

Protection against Cancer by Energy Restriction: All Experimental Approaches Are Not Equal¹

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During the 20th century, there were intermittent periods of interest in the role of energy restriction on the development of cancer in various model systems and in human populations (1). Since the mid-1980s there has been a sustained resurgence of interest in this topic, which recently has intensified, in part due to the availability of new tools to study the mechanisms underlying the beneficial effects of energy restriction (2). Currently, there is a general “lumping” of protocols designed to investigate energy restriction with little consideration of whether differences that reflect varying patterns of energy regulation in humans exist among these protocols. We propose that differences do exist and that they are largely unrecognized. This article is not intended to be exhaustive, but rather to focus attention on three different patterns observed in body weight regulation in response to energy restriction and to propose how each pattern translates to the study of cancer risk in human populations.

Perception vs. reality

This commentary was conceived in part on the basis of the authors' participation in numerous discussions that were generally critical of the potential translational value of studies of energy restriction in animal models to humans. Many such discussions ended with the question of what effects periods of undernutrition and/or starvation during wars and/or famines have been shown to have on cancer rates in human populations. Although the results of two such studies were reported recently (3,4), conversations such as these underscored an important perception among many investigators, i.e., that energy restriction studies are investigations of starvation. Although it is indeed possible to study the effects of starvation, the reality is that starvation is not being studied in most energy restriction work conducted using experimental models. In fact, in the mid-1980s, a series of papers were published that underscored this perspective (5–9). In those papers, the point was made that animals given a reduced number of calories in energy restriction studies were actually the “real control group” and that animals allowed to consume food ad libitum represented the experimental group that was “abnormal” by virtue of the fact that they were actually overfed.

Definitions

Many terms are used to identify experiments in which the effects of energy restriction have been studied (Table 1). They include: energy restriction, caloric or calorie restriction, diet restriction, dietary energy restriction, total dietary restriction, food restriction, fasting, starvation and underfeeding. Table 2 provides a list of experimental design factors that vary among energy restriction protocols. Of these, the most fundamental difference in methodology that distinguishes among the protocols represented by these terms is whether restriction is achieved by feeding a reduced amount of food without any adjustment in the nutrient density of the diets, or the nutrient density of dietary formulations is altered to permit investigation of the effects of energy restriction per se, without covariation in the amounts of nutrients and other dietary factors that are ingested. In our judgment, the former approach is best referred to as total dietary restriction, whereas the latter approach more accurately describes energy (calorie) restriction. The remaining discussion will be limited to energy restriction. Although similar models can be proposed for total dietary restriction, it is less clear if results are due to the restriction of energy per se or to other nutrients and dietary factors.

Models of energy restriction

A key point made in this commentary is that attention must be directed to the patterns of body weight change that are induced by various restricted feeding protocols and how these patterns compare with patterns of weight regulation observed in human populations. The following discussion operationally defines three models of energy restriction and the human state that each pattern models.

Model 1. Weight gain prevention. Strong evidence is emerging that individuals who experience <5 kg of adult weight gain and maintain a body mass index < 25 kg/m², have a lower risk for cancer at several major sites (10). We propose that this situation is modeled in energy restriction experiments in which the pattern of body weight gain is like that shown in Figure 1. A key point illustrated by these growth curves is that weight loss is not an obligatory component of energy restriction, i.e., it is possible to maintain animals in an energy-restricted state while sustaining positive energy balance. It should be noted that this pattern of weight change has been reported in the literature to be induced by energy restriction, and its induction is associated with protection against experimentally induced cancer (11–16).

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TABLE 1

Terms commonly used to identify restriction protocols

Energy restriction ¹	Total dietary restriction ²
Calorie restriction	Dietary restriction
Caloric restriction	Food restriction
Dietary energy restriction	Fasting
Energy restriction	Starvation
	Total dietary restriction
	Underfeeding

¹ The nutrient density of dietary formulations is altered to permit investigation of the effects of energy restriction per se, without covariation in the amounts of nutrients and other dietary factors that are ingested.

² Restriction is achieved by feeding a reduced amount of food without any adjustment in the nutrient density of the diets.

