Dietary Fat, Body Weight, and Cancer: Contributions of Studies in Rodents to Understanding these Cancer Risk Factors in Humans

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Understanding diet and energy balance as risk factors for breast, colon, and other cancers requires information on the contribution of each factor and of interactions among factors to cancer risk. Rodent models for breast cancer provide extensive data on effects of dietary fat and calories, energy balance, body weight gain, and physical activity on tumor development. Analyses of the combined data from many studies have shown clearly that quality and quantity of dietary fat and energy balance contribute independently to increased mammary gland tumorigenesis. These findings were seen in female rats fed diets high in fat (35–40% of calories) compared to rats fed control diets, with approximately 10% of calories as fat (Fay and Freedman, 1997, Breast Cancer Res. Treat. 46, 215–223). The methods used permit comparison of experimental and epidemiological data, and they may be useful in extrapolating between species and developing public health recommendations. In addition to the contributions of lifetime-diet composition, intake, energy balance, and physical activity to cancer risk, there are questions about the timing and duration of alterations in these factors and about the “dose-response” characteristics of cancer risk to the factors. Endocrine mechanisms may be significant in mammary gland tumor risk, but experimental and epidemiological data indicate that cancers at other sites, such as colon and liver, also are influenced by the factors listed. Other diet and lifestyle factors that influence energy, or specifically fat, metabolism may also affect risk for cancers that are promoted by increased intake of fat and calories. Studies of separate and interactive effects of dietary fat, black tea, weight gain, and mammary gland tumorigenesis (Rogers, et al, 1998, Carcinogenesis 19, 1269–1273) have been analyzed. Using adjustment of carcinogenesis endpoints for body weight, tumor burden, and latency, they were found to be related to weight gain within treatment groups in 2 of 3 experiments.

Key Words: mammary tumors; calories; dietary fat; weight gain; rats; exercise; black tea.

The interactions among dietary fat and calories, body mass index, weight gain, and physical activity and between those factors and the development of cancer are the subjects of extensive epidemiological and experimental investigation. The results of such investigations are potentially applicable to understanding mechanisms of cancer development and to designing methods for prevention, prognosis, and treatment of cancer. Because they are modifiable, the factors listed are of great importance. Of the 3 major causes of cancer deaths in the U.S., aside from lung cancer for which the major cause is known, two (breast and colon) are generally thought to be related to dietary fat and calories, body mass, and physical activity. For the third, prostate, data are accumulating that suggest the same conclusions (Huang et al, 1997; Rose, 1997a,b, 1998; Willett, 1998).

In female laboratory rodents, the promotion of spontaneous or induced mammary gland carcinogenesis (measured by tumor incidence, burden, and latency) by ad libitum (AL) intake of high fat diets has been demonstrated repeatedly. In addition, meta analysis, showed this promotion to be independent of total dietary calorie content and intake or final body weight (Fay and Freedman, 1997; Freedman et al., 1990). In male and female rodents, there is considerable evidence for an influence of dietary fat on carcinogen-induced colon tumorigenesis, but enhancement has not been as consistently demonstrable as in the mammary gland (Nauss et al, 1987; Reddy et al, 1997). Studies of dietary influences on carcinogenesis in the prostate await development of satisfactory animal models (Rose, 1997, a,b).

In laboratory rodents fed control, generally natural-product diets, there is a positive correlation between body weight gain and the incidence of common spontaneous tumors of the mammary gland, liver, and pituitary (Keenan, 1998; Keenan et al, 1996; Seilkop, 1995). In male mice fed a caloric reduction (CR) diet of 60% full intake, there was a significant reduction in age-specific death rate from spontaneous tumors. The reduction was independent of p53, since it occurred in both wild type and p53-deficient mice (Hursting et al, 1997). There is a reduction in spontaneous tumors and in chemical carcinogenesis in the mammary gland in rats and mice when dietary caloric intake is restricted and thus, weight gain is reduced. Feed restriction led to 35–50% lower body weight at 2 years. Full-fed (AL) control results reduced spontaneous mammary gland, endocrine, and hematopoietic tumors in Fisher 344
et al (Keenan (F344) and Sprague-Dawley (S-D) male and female rats (N-6-PUFA), but saturated fats also had an effect (Fay and effect on tumorigenesis was due to N-6-polyunsaturated fats 1990). Subsequent analyses showed that the largest dietary fat independently increased tumorigenesis, but there was no clear analysis of studies of mammary tumorigenesis in rats and mice mass complicate the interpretation of results. In a large meta- interactions of the supply and utilization of calories and body metabolism, per se effects in rodents (Fay and Freedman, 1997). They then applied the model to hypothetical diet designs for humans, and calculated the reported evidence on dietary fats in humans was similar to, but less marked than, effects in rodents (Fay and Freedman, 1997). They then applied the model to animal studies, fat calories (except those from fish oil) would have a greater effect than nonfat calories, i.e., that the effect of fat on breast cancer would not be purely a caloric effect, and that N-6-PUFAs would have the most harmful effect.

