Editorial

Cancer Prevention Research

Are You What You Eat or What Your Mother Ate or Both?

Stephen J. Freedland

Abstract

A high-fat high-sugar (HF-HS) diet promotes cancer development and progression. However, does the timing of diet matter? This is an important question with profound public health relevance. By exposing mice to a HF-HS diet either through feeding to a pregnant mother or nursing mother or after weaning and then chemically inducing breast cancer, the authors found the most crucial time for breast cancer risk was after weaning, while a HF-HS *in utero* diet actually slowed tumor development. Understanding early-life events provides valuable insight for later life events and proves it is never too early to start preventing disease. *Cancer Prev Res; 10(10); 551–2. ©2017 AACR.*

See related article by Lambertz, p. 553–62.

The age-old adage goes, "you are what you eat." What if, the adage should be "you are what your mother ate when she was pregnant with you."? This would radically change the way health promotion was delivered. Instead of focusing on adults to change their lifestyle, we could merely target recommendations to women during a 9-month period. Imagine, if both were true, "you are what you eat" and "you are what your mother ate when she was pregnant with you." This would further change how we think about health as we need to target both adults *and* pregnant women. Answering this question is not only biologically important and provides tremendous insight into cancer etiology, but has profound public health implications.

To answer this question, Lambertz and colleagues fed female mice that develop breast cancer in response to a known carcinogen either a restricted calorie diet or a high-fat/high-sugar (HF-HS) diet at varying points in their early life: *in utero* (fed to the pregnant mothers), during nursing (fed to the nursing mother), or after weaning. They then treated the mice with the carcinogen 5 days per week for 6 weeks starting at age 7 to 9 weeks and followed the mice to assess which developed tumors. There were several key findings: (i) an HF-HS diet fed to the pregnant mother actually slowed tumor development; (ii) the diet fed to the nursing mother did not affect tumor growth; (iii) the diet postweaning promoted tumor growth.

To better understand these results, the authors examined diet/obesity–related factors, such as body weight and insulin resistance. Only body weight correlated with tumor incidence in this model. Not surprising, body weight was strongly influenced by the postweaning diet but unrelated to *in utero* diet. Nursing mothers fed a calorie-restricted diet resulted in offspring with slightly lower body weight. Along with the importance of body weight, groups with high tumor burdens had systemic changes linked with obesity like high leptin, low adiponectin, and high IGF-1. Finally, groups with high tumor incidence had higher numbers of mammary stem cells even in the prepubertal state.

Although this article is very important and has several key takeaways, first, we must define its limitations. First, the authors used a single mouse carcinogen-induced cancer model. Perhaps the cancer-causing effects of this carcinogen are so strong as to be unaffected by modifiable risk factors. For example, a recent meta-analysis found a strong relationship between insulin resistance and breast cancer risk (1), and yet no association was seen in this study. Second, many breast cancers are related to genetic predisposition. Would results vary if the authors had used genetically induced breast cancer models? Third, the authors studied a single dietary intervention that induces multiple changes: high-fat and high-sugar that in adulthood leads to obesity. Thus, not only were the pregnant and nursing mothers consuming a HF-HS diet, but they were likely obese. Thus, is it the high fat? The high sugar? The obesity? If a different diet were used to induce obesity, would results be the same? We recently showed that an extreme high-fat/low-carbohydrate diet induces weight gain and yet slows tumor growth (2). This argues that how one becomes obese matters. Similarly, prior studies found weight loss via being placed in a colder ambient environment results in weight loss and slowed tumor growth (3), further supporting the argument that calories consumed are not the end-all. Third, could these adverse dietary effects have been overcome by exercise? If we exercise hard enough, can we eat what we want? Finally, are these findings unique to breast cancer? According to the authors, breast branching and formation of terminal buds occurs in mice at age 4 to 5 weeks (years 10–11 in humans). Would results differ for other organs where development occurs earlier? Does postweaning diet only matter because that is when final maturation of the breast occurs, or does adult diet matter for all cancer types?

These limitations notwithstanding, what does this article teach us? First, as the primary driver of tumor growth was the postweaning diet, it teaches us that we cannot simply blame our mothers for our diseases, but need to take responsibility ourselves (sorry, Dr. Freud). Second, obesity is linked with increased cancer risk, a fact well-supported in literature (4). More efforts are needed to targeting the obesity epidemic to prevent chronic diseases, such as cancer. Third, in reviewing Fig. 3A (the tumor growth curves),

Cedars-Sinai Medical Center, Los Angeles, California.

Corresponding Author: Stephen J. Freedland, Cedars-Sinai Medical Center, 8635 West 3rd Street, Suite 1070W, Los Angeles, CA 90048. Phone: 310-423-3497; Fax: 310-423-4711; E-mail: Stephen.Freedland@cshs.org

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the groups that did the best were either restricted postweaning or fed the same diet the whole time (i.e., the HF-HS diet throughout had intermediate to slightly slower tumor growth than the rest). The implication is that in the absence of being able to consistently restrict diet postweaning (the best scenario), there may be harms to a yo-yo diet (where weight goes up and down due to periods of intermittent dieting mixed with an obesogenic diet). Fourth, the finding that an HF-HS diet during gestation reduced tumor growth is unexpected. Why such an observation would be seen is unclear and certainly requires further study. Fifth, a key implication is that examining adult diets and cancer risk may miss much of the time window during which cancer risk can be influenced. This may explain the often inconsistent and null findings in epidemiologic studies of diet and cancer (5, 6). Importantly, this does not mean diet is not important, just that we do not know when to look.

In summary, although what you mother ate when she was pregnant and nursing you may matter, what you eat matters too. It is hoped that with future research aimed at understanding the molecular effects of diet at various time points throughout life, we can best design diets and interventions to reduce and ultimately prevent cancer. Studies like this help answer some questions, but like all good studies, raise more questions than they answer.

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References

1. Hernandez AV, Guarnizo M, Miranda Y, Pasupuleti V, Deshpande A, Paico S, et al. Association between insulin resistance and breast carcinoma: a systematic review and meta-analysis. PLoS One 2014;9:e99317.
2. Allott EH, Macias E, Sanders S, Knudsen BS, Thomas GV, Hursting SD, et al. Impact of carbohydrate restriction in the context of obesity on prostate tumor growth in the Hi-Myc transgenic mouse model. Prostate Cancer Prostatic Dis 2017;20:165–71.
3. Huffman DM, Johnson MS, Watts A, Elgavish A, Eltoum IA, Nagy TR. Cancer progression in the transgenic adenocarcinoma of mouse prostate mouse is related to energy balance, body mass, and body composition, but not food intake. Cancer Res 2007;67:417–24.
4. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625–38.
5. Shrivastava SR, Shrivastava PS, Ramasamy J. Exploring the role of dietary factors in the development of breast cancer. J Cancer Res Ther 2016;12:493–7.
6. Masko EM, Allott EH, Freedland SJ. The relationship between nutrition and prostate cancer: is more always better? Eur Urol 2013;63:810–20.