Model II. Weight loss followed by maintenance of reduced body weight. An interesting question emerging from studies in human populations is whether risk for cancer is affected by the process of weight loss per se or if reduced cancer risk is attributed to maintenance of a lower weight, especially if weight loss results in weight maintenance below a body mass index of 25 kg/m² and an adult weight gain of <5 kg (10). This pattern of weight regulation, i.e., weight loss followed by maintenance of a lower body weight, is shown in **Figure 2**, and it is characteristic of changes in body weight reported by many investigators studying the effects of energy restriction in laboratory models (17–23). However, to our knowledge no one has designed an experiment that takes advantage of this profile of weight change to address specifically the question of the effects of the weight loss component of the experiment vs. the weight maintenance component of the experiment. Nevertheless, this point is potentially of considerable importance.

Model III. Cyclic periods of dieting. For large numbers of individuals, the pattern of adult weight regulation can best be characterized as cyclic, i.e., repetitive periods of weight gain followed by periods of weight loss, frequently with an overall pattern of increase in body weight over time. This pattern of weight regulation is shown in **Figure 3**. Laboratory experiments, although few in number, have been reported in which the effects of weight cycling on carcinogenesis have been studied (24–30). In general, intermittent periods of energy restriction do not inhibit carcinogenesis, and some reports have suggested that weight cycling may be associated with a modest acceleration of the carcinogenic response (25,30). From our perspective, more discussion of

TABLE 2

Experimental design factors that vary among energy restriction protocols

- Nutrient density of diets
- Use of an adaptation period to transition from ad libitum consumption to restricted feeding
- Use of meal feeding protocol: timing and duration of meals
- Age of onset of restriction
- Length of time restricted diets are fed
- Timing of restriction during the carcinogenic process

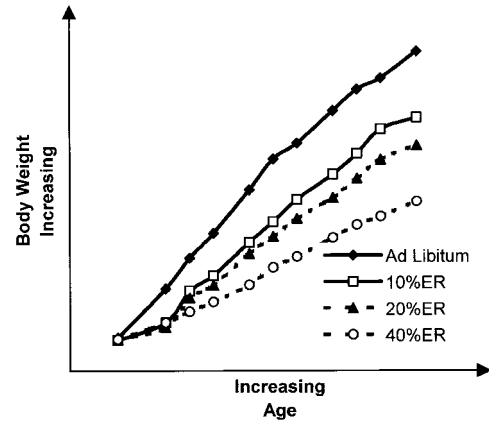


FIGURE 1 A model for weight gain prevention. Animals can be fed a wide range of a restricted amount of energy (ER) yet continue to gain weight, albeit at a rate that is slower than animals that consume food ad libitum. Examples of this model can be found in references (11–16); this figure was adapted from (11).

the basic model and the manner in which experiments are designed is required, but it is clear that such work is central to human health and illustrates that much remains to be learned about patterns of energy restriction, particularly those that may not be associated with protection against carcinogenesis.

In summary, although the perception may be that experimental protocols in which the effects of energy restriction are studied are relatively uniform, there are both blatant and subtle differences among these protocols. These differences can be used to advantage because they appear to model various approaches to and patterns of adult weight regulation in human populations. It is hoped that this discussion will create an awareness among investigators in this field of these differences and the many research opportunities that they engender. Moreover, it is hoped that this commentary will dispel the perception that studies of energy restriction are models for starvation with little relevance to common states in human populations.

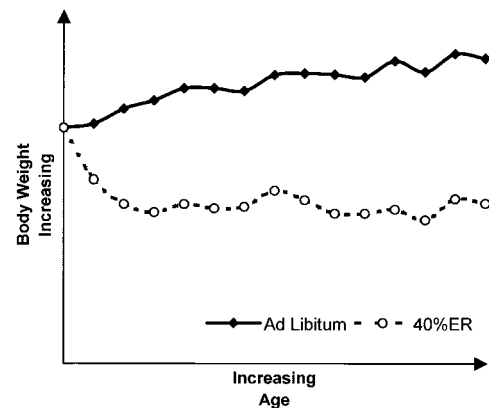


FIGURE 2 A model for weight loss followed by maintenance of reduced body weight. Animals respond to energy restriction first by losing weight, and then by maintaining a weight that is lower than observed in their control counterparts that consumed food ad libitum. Examples of this model can be found in references (17–23); this figure was adapted from (19).