A recent review of studies on the influence of physical activity or exercise on the incidence of mammary-gland carcinoma in rats concluded that there is consistent evidence that intensive exercise (>70% maximal aerobic capacity or exercise to exhaustion) reduces tumor incidence by more than 50% and increases tumor latency. Studies of less intensive exercise did not yield evidence of a consistent effect, although there are reports of inhibition of carcinogenesis by exercise at >35% maximal aerobic capacity (Thompson, 1997). In that review, Thompson discusses important points about methods for studying the effect of exercise in rodents, definitions of terms, and major questions to be answered about the influence of exercise type, intensity, and duration on incidence of carcinoma and the mechanisms by which exercise might act. From studies in rats on the effects of caloric balance on mammary gland tumorigenesis, using either exercise to increase energy expenditure or diet restriction to reduce intake, it has been reported that adrenal corticosteroid responses to exercise or diet restriction, rather than caloric balance per se, are responsible for reducing tumorigenesis (Gillette et al, 1997; Zhu et al, 1997). Harris et al (1995) studied DMBA-induced mammary gland tumorigenesis in full-fed S-D rats that were restricted to 60% of the energy intake of full-fed rats and rats fed in 2-day full-fed feeding cycles alternated with 2 days of 60% feeding. The latter, cycled rats had 81% of the energy consumption of the full-fed rats, weighed 15% less, and had a slightly but not significantly lower tumor incidence and burden. The continuously restricted rats weighed 28% less than the full-fed rats and had significant reductions in tumor endpoints. Both restricted groups had elevated serum corticosterone and reduced estradiol, so the significance for carcinogenesis of the corticosterone changes with feed restriction is not clear.

We have carried out 3 experiments examining DMBA-induced mammary gland carcinogenesis in female S-D rats fed control or, in one experiment, a high-fat diet with black tea or water to drink. The carcinogenesis results have been reported (Rogers et al, 1998) and are discussed below. We have now examined, from these 3 experiments, the data on individual body-weight gain and tumorigenesis end points, in order to determine if there was a relationship between weight gain and one or more tumorigenesis end points (tumor number, weight, burden, and latency). In addition, we were interested in determining whether either tea, which has the potential to reduce weight gain, or dietary fat, which has the potential to increase weight gain, would change any relationship we might detect between tumorigenesis end points and body-weight gain.

**MATERIALS AND METHODS**

Three experiments were performed with female S-D rats, comparing tumorigenesis: (1) rats given 25 mg/kg DMBA by gavage, fed AIN-76A diet, and given 1.25% or 2.5% black tea extract or water to drink; (2) rats given 15 mg/kg DMBA and the same diet and drinking fluids as in Experiment 1; (3) rats fed AIN-76A or a high-N-6-PUFA diet and given 15 mg/kg DMBA and 2% tea or water to drink. The rats readily accepted tea, and they ate and gained weight normally. Total tea intake in Experiment 1 represented 58 ± 13 or 106 ± 22 grams of extracted tea leaf (Rogers et al, 1998).

