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EFFECT OF CALORIC RESTRICTION ON AGE-ASSOCIATED CANCERS

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Abstract — Caloric restriction (CR) without malnutrition in mice and rats reduces the incidence of spontaneous tumors and delays their appearance while increasing maximum life span. These results depend largely on CR per se, and not on low intakes of fat or other nutrients. Although most studies have tested CR imposed early in life, CR started in midadulthood also retards cancer and aging. The way(s) by which CR impedes cancers remain unclear, but possibilities include less cellular oxidative damage, retarded immunologic aging, hormonal changes, less energy available for cell proliferation, reduced exposure to dietary carcinogens and promoters, enhanced DNA repair, and less carcinogen activation. Far less is known about the relationship between caloric intake and cancer incidence in humans; however, recent findings suggest a positive association for certain cancers.

Key Words: caloric restriction, cancer, aging

INTRODUCTION

MCCAY AND coworkers (1935) were the first to find that caloric restriction (CR) increased the life span of rats. They observed that rats allowed to grow rapidly showed an average life span of only 16 months whereas animals underfed so as to minimize growth (10 g every 2–3 months) lived to an average age of 28 months. Underfeeding, as opposed to CR per se, may lead to essential nutrient deficiencies, but McCay was aware of this possibility and supplemented the diets of the restricted rats with small amounts of cod liver oil and dried yeast to prevent malnutrition.

McCay's founding study began the evolution of CR from it being an interesting curiosity to its present place as an experimental paradigm of high significance. It is now recognized that CR uniquely retards the rate of aging and the development of tumors (spontaneous and induced) as well as several other late-life diseases in mice and rats (reviewed in Masoro, 1985; Holehan and Merry, 1986; Hocman, 1988; Weindruch and Walford, 1988; Weindruch *et al.*, 1991). The increase in life span also occurs in spiders, water fleas, rotifers, fish, and other animals subjected to CR (Weindruch and Walford, 1988). The mechanism(s) by which CR extends life and forestalls disease are unknown, but are being actively investigated.

This review begins with a discussion of CR's inhibitory effects on spontaneous tumors in rodents. A consideration of potential underlying mechanisms follows. Lastly, studies that evaluated cancer incidence and caloric intake in humans are briefly discussed.

SPONTANEOUS TUMORS IN MICE AND RATS

A comprehensive survey of CR's inhibitory actions on spontaneous tumors in rodents is nonessential because of the subject's thorough review earlier (Tannenbaum, 1947; Tannenbaum and Silverstone, 1957) and recently (Albanes, 1987a, b; Weindruch and Walford, 1988; Ruggeri, 1991). Instead, a historical overview and a discussion of selected recent findings is presented.

An early major work in this area was reported by Tannenbaum (1940), who found that underfeeding retarded the appearance and reduced the incidence of spontaneous breast and lung tumors in mice from highly susceptible strains. This finding was soon confirmed and extended to CR per se (Tannenbaum, 1942; Visscher *et al.*, 1942; Saxton *et al.*, 1944).

In the 1960s and 1970s, Ross evaluated CR's effects on spontaneous tumors and longevity in male Sprague-Dawley rats (reviewed in Ross, 1976). The most common neoplasms (pituitary and pancreatic adenomas, lung reticulum cell sarcomas) were reduced in incidence by CR, while the incidence of uncommon tumors was either unaffected or increased by CR. In one study (Ross and Bras, 1971), both long-term CR and a short period of CR (7 weeks) initiated at weaning were tested. The control rats (fed ad libitum) lived less than 33 months, exhibited a 26% incidence of benign tumors, and a 10% incidence of malignant tumors. Rats subjected to severe, long-term CR (~35% of ad libitum) lived up to 46 months and had 90% fewer tumors. The rats on CR for 7 weeks showed a lowered risk for developing benign tumors, but did not show increased life span.

Longevity and tumor incidence for female mice from a long-lived first filial generation (F_1) hybrid strain fed either 40 kcal/week (restricted) or 85 kcal/week (control) diets from 3 weeks of age are shown in Fig. 1 (Weindruch *et al.*, 1986). These control mice were fed 20% less than the normal ad libitum intake. Life span (average and 10th decile) was increased by about 35% in the restricted group. The overall tumor incidence was 78% for the control group and 38% for the restricted mice. Lymphoma was the most common neoplasm occurring in 46% of the control mice and only 13% of the CR cohort. Lymphoma-bearing mice in the control and CR groups showed average life spans of 31 and 42 months, respectively. The next most common tumor was hepatoma. It was found in about 20% of mice from each cohort; however, the average life span for hepatoma-bearing CR mice was 44 months, which exceeded that of hepatoma-bearing controls by 10 months.

