the breast, endometrium, ovary, or kidney. Adult weight

gain has also been implicated in some studies of breast and large bowel cancer. Body weight has been correlated with cancer incidence or mortality rates in several international studies. Reduced breast cancer survival and higher recurrence rates have also been consistently shown in pre- and postmenopausal patients of greater absolute body weight.

Further research in this field must address several important issues. To begin with, caloric intake data should be collected in diet-cancer studies whenever possible. This has not generally occurred and is important not only from the standpoint of evaluating the primary effect on cancer of calories but also for affording a better understanding of any calorie-nutrient-cancer interrelationship that may be present. For example, the independence of the effects of specific nutrients (e.g., fat) on cancer risk from those of calories, or the relative importance of absolute nutrient intake versus nutrient density (i.e., nutrient intake/caloric intake), can only be tested if calorie data are available. The importance of such considerations has been highlighted by Willett and Stampfer.<sup>77</sup> Likewise, attention should also be paid to other components of energy metabolism (e.g., physical activity expenditure and body fatness), so that a more complete picture of the effects of caloric intake (especially relative to requirements) on human carcinogenesis can be obtained. In one study,<sup>35</sup> for example, adjustment for differences in body mass index did not influence the caloric effects. Only when a large number of epidemiologic studies of nutrition and cancer have evaluated these various facets will a more complete understanding of the complex relationships be possible.

### SUMMARY

Studies in mice and rats show that caloric restriction (CR) without malnutrition lowers the incidence of most spontaneous and induced tumors and delays their onsets. The maximum life spans of rodents and other experimental animals (e.g., fish, spiders, water fleas) are extended by CR. The molecular events that underlie these outcomes remain unelucidated. Although epidemiologic studies have not usually examined the relationship between caloric intake and cancer incidence, recent findings suggest a positive association for certain cancers such as colorectal, breast, and stomach. It is apparent that future studies of diet and cancer in humans must seriously assess the role of calories and energy balance as well as their interaction with the effects of specific nutrients.

### REFERENCES

1. Albanes D: Total calories, body weight, and tumor incidence in mice. *Cancer Res* 47:1987, 1987
2. Albanes D: Caloric intake, body weight, and cancer: A review. *Nutr Cancer* 9:199, 1987
3. Albanes D: Energy balance, body size, and cancer. *CRC Crit Rev Oncol Hematol*, 10:283, 1990
4. Albanes D, Blair A, Taylor PR: Physical activity and risk of cancer in the NHANES I population. *Am J Public Health* 79:744, 1989

