Looking Farther Afield

Julie A. Ross, Senior Editor

Having Your Cake and Living Long, Too?

Caloric restriction (CR) has been shown to prolong life in several animal models and to reduce possibly the occurrence of cancer and other chronic diseases. While numerous cross-sectional studies have demonstrated changes in gene expression associated with CR, few studies have investigated this relationship prospectively. In this report by Dhahbi et al. (1), the effect of CR on survival, cancer occurrence, and gene expression was explored further. Importantly, the investigators used 19-month-old male mice (hybrid strain: B6C3F1) in their studies of survival, which, in mouse age, is only a few months before age-associated mortality. The mice were randomized to a control diet (providing 93 kcal/wk, which is about 90% of calories required by a typical mouse) or a CR diet (providing an initial 77 kcal/wk for 2 weeks followed by a further reduction to 52.2 kcal/wk thereafter). For the gene expression studies, 7-month-old male mice were randomly assigned to either the control diet or the CR diet described above; their livers were examined at about 34 months of age. Additional experiments included mice on the long-term CR diet that were subsequently fed the control diet (93 kcal/wk) for 8 weeks to determine whether gene expression can rapidly change.

In the survival studies, the control mice that were later shifted to the CR diet had an increase in mean time to death of 5 months (a 42% increase). Interestingly, this effect was similar to a study that investigated long-term CR in mice shortly after weaning (2). For the first period of evaluation (21 to 31 months of age, which allowed for a 2-month lag time following diet initiation), CR reduced the overall mortality rate and cancer as a cause of death. Eventually, however, after 31 months of age, both the CR mice and the control mice died mostly of tumors, with the number being similar between the two groups. The authors conclude that CR initiated late in life has no overall effect on the incidence of tumors, but it can delay the onset or growth of tumors and extend the life span. For the gene expression studies, long-term CR altered the expression of 6% of transcripts, including genes important in metabolism, signal transduction, and immune and stress response. Further, the mice that were transitioned from CR diet to the control diet demonstrated a 90% return to control gene expression within 8 weeks, indicating that expression of genes altered by long-term CR is rapidly altered by shifts in dietary intake.

Comment. This study provides new evidence that CR initiated later in life, at least in mice, can decrease cancer death and prolong life span. Further, the demonstration of rapid changes in gene expression associated with dietary changes provides further evidence of a dynamic process that can be altered over a short period of time. While it is not clear how a 19-month-old mouse compares in human age, for most people, one of the pleasures in life is eating. Thus, the prospect of long-term CR to extend life would not be high on most people's priority list. However, if this paradigm holds for other animal models, apparently a choice of CR could be made late in life, when the prospect of living a few years longer is more attractive than having another piece of cake. Further, if gene expression responds so rapidly to dietary changes, it raises the question of how fad diets may influence genes important in the carcinogenic process. —*Julie A. Ross, University of Minnesota, Minneapolis, MN*

Alcohol Consumption: A Leptin Buzz?

Alcohol drinking, particularly in postmenopausal women, has been associated with an increased risk of breast cancer. Mechanisms to explain this relationship include direct effects on increasing hormonal levels (e.g., estrogen, androgen, and leptin) as well as indirect pathways such as DNA damage (3). Roth et al. (4) conducted a randomized three-period crossover feeding study in nonsmoking healthy postmenopausal women. A total of 53 women (ages 49 to 79 years) completed the study, which included zero alcohol, 15 g per day, or 30 g per day during each 8-week treatment period followed by a 2- to 5-week washout period. All food and beverages were supplied and participants were weighed each weekday to maintain a constant body mass. Blood samples were collected after an overnight fast in the last week of each feeding period and were analyzed for serum leptin. After adjusting for body mass index, the authors found that leptin levels were significantly (P for trend = 0.018) elevated when women consumed 15 or 30 g of alcohol per day compared with no consumption (7.3% higher, 95% CI 3.0-15.1 and 8.9%, 95% CI 1.6-16.7, respectively). There was little evidence for a carryover effect with alcohol level or treatment order, suggesting that increases in leptin levels were transient. Interestingly, younger women (ages 49 to 54 years) had a significantly larger increase in serum leptin levels with 30 g of alcohol (compared with no alcohol) than did older women [55 to 59 years; 24.4% (95% CI 9.3-42.0) vs. 3.7% (95% CI −4.1 to 12.1)].

Comment. As the authors acknowledge, some studies have demonstrated similar findings, while others have not (reviewed in ref. 4). Importantly, the current study was highly controlled (alcohol level, food composition, energy intake, etc.), which is a distinct advantage. Few studies have explored the potential relationship between leptin and breast cancer. Leptin and its receptor, the products of the obesity (*ob*) and diabetes (*db*) genes,

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respectively, are established indicators for obesity (5). Obesity is also associated with breast cancer in postmenopausal women (6). One recent study in genetically obese mice demonstrated that leptin controlled the proliferation of both normal and malignant breast epithelial cells (7). Given that polymorphisms exist in both leptin and leptin receptor genes (5, 8-10), it will be of interest to evaluate potential relationships with breast cancer. —*Julie A. Ross, University of Minnesota, Minneapolis, MN*

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