Analysis of variance was used to compare unadjusted (for weight) end points between comparison groups. Analysis of covariance was used to compare end points adjusted for weight gain over the 16-week duration of observation. To understand the adjustment, the relationships between weight gain over 16 weeks and each end point within each comparison group were estimated using simple linear regression analysis. The effect of weight gain on end point was considered statistically significant if it was greater than zero with a p value ≤ 0.05. The difference between groups in the relationships between weight gain and each end point was analyzed by testing whether the interaction between weight gain and group assignment was statistically significant. A p value ≤ 0.01 was considered statistically significant. All analyses were performed using SAS 6.12. Sample sizes of at least 10 rats per independent variable are required for these analyses.

**RESULTS**

As reported previously (Rogers et al, 1998), we found no consistent effect of tea on tumorigenesis in rats fed control diet, but we did find the expected increase in tumorigenesis in rats
fed the high-fat diet and drinking water. There was not a statistical increase in tumorigenesis in rats fed the high-fat diet and given tea to drink. Therefore, tea reduced the effect of the high-fat diet on tumorigenesis.

The tumor end points were, however, strongly associated with body weight in Experiments 1 and 3 where all DMBA-treated rats were considered, but the association was not seen in Experiment 2 (Table 1). In Experiments 1 and 3, tumor number and burden at termination increased significantly, and in Experiment 1, latency-to-first tumor decreased with the amount of body weight gain over the 16 weeks that rats were studied, beginning at 4 weeks of age. In Experiment 2, there was not a detectable relationship between weight gain and the tumorigenesis end points.

In examining the groups separately in Experiment 1, the magnitude of the change in end point with weight gain was quite consistent, except in the rats given 2.5% tea to drink, in which the effect of weight gain appeared somewhat (but not statistically) reduced. In the results of Experiment 3, there was a suggestion that the high-fat diet increased the magnitude of the effect of weight gain on tumor burden and that tea eliminated that effect, but the differences were not statistically significant.

**DISCUSSION**

In 2 of the 3 experiments, there was an effect of body weight gain on the tumorigenesis end points, and the magnitude of the
effect was similar in the 2 experiments. Adjustment of the results for weight gain in this and other tumor models is appropriate, and it can make an appreciable difference in the group means for the end points. However, it did not, in this case, change the outcome with respect to tea or to the high-fat diet previously reported.

The effects of tea, coffee, and caffeine on cancer risk have been of interest, and they could be related to body weight. In the experiments discussed here, the rats drank an average of 10–30 mg/kg/day of caffeine, comparable to the highest levels of human tea consumption reported in Western countries (7–15 mg/kg/day in Denmark, Barone and Roberts, 1996). There are many reports of a protective effect of tea against tumorigenesis for other tumor types in several animal models (Yang et al., 1996). Weisburger et al. (1997) reported protection by tea in DMBA-treated rats fed a high-fat diet; inconsistent effects of coffee have been reported in rats and mice (Welsch et al., 1984, 1998). In the gastrointestinal and respiratory-tract tumor models in which tea is a chemopreventive agent, decaffeinated teas have generally been active although somewhat less so than non-decaffeinated teas. Recently a significant chemopreventive effect of 2% black tea and of caffeine alone was demonstrated in male F344 rats given 4-(methylnitrosoamo)-1-(3 pyridyl)-1-butanone (NNK; Chung et al. 1998). In that study caffeine and tea did not significantly reduce the rats’ body weights, and lung tumorigenesis was inhibited.

Intake of relatively high levels of coffee has been reported to be related to reduced risk for cutaneous malignant melanoma in women (Veierod et al. 1997) and for carcinoma of the colon in men and women (Favero et al., 1998), but the epidemiological literature on coffee and tea and cancer risk is highly inconsistent (Kohlmeier et al., 1997; Yang et al., 1996). Coffee intake was found not to have an effect on breast cancer risk in a recent study (Tavani et al., 1998).

A major question that has not yet been adequately addressed in animal models is the role of physical activity in body weight and in carcinogenesis. Thompson’s (1997) review and discussion of results and methodological problems is valuable. Shephard (1996), and Shephard and Futcher (1997) presented detailed tables and analyses of studies of relationships between physical activity or exercise and cancer in laboratory animals and people that were reported between 1980–1997. They concluded that, in a total of 25 reports of studies in animals, there were 15 that showed positive findings of reduction of chemical carcinogenesis in exercised animals, 7 in which exercise may have been effective under certain conditions, and 3 in which exercise did not reduce carcinogenesis. Effects of the type and intensity of exercise and of diet, calorie balance and body weight could not be determined from the studies reviewed.