Albanes (1987b) evaluated the relationships among caloric intake, body weight, and tumor incidence (spontaneous and induced) in mice by combining data from 14 reports and 82 experimental groups. Compared to the ad libitum groups, mice subjected to CR showed a 29% lower average caloric intake and a 42% reduction in tumor incidence. A nearly linear relationship between caloric intake and tumor incidence was observed. Caloric intake appeared to be a more influential factor than fat intake in reducing neoplasia.

Two findings from the rodent studies are germane and promising from the standpoint of possible human use of CR. First, CR need not be severe for it to reduce cancer incidence, as a restriction of only 20–30% below the ad libitum intake level can lower and delay late-life neoplasia (Tannenbaum, 1945; Tucker, 1979; Rehm *et al.*, 1985; Pollard *et al.*, 1989).

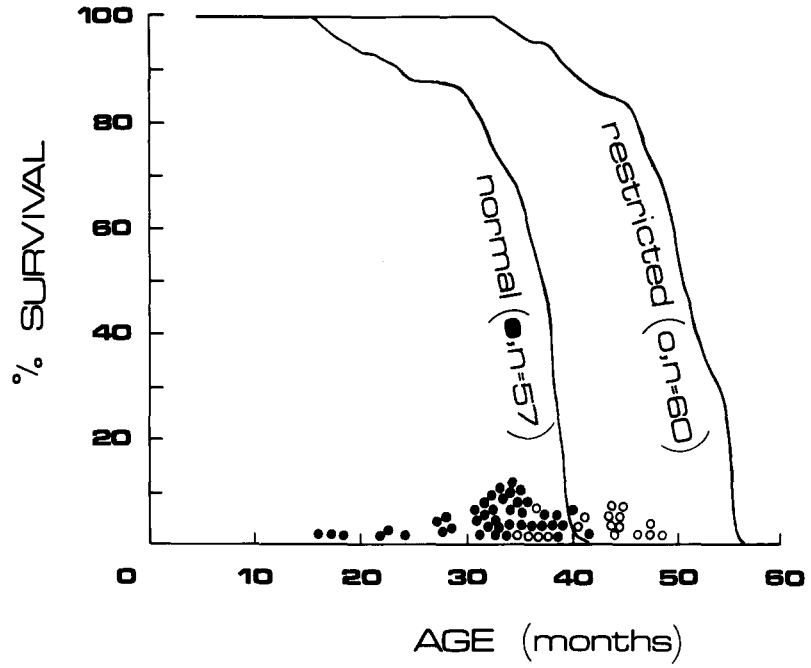

FIG. 1. Influence of caloric restriction initiated at 3 weeks of age on life span and tumor incidence in female mice from the long-lived C3B10RF$_1$ hybrid strain. The circles show the age of death for tumor-bearing mice. Adapted from Weindruch *et al.* (1986).

This result is pertinent because it is easier to follow a mild CR regimen than a severe one. Second, CR initiated in midadulthood (12 months) in mice from long-lived strains retards the development of spontaneous tumors and extends life span by 10–20% (Fig. 2) (Weindruch and Walford, 1982). A similar outcome occurred for the short-lived, mammary-tumor prone C3H/Bi mouse strain first restricted at 4–5 months of age (Shao *et al.*, 1990). It therefore appears that CR's actions on cancer and aging do not depend in large part on interfering with maturation.

POSSIBLE MECHANISMS

There are several explanations for how CR reduces tumor incidence and delays tumor onset. Tumor initiation could be reduced via one or more of the following: lower levels of ingested dietary carcinogens, less carcinogen activation, more efficient detoxification or removal of activated carcinogens (Pegram *et al.*, 1989), reduced expression of tumor virus genes or protooncogenes (Nakamura *et al.*, 1989; Chen *et al.*, 1990; Koizumi *et al.*, 1990), and enchanced DNA repair (Licastro *et al.*, 1988; Weraachakul *et al.*, 1989). CR's anticancer actions might also depend on a lessening of promotion, and once more, several reasonable, nonmutually exclusive possibilities can be listed: lowered basal rates of cell proliferation (Ogura *et al.*, 1989; Albanes *et al.*, 1990), possibly a result of reductions in

