Augmentation of Mammary Tumors in Castrated Obese C3H Mice

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Summary

Experimentally obese virgin female C3H mice showed a more marked increase and an earlier incidence of mammary tumors than did normal (weight) controls. When castrated, such animals showed a decrease in tumorigenesis, below that of unoperated obese animals or mice of normal weight. However, such obese castrated animals demonstrated a tumor incidence significantly greater than normal weight, castrated mice which were totally devoid of tumors.

Introduction

In 1953, Waxler et al. (15) reported that virgin C3H female mice made obese experimentally with gold thioglucose showed an earlier appearance and a greater incidence of spontaneous mammary carcinoma than did control mice of normal weight (4). The obese animals consumed a greater amount of food during the period of development and maintenance of this obesity (13). A correlation between tumor formation, obesity, and caloric consumption was apparent. Male C3H mice made obese in this fashion had a marked augmentation in the occurrence of spontaneous hepatomas (14).

Other aspects of the relationship of tumorigenesis to diet have been investigated by several workers. Diets which had been modified to include a high proportion of fat tended to promote or at least enhance the formation of occurrence of many types of tumors in these animals (2, 3, 7, 9). Those which were force fed to increase weight showed some increase in tumors, although these animals could not truly be considered as obese. In none of the above experiments were conclusions drawn which could definitely account for this significant augmentation of tumors with obesity or with an increased caloric consumption.

Conversely, some delay in the appearance of spontaneously occurring tumors and also in experimentally induced tumors could be accomplished by various forms of dietary restrictions (10). Mice on a caloric restricted diet had not only a decrease in the incidence of spontaneous mammary tumors, but also showed an irregularity of estrus (11). Both nutritional and histologic studies revealed that mice on diets deficient in calories or in essential amino acids were anestrus, and that mammary tissue failed to develop in the virgins and atrophied in the breeding females (6, 11, 16, 17, 18). In this same vein, mice made obese and then reduced and maintained at the weight of their controls by pair feeding showed a slower rate of appearance of tumors than did either the obese or normal weight control mice (12).

Early in cancer research it was noted that removal of the ovaries at an early age completely inhibited or greatly delayed the appearance of mammary tumors (8). The lack of estrogen produced as a result of such castration culminated in the underdeveloped breast which did not yield mammary carcinoma. For mature tissue development and the resultant tumors, an adequate nutritional status is necessary. However, either obesity or an increased caloric intake tip the scales so that a marked increase in tumors becomes apparent.

The intent of this study was to ascertain whether obesity, a factor which augments mammary tumor production, would override the tumor-depressant effects of castration and allow the occurrence of such tumors.

Materials and Methods

A pure line strain of C3H female mice with a known high incidence of spontaneous mammary tumors was obtained from the Department of Genetics, University of California Medical Center. The animals were obtained at 4 weeks of age and were kept in virgin state during the experiment. There were 6–7 animals housed per cage, and they were allowed free access to ground Purina chow and water throughout the entire study. At 3 months of age they were divided into 2 groups, and bilateral oophorectomy was performed on 1 group. Two weeks later, 0.5 of the castrated group and 0.5 of the control group were injected i.p. with 7.5 mg of gold thioglucose. Within 3 weeks most of the animals treated by injection became obese. The study therefore was based on 4 groups of mice: normal weight controls, normal weight castrated, unoperated obese, and castrated obese. The animals were weighed weekly and observed daily, and the time of tumor onset was noted.

Results

In Table 1, which lists the groups of animals, the effectual number of mice in each group, and the average weight of the mice, the results of obesity, castration, and tumor appearance are shown. The obese mice had the greatest percentage of tumors, 45%, followed by 36% for the controls and 18% in the castrated obese; no tumors were found in the castrated normal weight animals.

The average time of appearance of mammary tumors was
Discussion

The effect of obesity on the increased incidence and early appearance of spontaneous mammary tumors is in accord with our previously reported work (15). Likewise, the incidence of tumors in the controls (unoperated normal weight) is as expected from this strain of mice.

It is apparent that 4 factors are involved in the natural genesis of mammary cancer of inbred strains of mice such as the C3H, namely, the genetic constitution or strain susceptibility, the hormonal stimulation, the milk factor or agent, and adequate caloric consumption.

It has been shown that if the ovaries are removed from mice 2-3 months after birth, the incidence of mammary tumors is markedly reduced. However, if the gonadectomy is performed on mice within 17 days after birth, mammary tumors do occur (19). This is explained by the hyperplasia of the adrenal cortex of these animals and an associated extragenital production of estrogen (1,5). Conversely, if castration is performed extremely late in the life of the animal, there is little interference with tumor incidence.

The lack of tumors in the control castrated group is expected and well documented. The tumors found in the obese castrated groups, although fewer in number and later in time of appearance than unoperated controls or obese, demonstrate the operation of two factors: (a) the removal of the ovaries depresses tumor production, whereas (b) an increased caloric intake, or obesity per se, tends to override the inhibiting effect. The modus operandi of tumor production as related to obesity is being studied as related to estrogenic production by the hypertrophied adrenal of the obese animal.

Although the presented data covers a 1-year period, the experiment was continued for a much longer time. In essence the results in the extended period was similar to that presented, and no castrated controls showed tumors beyond a 15-month period.

References


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