

Dietary Restrictions and Cancer

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Dietary restriction (DR) alters a significant environmental factor in carcinogenesis, dietary intake, thus inhibiting both spontaneous and induced tumorigenesis. Potential mechanisms for the inhibition of spontaneous cancer may include the effects of DR to do the following: decrease body weight, which decreases cellular proliferation and increases apoptosis in a number of organs that increase and decrease with body size; decrease body temperature, thereby lowering the amount of endogenous DNA damage temperature generates; decrease oxidative damage, by increasing antioxidant damage defense systems; decrease, generally, cellular proliferation; and protect the fidelity of the genome by decreasing DNA damage, increasing DNA repair, and preventing aberrant gene expression. Potential mechanisms for reducing induced tumor incidence include lowering agent activation, changing agent disposition, decreasing the adducts most associated with agent toxicity, and inhibiting tumor progression through mechanisms similar to those that can effect spontaneous tumorigenesis. As a method to control a major source of environmental cancer, and as the major modulator of the agent induction of this disease, understanding how DR works may significantly contribute to the efforts to explain how diet impacts on development of cancer in the United States, and may suggest methods to reduce the adverse impacts of other environmental agents on the disease. — *Environ Health Perspect* 105(Suppl 4):989–992 (1997)

Key words: dietary restriction, cancer, diet, spontaneous carcinogenesis, induced carcinogenesis, body weight and cancer, oxidative damage, cellular proliferation

Introduction

Dietary restriction (DR) inhibits both spontaneous (1–3) and induced (3–5) carcinogenesis. Although many other environmental factors play a role in carcinogenesis [e.g., viruses (6)], diet remains the most significant overall (7–11). DR also modulates induced toxicity (10,12–16), inhibiting the induction of cancer by chemical (12–15), physical (ultraviolet light) (16), and viral (10) agents.

Despite its long history of study, the mechanism(s) by which DR inhibits cancer are not known. However, based on recent studies, there are a number of hypotheses that appear to provide a reasonable explanation for how DR modulates carcinogenesis.

DR has been used to describe a wide variety of protocols. As defined here, DR is a reduction in the amount of diet consumed to a level less than that eaten by

ad libitum (AL)-fed animals, without any observable malnutrition. Malnutrition is important to evaluate (and avoid) since it can cause immunodeficiency, which can enhance the expression of cancer (17). Restriction of dietary macronutrients can influence disease. For example, a reduction in fat intake reduces mammary tumors in rats (18), and protein restriction (PR) appears to inhibit certain cancers, such as liver or kidney tumors (19). However, fat restriction is almost always accompanied by total energy intake restriction, and fat restriction itself appears to be less important than total calorie restriction or protein (18,20). Additionally, the effect of PR is usually significantly less than with total DR (18,19). Thus, the rest of this discussion will focus on the anticarcinogenic action of caloric restriction without malnutrition.

Dietary Restriction and Spontaneous Cancer

Body Weight Considerations

DR delays the onset (8,10) and progression (21) of a number of cancers in rodents. A strong correlation among DR, body weight (BW), and cancer occurrence has been established (10,18,22,23). For instance, in B6C3F1 mice and F344 rats, the incidences of a number of common tumors appear to be correlated to BW at certain ages (10,18,22,23). The major tumor sites effected by DR in these animals are in the organs whose size is a function of animal BW. The factors that control organ weight have yet to be fully characterized, but appear to include levels of endogenous growth factors, whose presence stimulates increased proliferation and growth and whose absence induces increased apoptosis and organ shrinkage. Consistent with this idea is the observation that larger livers (even in the absence of increased BW, i.e., hepatomegaly) are correlated with an increased incidence of liver tumors (Figure 1). With DR, animals have smaller livers (1.07 vs 1.63 g in controls)(24), increased apoptosis (25), and a decrease in tumor incidences (11). Increased apoptosis may selectively remove damaged cells, thus reducing the chance of transformation (25). Exposure of cells with oxidative damage in organs to endogenous growth factors may be biologically the equivalent to promotion, for which oxidative damage is the initiator. Both BW and selected metabolic parameters are important predictors for

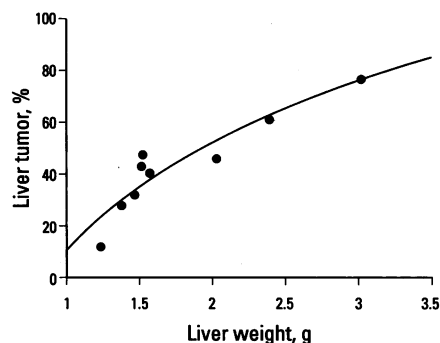


Figure 1. Relationship of liver weight to liver tumor incidence in male B6C3F1 mice. Each data point is a study with at least 48 animals derived from controls in National Toxicology Program studies (46–54). Relationship is a power function, where the power is approximately 1.5; $r=0.92$. Turturro et al. (22) present examples of techniques used.

This paper is based on a presentation at the symposium on Mechanisms and Prevention of Environmentally Caused Cancers held 21–25 October 1995 in Santa Fe, New Mexico. Manuscript received at *EHP* 16 April 1996; accepted 4 September 1996.

The authors acknowledge the support of the National Institute of Aging/National Center for Toxicological Research Interagency Agreement for the Project on Caloric Restriction for its ongoing support.

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Abbreviations used: AL, *ad libitum*; BW, body weight; DEN, diethylnitrosamine; DR, dietary restriction; PR, protein restriction.

breast cancer in women and colon cancer in men and women (26). These studies suggest common mechanisms may exist across species. This is not totally unexpected, since the mechanisms underlying the extrapolation are such basic biological processes.