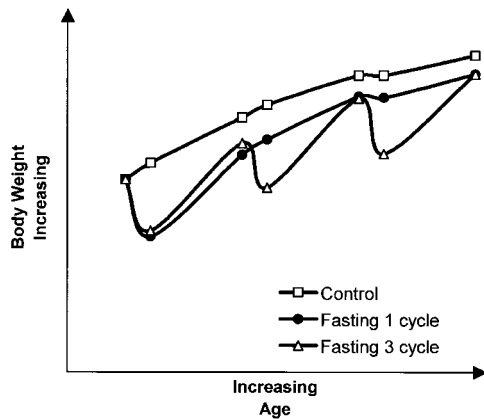


FIGURE 3 A model for cyclic periods of dieting. Animals can be subjected to intermittent periods of energy restriction (fasting) with cyclic patterns of weight loss and weight gain. Examples of this model can be found in references (24–30); this figure was adapted from (24).

LITERATURE CITED

1. Kritchevsky, D. (2001) Caloric restriction and cancer. *J. Nutr. Sci. Vitaminol. (Tokyo)* 47: 13–19.
2. Weindruch, R., Kayo, T., Lee, C. K. & Prolla, T. A. (2001) Microarray profiling of gene expression in aging and its alteration by caloric restriction in mice. *J. Nutr.* 131: 918S–923S.
3. Dirx, M. J., van den Brandt, P. A., Goldbohm, R. A. & Lumey, L. H. (2001) Energy restriction in childhood and adolescence and risk of prostate cancer: results from the Netherlands Cohort Study. *Am. J. Epidemiol.* 154: 530–537.
4. Nilsen, T. I. & Vatten, L. J. (2001) Adult height and risk of breast cancer: a possible effect of early nutrition. *Br. J. Cancer* 85: 959–961.
5. Boissonneault, G. A., Elson, C. E., & Pariza, M. W. (1986) Net energy effects of dietary fat on chemically induced mammary carcinogenesis in F344 rats. *J. Natl. Cancer Inst.* 76: 335–338.
6. Pariza, M. W. (1987) Dietary fat, calorie restriction, ad libitum feeding, and cancer risk. *Nutr. Rev.* 45: 1–7.
7. Pariza, M. W. & Boutwell, R. K. (1987) Historical perspective: calories and energy expenditure in carcinogenesis. *Am. J. Clin. Nutr.* 45: 151–156.
8. Pariza, M. W. (1986) Calorie restriction, ad libitum feeding, and cancer. *Proc. Soc. Exp. Biol. Med.* 183: 293–298.
9. Pariza, M. W. (1986) Calories and energy expenditure in carcinogenesis. *Bol. Asoc. Med. P. R.* 78: 456–458.
10. IARC (2002) *Weight Control and Physical Activity (6)*, IARC Handbook of Cancer Prevention. IARC Press, Lyon, France (in press).
11. Zhu, Z., Haeghele, A.D. & Thompson, H. J. (1997) Effect of caloric restriction on pre-malignant and malignant stages of mammary carcinogenesis. *Carcinogenesis* 18: 1007–1012.
12. Mukherjee, P., Sotnikov, A. V., Mangian, H. J., Zhou, J. R., Visek, W. J. & Clinton, S. K. (1999) Energy intake and prostate tumor growth, angiogenesis, and vascular endothelial growth factor expression. *J. Natl. Cancer Inst.* 91: 512–523.
13. Klurfeld, D. M., Welch, C. B., Davis, M.J. & Kritchevsky, D. (1989) Determination of degree of energy restriction necessary to reduce DMBA-

