Fat, Calories, and Cancer

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See related article by Lavick and Baumann, Cancer Res 1943; 3:749–56.

In this issue of *Cancer Research*, a seminal article from Lavick and Baumann published in the Journal in 1943 is highlighted in celebration of the Journal's 75th anniversary. In this article, the authors, following an earlier observation made in 1939 that diet restriction inhibited the formation of ultraviolet-induced tumors in mice (1), had examined in more detail the specific contribution of dietary fat to the development of methylcholanthrene-induced tumors in mice (2). Their initial experiment suggested that a high fat diet promoted the formation of cutaneous tumors in these mice. However, noticing that the animals fed with a high fat diet had a greasy fur, they suspected a local effect, which they demonstrated by showing that local administration of oil at the site of the skin treated with methylcholanthrene also promoted tumor formation. They then realized that a potential problem with their study was the fact that control mice were in fact receiving low calorie diets (10.8 to 13.5 cal/25 g/day) when compared with mice fed with a high fat diet who consumed 12% to 30% more calories. Then studying four different groups (low fat, low calorie; high fat, low calorie; low fat, high calorie; and high fat, high calorie), they observed the highest incidence of tumors in the high calorie groups whether mice were receiving low or high fat (54 and 66%, respectively) when compared with the low fat diet groups of mice receiving high or low fat (28% and 0% respectively). This observation led the authors to conclude that "at least part of the tumor-promoting action of fat was due to an accompanying increased consumption of calories." A few years later, Tannenbaum and colleagues (Michael Reese Hospital, Chicago, IL) published similar observations showing that caloric restriction *per se* inhibited the formation of carcinogen-induced skin and spontaneous mammary and liver tumors in mice (3). These publications in fact followed a much earlier report from Moreschi in 1909, who had reported the observation that tumors transplanted into underfed mice did not grow as well as those transplanted into mice fed *ad libitum* (4). The article of Baumann and colleagues was then followed by a series of articles in the 80s and 90s showing similarly that a low-caloric diet without malnutrition in animals prevents the formation of a variety of tumors including breast, prostate and skin, and leukemia induced by carcinogens and viruses (5). These studies led to the emergence of an endocrine theory postulating that caloric restriction results in a metabolic adaptation of the body, in which there is an overall decreased production of growth factors like insulin-like growth factor 1 (IGF-1), circulating hormones, and inflammatory cytokines. It was then shown that caloric restriction upregulates several tumor suppressor genes such as genes promoting DNA and cellular repair, protein turnover, stress resistance, and antioxidant genes, whereas it downregulates proinflammatory genes and genes modulating energy and metabolism (6). Evidence that caloric restriction can affect not only cancer development in rodents but also in humans then came from epidemiologic studies that were very informative. Studies on the incidence of breast cancer in women who had survived the 1944–1945 Dutch famine indicated not a decrease but an increase in the incidence of breast cancer in women who were exposed to a short but severe famine decades earlier, pointing to the important fact that calorie restriction can have a different effect if it is associated with malnutrition (7). On the other side, epidemiologic studies on cancer incidence in populations migrating from a low risk area for cancer to a high risk area revealed a rapid higher incidence of cancer as immigrants adopted a high calorie Western diet, which pointed to a protumorigenic role of a high calorie diet in humans (8).

In the early 2000s, as Western societies witnessed an obesity epidemic, attention further shifted to the effect of obesity and excessive caloric intake on cancer development. A clear association between adiposity and increased risk of development of multiple types of cancer was then demonstrated (9). Excessive adiposity is known to increase oxidative stress, insulin resistance and insulin levels, and inflammation and to induce changes in hormones and growth factors concentration that are all favorable to tumor cells (10). Fat cells produce protumorigenic molecules like IGF-1, IL6, and leptin that promote tumor cell survival and growth. The connection between high calorie diet, insulin resistance, and cancer growth led to the testing of metformin, an antidiabetic drug, in the prevention and treatment of cancer (11). Children who are part of this obesity epidemic are also affected. It has been shown that acute lymphoblastic leukemia (ALL), the most common childhood cancer, is affected by adiposity. Adipocytes act as a sanctuary for leukemia cells, protecting them from the injury of chemotherapy (12), and obesity in children with ALL at time of diagnosis negatively affects response to induction therapy (13).

We have thus come a long way since the original articles of Bauman and of Tannenbaum published in *Cancer Research* in the early 1940s in understanding the molecular mechanisms explaining their original observations. But the conclusion remains the same. Calorie restriction without malnutrition has a negative effect on cancer development, whereas excessive calorie intake and adiposity have a positive effect on cancer. A last and important point that these articles make is to remind us that cancer is not a disease limited to a number of proliferating and mutated cells but a process that results from complex interactions between these mutated cells and their surrounding environment, stromal cells and inflammatory cells, and extracellular matrix proteins that constitute the tumor microenvironment and socioeconomic factors that constitute the macroenvironment.

Disclosure of Potential Conflicts of Interest

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References

1. Baumann CA, Rusch HP. Effect of diet on tumors induced by ultraviolet light. Am J Cancer 1939;35:213–21.
2. Lavik PS, Baumann CA. Further studies on the tumor-promoting action of fat. Cancer Res 1943;3:749–56.
3. Tannenbaum A. The dependence of tumor formation on the degree of caloric restriction. Cancer Res 1945;5:609–15.
4. Moreschi C. Beziehungen zwischen ernährung und tumorwachstum. Z Immunitätsforsch Orig 1909;2:651–75.
5. Kritchevsky D, Klurfeld DM. Influence of caloric intake on experimental carcinogenesis: a review. Adv Exp Med Biol 1986;206:55–68.
6. Longo VD, Fontana L. Calorie restriction and cancer prevention: metabolic and molecular mechanisms. Trends Pharmacol Sci 2010;31:89–98.
7. Elias SG, Peeters PH, Grobbee DE, van Noord PA. Breast cancer risk after caloric restriction during the 1944–1945 Dutch famine. J Natl Cancer Inst 2004;96:539–46.
8. Kolonel LN, Altshuler D, Henderson BE. The multiethnic cohort study: exploring genes, lifestyle and cancer risk. Nat Rev Cancer 2004;4:519–27.
9. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004;4:579–91.
10. Kaaks R, Lukanova A. Effects of weight control and physical activity in cancer prevention: role of endogenous hormone metabolism. Ann N Y Acad Sci 2002;963:268–81.
11. Grossmann ME, Yang DQ, Guo Z, Potter DA, Cleary MP. Metformin treatment for the prevention and/or treatment of breast/mammary tumorigenesis. Curr Pharmacol Rep 2015;1:312–23.
12. Behan JW, Yun JP, Proektor MP, Ehsanipour EA, Arutyunyan A, Moses AS, et al. Adipocytes impair leukemia treatment in mice. Cancer Res 2009;69:7867–74.
13. Orgel E, Tucci J, Alhushki W, Malvar J, Sposto R, Fu CH, et al. Obesity is associated with residual leukemia following induction therapy for childhood B-precursor acute lymphoblastic leukemia. Blood 2014;124:3932–8.

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