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5. Albanes D, Salbe AD, Levander OA, et al.: The effect of early caloric restriction on colonic cellular growth in rats. *Nutr Cancer* 13:73, 1990
6. Armstrong B, Doll R: Environmental factors and cancer incidence and mortality in different countries with special reference to dietary practices. *Int J Cancer* 15:617, 1975
7. Blair SN, Kohl HW III, Paffenbarger RS Jr, et al: Physical fitness and all-cause mortality. *JAMA* 262:2395, 1989
8. Block G: A review of validations of dietary assessment methods. *Am J Epidemiol* 125:164, 1985
9. Block G, Hartman AM, Dresser CM, et al: A data-based approach to diet questionnaire design and testing. *Am J Epidemiol* 124:453, 1986
10. Boissonneault GA, Elson CE, Pariza MW: Net energy effects of dietary fat on chemically induced mammary carcinogenesis in F344 rats. *J Natl Cancer Inst* 76:335, 1986
11. Boutwell RK, Brush MK, Rusch HP: The stimulating effect of dietary fat on carcinogenesis. *Cancer Res* 9:741, 1949
12. Bristol JB, Emmett PM, Heaton KW, et al: Sugar, fat, and the risk of colorectal cancer. *Br Med J* 291:1467, 1985
13. Cerutti PA: Prooxidant states and tumor promotion. *Science* 227:375, 1985
14. Chen R-F, Good RA, Engelman RW, et al: Suppression of mouse mammary tumor proviral DNA and protooncogene expression: Association with nutritional regulation of mammary tumor development. *Proc Natl Acad Sci USA* 87:2385, 1990
15. Cornaro L: *The Art of Living Long*. Milwaukee, WI Butler, 1918
16. Garabrant DH, Peters JM, Mack TM, et al: Job activity and colon cancer risk. *Am J Epidemiol* 119:1005, 1984
17. Gehardsson M, Norell SE, Kiviranta H, et al: Sedentary jobs and colon cancer. *Am J Epidemiol* 123:775, 1986
18. Graham S, Haughey B, Marshall J, et al: Diet in the epidemiology of gastric cancer. *Nutr Cancer* 13:19, 1990
19. Hill M, MacLennan R, Newcombe K: Diet and large bowel cancer in three socioeconomic groups in Hong Kong (letter). *Lancet* 1:436, 1979
20. Hocman G: Prevention of cancer: Restriction of nutritional energy intake (joules). *Comp Biochem Physiol* 91A:209, 1988
21. Hoffman FL: *Cancer Incidence and Overnutrition*. Newark, New Jersey, Prudential Insurance Co, 1927
22. Holehan AM, Merry BJ: The experimental manipulation of ageing by diet. *Biol Rev* 61:329, 1986
23. Jain M, Cook GM, Davis FG, et al: A case-control study of diet and colorectal cancer. *Int J Cancer* 26:757, 1980
24. Kato I, Tomnaga S, Kuroishi T: Relationship between westernization of dietary habits and mortality from breast and ovarian cancers in Japan. *Jpn J Cancer Res (Gann)* 78:349, 1987
25. Klurfeld DM, Weber MM, Kritchevsky D: Inhibition of chemically induced mammary and colon tumor promotion by caloric restriction in rats fed increased dietary fat. *Cancer Res* 47:2759, 1987
26. Klurfeld DM, Welch CB, Davis MJ, Kritchevsky D: Determination of degree of energy restriction necessary to reduce DMBA-induced mammary tumorigenesis in rats during the promotion phase. *J Nutr* 119:286, 1989
27. Klurfeld DM, Welch CB, Lloyd LM, Kritchevsky D: Inhibition of DMBA-induced mammary tumorigenesis by caloric restriction in rats fed high-fat diets. *Int J Cancer* 43:922, 1989
28. Koizumi A, Weindruch R, Walford RL: Influences of dietary restriction and age on liver enzyme activities and lipid peroxidation in mice. *J Nutr* 117:361, 1987
29. Kritchevsky D: Influence of caloric restriction and exercise on tumorigenesis in rats. *Proc Soc Exp Biol Med* 193:35, 1990
30. Kritchevsky D, Weber MM, Klurfeld DM: Dietary fat versus caloric content in initiation and promotion of 7,12-dimethylbenz[a]anthracene-induced mammary tumorigenesis in rats. *Cancer Res* 44:3174, 1984
31. Kritchevsky D, Welch CB, Klurfeld DM: Response of mammary tumors to caloric restriction for different periods during the promotion phase. *Nutr Cancer* 12:259, 1989
32. Kune S, Kune CA, Watson LF: Case-control study of dietary etiological factors: The Melbourne colorectal cancer study. *Nutr Cancer* 9:21, 1987

