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Frej Stenback [a b], Bing Mu [c] & Gary Williams [c]
[a] Department of Pathology, University of Oulu, Oulu, Finland
[b] Nordic Council for Arctic Medical Research, Oulu, Finland
[c] American Health Foundation, Valhalla, NY, 10595
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Reports

Retinyl Acetate Effects on the Life Span and the Incidence of Cryptogenic Neoplasms in C3H Mice

Frej Stenbäck, Bing Mu, and Gary Williams

Abstract

The effect of feeding 0.02% retinyl acetate on the development of cryptogenic neoplasms and the life span of C3H/HeJ (+) mice of both sexes was studied. The survival at 105 weeks was 58% in untreated males and 28% in untreated females vs. 39% in treated males and 14% in treated females. The average weight in treated groups was also 10–15% lower. The incidence (percent) of neoplasm-bearing animals and total neoplasms was 87% and 57, respectively, in female controls vs. 93% and 55 in treated females. In male controls, these values were 57% and 39 compared with 50% and 38 in treated males. In treated animals, there was no reduction in the most common neoplasms, that is, neoplasms of the mammary gland and liver. The numbers of ovarian neoplasms and lung adenomas were slightly lower. Therefore, retinyl acetate exerted, at best, only a slight inhibitory effect on development of some types of cryptogenic neoplasms in mice.

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Introduction

Vitamin A is an essential nutrient that has the principal function of regulating the differentiation and maintaining the integrity of several epithelial tissues (1,2). A number of investigators have reported that vitamin A, or its retinoid analogues, reverse or prevent chemically induced carcinogenesis in experimental animals (3–18). These results suggest a potential usefulness of these compounds in the chemoprevention of human cancer. However, in several animal systems, retinoids were either ineffective in preventing chemically induced cancer (19–23) or actually enhanced carcinogenesis (24–31).

While some models of chemically induced cancer involve administration of carcinogens to which humans are exposed, many utilize agents that either could not or are very unlikely to be causes of human cancer. An alternative to such models for study of neoplasm development is an animal strain that predictably develops specific neoplasms without application of exogenous chemicals. Thus far, only two studies have specifically examined the effects of vitamin A

F. Stenbäck is affiliated with the Department of Pathology, University of Oulu, and the Nordic Council for Arctic Medical Research, Oulu, Finland. B. Mu and G. Williams are affiliated with the American Health Foundation, Valhalla, NY 10595.

on cryptogenic or "spontaneous" neoplasm development (32,33). Therefore, we undertook an investigation of the effect of retinyl acetate (RA) on cryptogenic neoplasm development in a strain of mouse known to develop breast, liver, lung, and lymphatic neoplasms.

Materials and Methods

Animals

C3H/HeJ (+) (MTV positive) mice were obtained from the National Institutes of Health (Bethesda, MD) at four weeks of age. They were maintained in the Research Animal Facility of the Naylor Dana Institute, which is a conventional facility. This facility was supervised by J. Silverman, DVM, and was accredited by the American Association for the Accreditation of Laboratory Animal Care. The care of animals conformed to the *Guide for the Care and Use of Laboratory Animals* (NIH 78-23).

Mice were housed five per polycarbonate cage (measuring 10.5 × 19.5 × 8″). Bedding consisted of heat-treated hardwood chips. The diet, Purina lab chow (Ralston Purina, St. Louis, MO), and tap water, supplied by an automatic distribution system, were given freely. The holding rooms were maintained at a temperature of 21 ± 1°C, had a humidity of 50 ± 10% (with a minimum of 14 air changes per hour), and had a 12:12-hour light/dark cycle. Cages and food were changed three times a week.

Chemicals and Administration

The RA (National Cancer Institute, Bethesda, MD) in the diet was prepared by adding 3 g thoroughly mixed with 15 kg powdered diet to yield 0.02% (i.e., 200 ppm). The RA diet was prepared monthly and kept refrigerated until used.

Groups

There were 200 C3H/HeJ (+) mice in the experiment. Group I was female untreated controls, Group II was females who received 0.02% RA, Group III was untreated male controls, and Group IV was males given 0.02% RA in diet. Further details are given in Table 1.