- duced mammary tumorigenesis in rats during the promotion phase. *J. Nutr.* 119: 286–291.
14. Kumar, S. P., Roy, S. J., Tokumo, K. & Reddy, B. S. (1990) Effect of different levels of calorie restriction on azoxymethane- induced colon carcinogenesis in male F344 rats. *Cancer Res.* 50: 5761–5766.
15. Engelman, R. W., Day, N. K. & Good R. A. (1994) Calorie intake during mammary development influences cancer risk: lasting inhibition of C3H/HeOu mammary tumorigenesis by peripubertal calorie restriction. *Cancer Res.* 54: 5724–5730.
16. Klurfeld, D. M., Lloyd, L. M., Welch, C. B., Davis, M. J., Tulp, O. L. & Kritchevsky, D. (1991) Reduction of enhanced mammary carcinogenesis in LA/N-cp (corpulent) rats by energy restriction. *Proc. Soc. Exp. Biol. Med.* 196: 381–384.
17. Birt, D. F., Pinch, H. J., Barnett, T., Phan, A. & Dimitroff, K. (1993) Inhibition of skin tumor promotion by restriction of fat and carbohydrate calories in SENCAR mice. *Cancer Res.* 53: 27–31.
18. Liu, Y., Duysen, E., Yaktine, A. L., Au, A., Wang, W. & Birt, D. F. (2001) Dietary energy restriction inhibits ERK but not JNK or p38 activity in the epidermis of SENCAR mice. *Carcinogenesis* 22: 607–612.
19. Przybyszewski, J., Yaktine, A. L., Duysen, E., Blackwood, D., Wang, W., Au, A. & Birt, D. F. (2001) Inhibition of phorbol ester-induced AP-1-DNA binding, c-Jun protein and c-jun mRNA by dietary energy restriction is reversed by adrenalectomy in SENCAR mouse epidermis. *Carcinogenesis* 22: 1421–1427.
20. Yoshida, K., Inoue, T., Nojima, K., Hirabayashi, Y. & Sado, T. (1997) Calorie restriction reduces the incidence of myeloid leukemia induced by a single whole-body radiation in C3H/He mice. *Proc. Natl. Acad. Sci. U.S.A.* 94: 2615–2619.
21. Hursting, S. D., Perkins, S. N. & Phang, J. M. (1994) Calorie restriction delays spontaneous tumorigenesis in p53-knockout transgenic mice. *Proc. Natl. Acad. Sci. U.S.A.* 91: 7036–7040.
22. Shields, B. A., Engelman, R. W., Fukaura, Y., Good, R. A. & Day, N. K. (1991) Calorie restriction suppresses subgenomic mink cytopathic focus-forming murine leukemia virus transcription and frequency of genomic expression while impairing lymphoma formation. *Proc. Natl. Acad. Sci. U.S.A.* 88: 11138–11142.
23. Klurfeld, D. M., Weber, M. M. & Kritchevsky, D. (1987) Inhibition of chemically induced mammary and colon tumor promotion by caloric restriction in rats fed increased dietary fat. *Cancer Res.* 47: 2759–2762.
24. Laconi, E., Tessitore, L., Milia, G., Yusuf, A., Sarma, D. S., Todde, P. & Pani, P. (1995) The enhancing effect of fasting/refeeding on the growth of nodules selectable by the resistant hepatocyte model in rat liver. *Carcinogenesis* 16: 1865–1869.
25. Mehta, R. S., Harris, S. R., Gunnett, C. A., Bunce, O. R. & Hartle, D. K. (1993) The effects of patterned calorie-restricted diets on mammary tumor incidence and plasma endothelin levels in DMBA-treated rats. *Carcinogenesis* 14: 1693–1696.
26. Rozen, R., Brigant, L. & Apfelbaum, M. (1994) Effects of cycles of food restriction followed by ad libitum refeeding on body composition and energy expenditure in obese rats. *Am. J. Clin. Nutr.* 59: 560–565.
27. Chambon-Savanovitch, C., Felgines, C., Walrand, S., Raul, F., Zarrabian, S., Meunier, M. T., Farges, M. C., Cynober, L. & Vasson, M. P. (2001) A pancreatic extract-enriched diet improves the nutritional status of aged rats. *J. Nutr.* 131: 813–819.
28. Chiara, M., Sesca, E., Binasco, V. & Tessitore, L. (1996) Fasting/refeeding enhances the development of mammary tumors induced by methylnitrosourea in the rat. *Boll. Soc. Ital. Biol. Sper.* 72: 211–216.
29. Premoselli, F., Sesca, E., Chiara, M., Binasco, V. & Tessitore, L. (1996) Fasting/refeeding enhances the crypt multiplicity in rat colon carcinogenesis induced by azoxymethane. *Boll. Soc. Ital. Biol. Sper.* 72: 239–245.
30. Tagliaferrro, A. R., Ronan, A. M., Meeker, L. D., Thompson, H. J., Scott, A. L. & Sinha, D. (1996) Cyclic food restriction alters substrate utilization and abolishes protection from mammary carcinogenesis female rats. *J. Nutr.* 126: 1398–1405.