33. Lavik PS, Baumann CA: Further studies on the tumor promoting action of fat. *Cancer Res* 3:739, 1943
34. Licastro F, Weindruch R, Davis LJ, et al: Effect of dietary restriction upon the age-associated decline of lymphocyte DNA repair activity in mice. *Age* 11:48, 1988
35. Lyon JL, Mahoney AW, West DW, et al: Energy intake: Its relationship to colon cancer risk. *J Natl Cancer Inst* 78:853, 1987
36. Masoro EJ: Nutrition and aging—a current assessment. *J Nutr* 115:842, 1985
37. McCay CM, Crowell MF: Prolonging the life span. *Sci Monthly* 39:405, 1934
38. McCay CM, Crowell MF, Maynard LA: The effect of retarded growth upon the length of the life span and upon the ultimate body size. *J Nutr* 10:63, 1935
39. Miller AB, Kelly A, Choi NW, et al: A study of diet and breast cancer. *Am J Epidemiol* 107:499, 1978
40. Moreschi C: Beziehungen zwischen Ernährung und Tumorwachstum. *Z Immunitätsforsch* 2:651, 1909
41. Nakamura KD, Duffy PH, Lu M-H, et al: The effect of dietary restriction on *myc* protooncogene expression in mice: A preliminary study. *Mech Ageing Dev* 48:199, 1989
42. Ogura M, Ogura H, Ikehara S, et al: Decrease by chronic energy intake restriction of cellular proliferation in the intestinal epithelium and lymphoid organs in autoimmunity-prone mice. *Proc Natl Acad Sci USA* 86:5918, 1989
43. Paffenbarger RS, Hyde RT, Wing AL: Physical activity and incidence of cancer in diverse populations: A preliminary report. *Am J Clin Nutr* 45:312, 1987
44. Pariza MW: Caloric restriction, *ad libitum* feeding, and cancer. *Proc Soc Exp Biol Med* 183:293, 1986
45. Pegram RA, Allaben WT, Chou MW: Effect of caloric restriction on aflatoxin B<sub>1</sub>-DNA adduct formation and associated factors in Fischer 344 rats: Preliminary findings. *Mech Ageing Dev* 48:167, 1989
46. Pietinen P, Hartman AM, Haapa E, et al: Reproducibility and validity of dietary assessment instruments. *Am J Epidemiol* 128:655, 1988
47. Polednak AP: College athletics, body size, and cancer mortality. *Cancer* 38:382, 1976
48. Pollard M, Luckert PH, Snyder D: Prevention of prostate cancer and liver tumors in L-W rats by moderate dietary restriction. *Cancer* 64:686, 1989
49. Rehm S, Rapp KG, Deerberg F: Influence of food restriction and body fat on life span and tumour incidence in female outbred Han:NMRI mice and two sublines. *Z Versuchstierkd* 27:249, 1985
50. Ross MH: Nutrition and longevity in experimental animals. In Winick M (ed): *Nutrition and Aging*. New York, John Wiley, 1976, p 43
51. Ross MH, Bras G: Lasting influence of early caloric restriction on prevalence of neoplasms in the rat. *J Natl Cancer Inst* 47:1095, 1971
52. Rous P: The influence of diet on transplanted and spontaneous mouse tumors. *J Exp Med* 20:433, 1914
53. Ruggeri BA: The effects of caloric restriction on neoplasia and age-related degenerative processes. In Alfin-Slater RB, Kritchevsky D (eds): *Human Nutrition 7: Cancer and Nutrition*. New York, Plenum, 1991, pp 187–210
54. Ruggeri BA, Klurfeld DM, Kritchevsky D: Biochemical alterations in 7,12-dimethylbenz[*a*]anthracene-induced mammary tumors from rats subjected to caloric restriction. *Biochim Biophys Acta* 929:239, 1987
55. Ruggeri BA, Klurfeld DM, Kritchevsky D, et al: Caloric restriction and 7,12-dimethylbenz[*a*]anthracene-induced mammary tumor growth in rats: Alterations in circulating insulin, insulin-like growth factors I and II, and epidermal growth factor. *Cancer Res* 49:4130, 1989
56. Ruggeri BA, Klurfeld DM, Kritchevsky D, et al: Growth factor binding to 7,12-dimethylbenz[*a*]anthracene-induced mammary tumors from rats subject to chronic caloric restriction. *Cancer Res* 49:4135, 1989
57. Rusch HP, Kline BE: The effect of exercise on the growth of a mouse tumor. *Cancer Res* 4:116, 1944
58. Saxton JA Jr, Boon MC, Furth J: Observations on the inhibition of development of spontaneous leukemia in mice by underfeeding. *Cancer Res* 4:401, 1944
59. Semsei I, Rao G, Richardson A: Changes in the expression of superoxide dismutase and