Administration of RA was maintained for the entire duration of the experiment. The animals were followed regularly and weighed weekly; observations were made of all gross changes, including palpable mammary nodules. Animals were killed when moribund or allowed to survive until death. All were autopsied except those which were cannibalized or severely autolyzed; these animals were not included in the effective number of animals. At autopsy, all altered organs, in addition to parenchymatous organs, were described and sections taken for histological examination. The specimens were fixed in buffered formalin. Tissue slices were embedded in paraffin, and sections were prepared in the Histopathology Laboratory supervised by Dr. A. Rivenson. Hematoxylin-eosin stain was used; other stains were used where appropriate.

Results

The effect of a lifetime feeding to mice of 0.02% RA on survival and neoplasm incidence was studied. The survival of the animals (Figure 1) was higher in males (Groups 3 and 4) compared with females (Groups 1 and 2). In RA-treated groups, the average life span was shorter, less so in females, whereas RA-treated male animals (Group 4) had a reduced average life span compared with controls (Group 3).

For the first 60 weeks of the study, the control males continued to gain weight, whereas treated males began to lose weight after 30 weeks (Figure 2). Untreated females gained weight over the entire duration of the study, whereas treated females did not gain weight after 30 weeks.

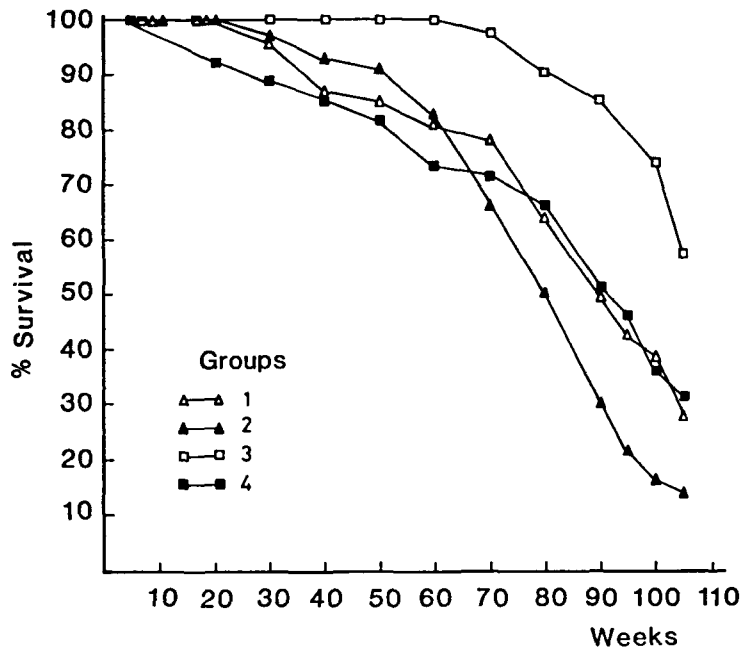

Figure 1. Survival of C3H/HeJ(+) mice. Group 1, female controls; Group 2, female RA-treated animals; Group 3, male controls; and Group 4, male RA-treated animals.

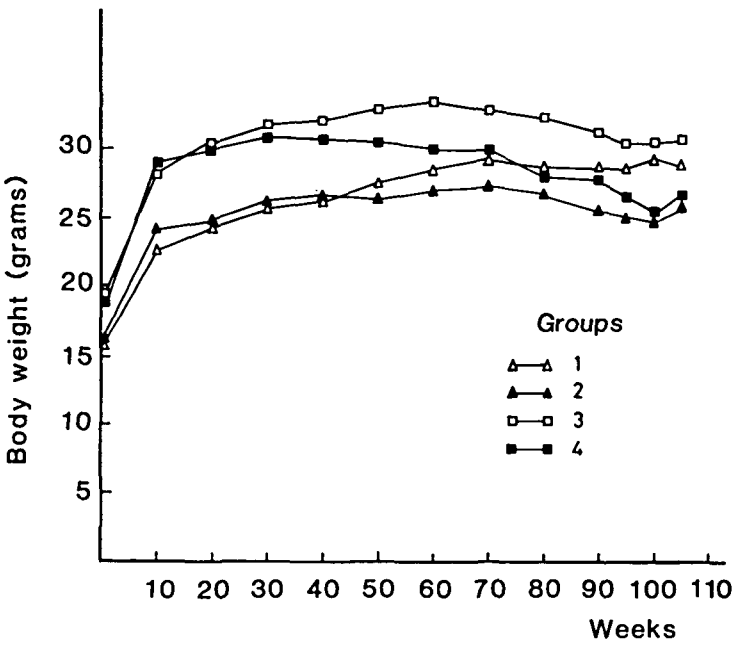

Figure 2. Average body weight of C3H/HeJ(+) mice. Group 1, female controls; Group 2, female RA-treated animals; Group 3, male controls; Group 4, male RA-treated animals.