In the epidemiological studies reviewed, risk ratios were inversely related to physical activity/exercise indicators in men for all cancers combined: colorectal adenomas, malignant colon, prostate, testicular, and, possibly, lung tumors. In women, an inverse relationship was found for colon and premenopausal breast, and perhaps uterine, tumors. The authors discuss issues of assessment, timing, type, and intensity of physical activity, baseline physical condition, body mass, and other variables. The studies reviewed indicate a potential reduction overall in cancer incidence by about 46% by increasing physical activity (Shephard, 1996; Shephard and Futcher, 1997). In a brief discussion of potential factors or mechanisms related to the reduction of cancer risk by physical activity, Shephard (1996) lists diet and other life-style qualities, gastrointestinal tract transit time, free radicals, body type (genetic or acquired), energy balance, weight gain (time and amount), and endocrine responses.

In another recent review, Oliveria and Christos (1997) add consideration of immunological factors in general and of prostaglandins F2 alpha and E2 specifically for colon cancer, in evaluating mechanisms of an exercise effect. They postulate that prostaglandins F2 alpha, which was reported to inhibit growth of xenografts of colon tumors and to be increased in serum by physical activity, and E2, which was reported to be related to colon tumor growth and to be reduced by exercise, might mediate reported reductions of colon cancer associated with physical activity. Conclusions from a recent large prospective study of breast cancer risk (Thune et al. 1997) were that physical activity was inversely related to breast cancer risk. The risk reduction was most marked in premenopausal women, in women less than 45 years old at entry into the study, and in lean women (body mass index <22.8). The lowest risk, 0.28, 95% CI 0.11–0.70 was associated with lean women who exercised at least 4 h per week; the association was shown for both pre- and postmenopausal women. Body mass index and fat or energy intake did not influence risk. Women active in leisure time had only slightly greater energy intake than sedentary women and were, consequently, leaner and had lower net available energy. The authors raise the possibility of genetic determination of physical activity as well as of body type and breast cancer risk. They propose also that the lower serum triglycerides in active women permit greater binding of estradiol to sex hormone-binding globulin with reduction of tissue exposure to estradiol. Mezzetti et al. (1998) reported in a different population that relatively low body mass index (<23.3) and high physical activity were associated with reduced breast cancer risk in postmenopausal women.

In a detailed review, analysis, and discussion of recent studies Gammon et al. (1998) conclude that, while there are many studies reporting that physical activity reduces breast cancer risk, consistent evidence on the importance of timing, intensity, and frequency of physical activity is lacking, and methods for determining these variables are inadequate. They propose that methods to characterize physical activity be improved and validated to permit evaluation of lifetime physical activity and to examine interactions of activity, diet, and weight.

The large literature on colon cancer risk and physical
activity can be criticized similarly. Slattery et al. (1997) reported a study in which they addressed the questions of interactions of lifetime physical activity, energy balance, body-mass index, and colon cancer risk. They found increased risk with the lowest level of lifetime vigorous leisure-time activity, high-energy intake, and large body-mass index. If all 3 risk factors were present, the odds ratio was 3.35, 95% CI, 2.09–5.35. High physical activity reduced significantly the effect of the other 2 factors. The magnitude of the effects of body mass index and energy intake decreased with age.

Studies of interactions of physical activity, diet, and weight in determining cardiovascular disease risk may be of help. Since low-fat diets designed to reduce LDL cholesterol and coronary heart disease risk may reduce HDL cholesterol unless weight loss or increased physical activity or both are also present (Expert Panel, 1993; Stefanick et al, 1998; Wood et al, 1988, 1991), research results in this area may be highly relevant to questions posed in cancer research.

In summary, in epidemiological and laboratory animal studies, the influences of diet, body weight, and physical activity on cancer risk are being elucidated. Definitive studies require better methods and questions that are more specific. If studies in animals can be designed or combined to provide larger groups, certain statistical methods used in epidemiological investigations may be applicable, such as the adjustment for body-weight gain described herein.

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REFERENCES


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