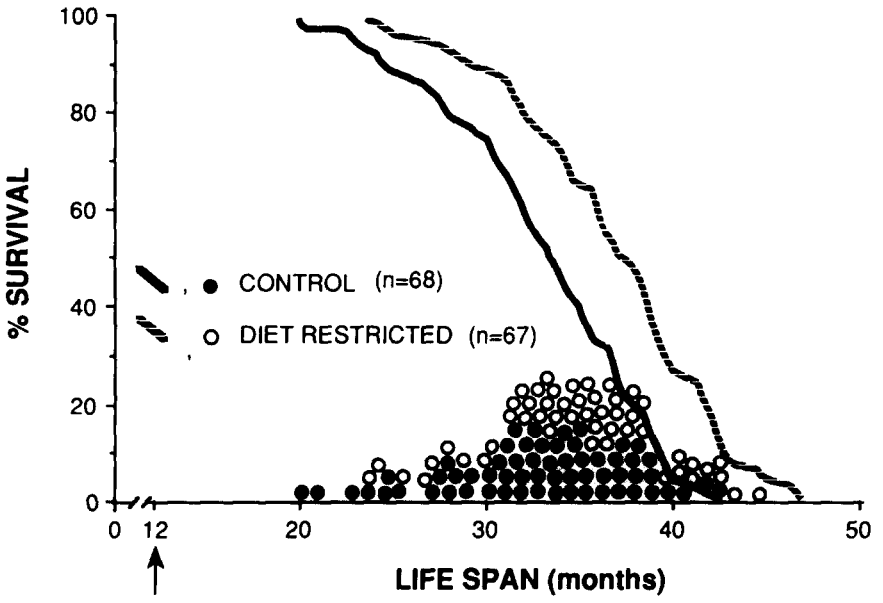

FIG. 2. Influence of caloric restriction initiated at 12 months of age on life span and tumor incidence in male mice from the long-lived B10C3F$_1$ hybrid strain. The overall tumor incidence was 87% for the normally fed mice and 75% for the restricted cohort. The circles show the age of death for tumor-bearing mice. Adapted from Weindruch and Walford (1982).

plasma insulin and related growth factors (Ruggeri *et al.*, 1989); a lower production of free radicals (which are thought to be involved in promotion [Cerutti, 1985]); increased rate of free radical removal due to increased activities of the free radical scavenging enzymes catalase and superoxide dismutase (Koizumi *et al.*, 1987; Semsei *et al.*, 1989; Yu *et al.*, 1989); more vigorous immune responses (Weindruch and Walford, 1988); and less energy for tumor growth (Ruggeri *et al.*, 1987). It is unknown which (if any) of these postulated mechanisms underlie the antineoplastic actions of CR.

TABLE 1. CROSS-SECTIONAL STUDIES ON THE RELATIONSHIP BETWEEN CALORIC INTAKE AND CANCER

Type of cancer	*Main finding*	*Reference*
Many	Countries with higher total per capita food calories showed greater cancer incidence and mortality compared to those with low per capita caloric intake.	Armstrong and Doll (1975)
Colorectal	High income persons in Hong Kong reported much higher calorie intakes and showed a twofold increased cancer rate as compared to persons in the lowest income group.	Hill *et al.* (1987)
Breast, Ovary	No correlation was found between caloric intake and cancer mortality in a Japanese population.	Kato *et al.* (1987)

TABLE 2. CASE-CONTROL STUDIES ON THE RELATIONSHIP BETWEEN CALORIC INTAKE AND CANCER

Type of cancer	*Main finding*	*References*
Breast	The average daily caloric intake of cases was higher than that of controls.	Miller *et al.* (1978)
Colorectal	A positive dose–risk relationship for total calories and cancer incidence was observed among men and women.	Jain *et al.* (1980), Bristol *et al.* (1985), Lyon *et al.* (1987)
Colorectal	Negligible case-control differences in caloric intake were seen.	Graham *et al.* (1990)
Gastric	Men and women reporting high calorie intakes had elevated risk of the disease.	Kune *et al.* (1987), Stemmerman *et al.* (1984)

CALORIES AND CANCER IN HUMANS

Very early literature links CR to longevity and cancer prevention. Luigi Cornaro (1464–1566) lived a life of excess until age 40, when he switched to a daily regimen of 14 ounces of food (plus wine and exercise). In his 80s and 90s he wrote *The Art of Living Long* (Cornaro, 1918), wherein he stated, "Not to satiate oneself with food is the science of health." Early in the 20th century, Rabagliati (1904) reached the conclusion that overfeeding was an important cause of cancer, a view also expressed by Hoffman (1927).

Recently, caloric intake and high body weight have been linked to human cancer risk (reviewed by Albanes, 1990), but to a far lesser extent than in experimental animals. Four cross-sectional (Table 1) and seven case-control studies (Table 2) describe relationships between caloric intake and cancer in humans. The results from most of these studies support the view that high caloric intakes are associated with the development of certain human cancers. The relationship between body weight, body-mass indices or relative body weight, and site-specific cancer has been investigated in more than 90 epidemiological studies. A positive association between body-mass index or relative body weight has been demonstrated in most of these investigations. Adult weight gain has also been implicated in some studies of breast and large bowel cancer. Reduced breast cancer survival and higher recurrence rates have been consistently shown in pre- and postmenopausal patients of greater absolute body weight.

Although not conclusive, the above findings suggest that the anticancer actions of CR that are so clear in rodents may also apply to humans. A definitive answer should come from future epidemiologic studies of diet and cancer designed to critically evaluate the role of calories in human carcinogenesis.

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