A high incidence of neoplasms occurred in these mice (greater in females than in males) (Table 1). The overall incidence was slightly, but not significantly, higher in RA-treated mice of both sexes. Mammary neoplasms in females were the most common neoplasm in the study. In treated animals, the numerical incidence was slightly higher (Table 2), but it was not significantly different. However, the time until first palpation of gross tumors was also slightly shorter (Figure 3). Histologically, the neoplasms in both control and RA-treated mice were solid adenocarcinomas with scanty mucin production (Figure 4). In males, the most common neoplasm was hepatocellular carcinoma (Table 2). The numerical incidence in RA-treated mice was less than in controls, but differences were not significant.

In two organs, the incidences of neoplasms were reduced by RA. Ovarian tumors, tubular adenomas, and granulosa cell tumors were marginally significantly less common in RA-treated animals ($p < 0.05$). The histological structure of these neoplasms was also not affected by RA treatment. A high number of ovarian cysts, frequently bilateral, occurred in both untreated and treated animals. Endometrial hyperplasia was also observed in both groups. The incidence of lung adenomas also was marginally lower in RA-treated mice ($p < 0.05$). The lung neoplasms were mainly adenomas, and invasion into surrounding tissues or metastasis to other organs were not observed. In these neoplasms, morphological effects of RA treatments, such as excessive keratin or mucin production, were not seen.

In contrast, hemangiomas of different organs, lymph nodes, spleen, liver, and subcutaneous tissues were numerically greater in incidence in RA-treated animals: in females, 21% compared with 9% in controls; and in males, 33% compared with 18% in controls. These differences were not highly significant ($p < 0.054$). The hemangiomas consisted of endothelial cells lining dilated vascular spaces separated by a collagenous stroma (Figure 5). Histological differences related to treatment or malignant transformation were not observed. The number of nonepithelial neoplasms, such as lymphomas, was slightly, though not statistically significant, higher in RA-treated animals of both sexes, and the morphology was unaffected by RA.

Most of the neoplasms in this study were not the cause of death of the affected animal. Early mortality occurred at a time when neoplasms were not present. Specific, morphologically detectable changes attributable to toxicity were not observed.

Discussion

This study examined the effect of lifetime dietary administration of RA on the development of cryptogenic neoplasms in female and male C3H/HeJ (+) mice. The dose chosen for study, 0.02% in the diet, proved to be one that reduced mature body weights. At this slightly toxic dose, RA had only some minor effects of the incidences of neoplasms.

A slight decrease in cryptogenic neoplasms of the ovary and lung was seen. This was, however, small in comparison to reports of inhibition of chemically induced neoplasms of the

Table 1. Number of Neoplasm-Bearing Animals and Neoplasms in Retinyl Acetate–Treated C3H Mice and Controls

Group	Treatment	Sex	Total No. of Animals	EF[a]	TBA[b]	Neoplasms	Incidence of TBA[b]
1	Control	F	50	44	39	57	89%
2	Retinyl acetate	F	50	45	42	55	93%
3	Control	M	50	44	25	39	57%
4	Retinyl acetate	M	50	48	28	38	58%

a: EF, effective no. of animals.
b: TBA, tumor-bearing animals.