Body Temperature Considerations

Another mechanism that may inhibit cancer is the lowering of body temperature that occurs with DR. Core body temperature is significantly lower in animals with DR (27). This decrease occurs whether the animals are fed every other day or every day, and the magnitude of the average decrement appears to be similar. A lowered body temperature will result in a decrease in the number of apurinic sites, apyrimidinic sites, and cross-links in the cellular DNA. This factor may also contribute to decrease in oxidative damage.

Free Radical Considerations

It has been suggested that DR operates via modulation of free radical metabolism, both by reducing the formation of free radicals and by a stimulation of free radical scavenger enzymes (28). This approach is supported by the impact of DR on catalase. Catalase is better protected from autooxidation in DR-fed animals (28), which enhances its activity. The activities of other liver free radical scavenger enzymes are also enhanced.

If the enzymes that protect from free radical scavenging are preserved in animals on DR, they may prevent oxidative damage from accumulating in DNA and other macromolecules. This would lead to fewer damage sites and, in cellular DNA, fewer mutations. The situation, however, is not simple. Recent studies in Emory mice have shown that another free radical scavenger, plasma ascorbate, is reduced up to 50%, with glutathione significantly reduced, when animals are fed at 60% of AL (29). DR appears to differentially affect different tissues in the same animal, e.g., liver versus muscle (28). At this point, it would appear that any hypotheses suggesting that the benefits of DR occur through its impact on free radical generation or inactivation will have to account for these strain- and species-specific differences.

Cellular Proliferation Considerations

A more traditional explanation for the effects of DR on cancer is that it slows cellular proliferation in general, which somehow reduces the age-specific incidence of carcinogenesis (30). However, DR

appears to have little or no effect on cell proliferation in certain tissues, such as bone marrow (31). Based on these observations, it is hard to see how changes in cellular proliferation could be responsible for the slowing of tumors related to these tissues, e.g., induction of lymphoma by DR in the mouse (8,11). In addition, recent studies show that what few differences in cell proliferation exist between AL and DR animals seem to disappear after 10 months of age (32), thereby further complicating the interpretation of the relationship between induction of tumors in animals on DR and cellular proliferation.

Genome Integrity Considerations

Another way to explain the beneficial effects of DR on tumor induction would be to suggest that DR enhances the stability and integrity of the genetic information (in DNA) and its expression. DR does appear to reduce the induction of DNA damage (33). Likewise, DNA repair appears to be enhanced by DR, but different DNA repair systems may be altered differently (33,34). Studies by Srivastava et al. (35) demonstrate that the fidelity of certain forms of DNA polymerase are enhanced (pol α) in animals on DR compared to AL-fed ones. The impact of DR on the fidelity of replication of other DNA polymerases is yet to be studied. Finally, DR also appears to alter the expression of a number of genes associated with cancer (33), including, but not likely limited to, *p53* (36) and *H-ras* (37). These observations are consistent with a general DR impact of reducing DNA damage, increasing capacity to fix DNA damage that does occur, and preventing aberrant gene expression. Understanding the relationship of these changes to the beneficial impact of DR on cancer requires better understanding of the role that DNA damage plays in carcinogenesis and of how DR induces these effects.

Dietary Restriction and Induced Carcinogenesis

The effects of DR on induced carcinogenesis are striking (12,13). Even a moderate level of DR (to 70% of AL) can eliminate the expression of various agent-induced diseases (12,38). DR appears to have many effects, interacting at various levels of organization and with many factors important to the induction of toxicity (39).

Agent disposition is altered with DR, as DR increases urinary output up to 4-fold (29), thereby enhancing compound conjugation and elimination (14). As specific

cytochrome P450 isoenzyme activities are decreased by DR (decreasing agent activation) the activities of certain glucuronidases are increased, with a result of improved agent detoxification (40). Even when the total amount of agent that combines with the genome is not effected by DR, the formation of specific adducts correlated with carcinogenicity can be inhibited (41). Thus, by a myriad of mechanisms, DR can reduce the amount of carcinogenic insult that results from interaction with an agent.

Another factor that impacts induced toxicity is the effect of DR on toxicodynamics. This was illustrated in a recent experiment using the newborn mouse assay (42). In these studies, starting DR 4 months after the carcinogenic insult resulted in an elimination of the carcinogenic action of the agent. Other experiments have shown that DR can not only slow the growth of diethylnitrosamine (DEN)-induced preneoplastic foci in liver, but can even induce foci regression (43). The mechanism(s) important for the inhibition of spontaneous tumorigenesis may also be important for this effect of DR on induced tumorigenesis. For instance, endogenous factors that promote the damage induced by oxidative metabolism may also promote the damage induced by agents such as DEN. Thus the effects of DR on spontaneous and induced cancer may be linked at this step.

Conclusion

DR is a complex, broad paradigm that interacts with many different stages or steps in the carcinogenic process. Despite this complexity and unlike many agents that can either increase or decrease carcinogenesis depending on the specific paradigm of exposure used (44), DR has not been found to increase the incidence of any form of cancer or the carcinogenicity of any compound. This observation has led to speculations about the role of DR as an adaptive mechanism to ensure animal survival during times of food deprivation until food again becomes available, to help perpetuate the species (45).

Whatever the reason for the evolution of DR, however, because of its potent anti-tumor action and its apparent extrapolation to humans, elucidation of its mechanism(s) may add more tools to the antitumor armamentarium used to fight cancer. Also, since this approach takes advantage of components involved in simple nutrition, the application of these mechanisms to improve public health may be fairly straightforward and easy to establish.

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