- catalase as a function of age and dietary restriction. *Biochem Biophys Res Commun* 164:620, 1989
60. Shao R, Dao ML, Day NK, et al: Dietary manipulation of mammary tumor development in adult C3H/BI mice. *Proc Soc Exp Biol Med* 193:313, 1990
  61. Snyder DL, Pollard M, Westmann BS, et al: Life span, morphology, and pathology of diet-restricted germ-free and conventional Lobund-Wistar rats. *J Gerontol* 45:B52, 1990
  62. Stemmermann GN, Nomura AMY, Heilbrun LK: Dietary fat and the risk of colorectal cancer. *Cancer Res* 44:4633, 1984
  63. Tannenbaum A: The initiation and growth of tumors. Introduction. I. Effects of under-feeding. *Am J Cancer* 38:335, 1940
  64. Tannenbaum A: The genesis and growth of tumors. II. Effects of caloric restriction per se. *Cancer Res* 2:460, 1942
  65. Tannenbaum A: The dependence of the genesis of induced skin tumors on the caloric intake during different stages of carcinogenesis. *Cancer Res* 4:673, 1944
  66. Tannenbaum A: The dependence of tumor formation on the degree of caloric restriction. *Cancer Res* 5:609, 1945
  67. Tannenbaum A: Effects of varying caloric intake upon tumor incidence and tumor growth. *Ann NY Acad Sci* 49:5, 1947
  68. Tannenbaum A, Silverstone H: Nutrition and the genesis of tumors. In Raven RW (ed): *Cancer*, vol 1. London, Butterworth, 1957, p 306
  69. Tucker MJ: The effect of long-term food restriction on tumours in rodents. *Int J Cancer* 23:803, 1979
  70. Vena JE, Graham S, Zielezny M, et al: Lifetime occupational exercise and colon cancer. *Am J Epidemiol* 122:357, 1985
  71. Visscher MB, Ball ZB, Barnes RH, et al: The influence of caloric restriction upon the incidence of spontaneous mammary carcinoma in mice. *Surgery* 11:48, 1942
  72. Weindruch R: Dietary restriction, tumors and aging in rodents. *J Gerontol* 44:67, 1989
  73. Weindruch R, Walford RL: Dietary restriction in mice beginning at one year of age: Effects on lifespan and spontaneous cancer incidence. *Science* 215:1415, 1982
  74. Weindruch R, Walford RL: *The Retardation of Aging and Disease by Dietary Restriction*. Springfield, IL, Charles C Thomas, 1988
  75. Weindruch R, Walford RL, Fligiel S, et al: The retardation of aging by dietary restriction: Longevity, cancer, immunity and lifetime energy intake. *J Nutr* 116:641, 1986
  76. Weraachakul N, Strong R, Wood WC, et al: The effect of aging and dietary restriction on DNA repair. *Exp Cell Res* 181:197, 1989
  77. Willett W, Stampfer MJ: Total energy intake: Implications for epidemiologic analyses. *Am J Epidemiol* 124:17, 1986
  78. Yu BP, Laganieri S, Kim J-W: Influence of life-prolonging food restriction on membrane lipoperoxidation and antioxidant states. In Simic MG, Taylor KA, Ward JF, et al (eds): *Oxygen Radicals in Biology and Medicine*. New York, Plenum, 1989, p 1067

*Address reprint requests to*

Richard Weindruch, PhD  
Associate Director  
University of Wisconsin  
Institute on Aging  
425 Henry Mall, Room 330  
Madison, WI 53706