Table 2. Incidences[a] of Neoplasms of Different Types in Retinyl Acetate–Treated C3H(+) Mice and Controls

							Hemangiomas					Ovary				
Group	Treatment	Sex	Mammary Tumors (tumors/TBA[b])	Liver Cell Carcinomas	Lung Adenomas	Lymphomas	Spleen	Lymph node	Sub-cut.	Liver	Total	Tubular adenoma	Granulosa cell tumor	Total	Cyst (cyst/animal)	Other
1	Control	Female	61.4 (32/27)	9.1	6.8	0	2.3	2.3	4.6	0	9.1	20.5	4.6	25.0	59.1 (35/26)	3[c]
2	RA	Female	77.8 (39/35)	2.2	0	6.7	4.4	4.4	4.4	6.7	20.5	4.4[g]	2.2	6.7[g]	66.7 (43/30)	1[d]
3	Control	Male	0	43.2	13.6	0	11.4	4.6	0	2.3	18.2	0	0	0	0	6[e]
4	RA	Male	0	37.5	2.1[g]	2.1	16.7	8.3	6.3	2.1	33.3	0	0	0	0	2[f]

a: All incidences were calculated from the effective number of animals.
b: TBA, tumor-bearing animals.
c: 1 Endometrial adenocarcinoma, 2 luteomas.
d: 1 Luteoma.
e: 1 Squamous cell carcinoma of the ear skin, 1 subcutaneous fibrosarcoma, 4 adrenal tumors.
f: 2 Adrenal tumors.
g: Significantly reduced, $p < 0.05$.

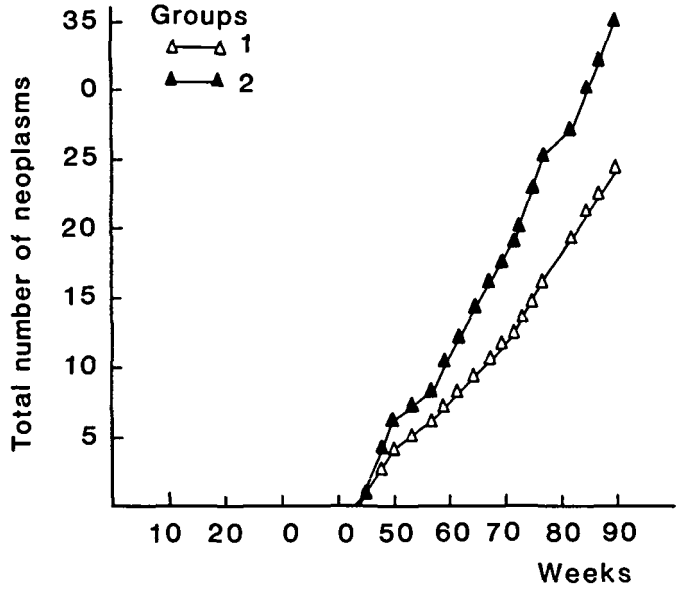

Figure 3. Number of gross palpable mammary neoplasms in C3H/HeJ(+) female mice. Group 1, untreated controls; Group 2, RA-treated animals.

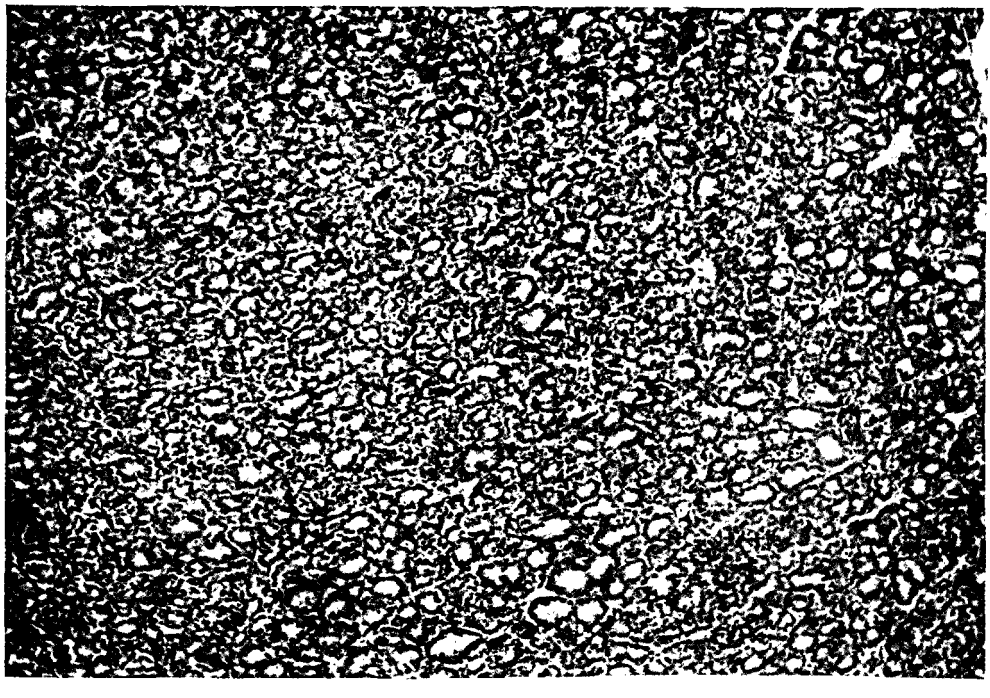

Figure 4. Mammary adenocarcinoma in RA-treated C3H/HeJ(+) mouse. Neoplasm consists of densely packed neoplastic glands. Hematoxylin-eosin stained. Magnification × 180.

Figure 5. Hemangioma of the spleen in RA-treated C3H/HeJ(+) mouse. Neoplasm is composed of dilated blood-filled vascular spaces. Hematoxylin-eosin stained. Magnification ×180.

breast (14,17,18), urinary tract (9), skin (4–7), and lung (3,8,10,11). In another study of the effects of vitamin A on cryptogenic neoplasm formation, Maiorana and Gullino (32) fed RA to female C3H^{vy} mice from weaning to death with no effect on mammary tumor incidence; however, there was a decrease in hepatoma incidence. In the present study, the number of mammary neoplasms was definitely not reduced and may even have been marginally increased. The number of liver neoplasms was lower in RA-treated animals, but it was not to a statistically significant degree. The decrease in lung adenoma incidence in this study was small, but perhaps noteworthy, because a higher lung cancer incidence was reported in smokers with low levels of vitamin A (34). Inhibition of lung tumorigenesis by RA is not unreasonable, because vitamin A is required for differentiation of epithelial cells (2). For the slight decrease of ovarian neoplasms, however, no explanation is evident, although vitamin A and retinoids exert a variety of effects that could influence carcinogenesis (35–38). Even though ovarian and lung neoplasms were significantly reduced in the RA groups, the level of significance was low, and thus the biological significance remains to be established by additional studies.

The lack of substantial inhibition of cryptogenic neoplasm development in the study of Maiorana and Gullino (32) and our own requires consideration. One factor might be the doses used. In a study of rats by Kurokawa and co-workers (33), only in the highest dose group (0.25%) was a marginal reduction in mammary tumor incidence found. In the study of mice by Maiorana and Gullino (32), the high doses of RA (0.033% diet and 0.017%) were toxic, whereas the lower doses (0.008% and 0.004%) were below inhibitory doses in rat studies. In rat studies, neoplasm-inhibitory doses such as 0.033% in the diet reduce body weight gain by more than 10% (15), which is clearly indicative of toxicity. The dose in our study, 0.02%, was about two-thirds of the highest dose used by Maiorana and Gullino (32); however, it was lower than that in most rat studies, because mice tolerate only approximately 20% of the dietary concentration of RA tolerated by rats. At this dose, we observed slight toxicity in the form of reduced weight gain or weight loss after 30 weeks of treatment. The lack of substantial inhibition

of cryptogenic neoplasms by RA, therefore, cannot be ascribed to inadequate dosage. This leaves the following four other main interpretations: a) the form of vitamin A (i.e., RA) may be one that does not affect the tissues which were the sites of cryptogenic neoplasms; b) the oral route of administration may not be effective for RA; c) the effects of vitamin A may be so exquisitely dose related that even slightly excess doses are without efficacy; and d) vitamin A may not be effective in inhibiting "spontaneous," as opposed to chemically induced, neoplasms. Further research would obviously be required to evaluate these possibilities; however, if any of them holds, the implications for successful design of human cancer prevention are serious.

In the present study, a small increase in hemangiomas of different organs was observed in addition to a slight increase in the incidence of lymphomas. Retinoid enhancement of chemically induced carcinogenesis has been reported (24–31). For example, toxic levels of retinoids exerted a promoting effect on epithelial carcinogenesis in the hamster cheek pouch (24), possibly by enhancing prostaglandin synthesis similar to the effect of phorbol esters (39). Also, in rats, an increase of "spontaneous" adrenal medullary neoplasms occurred with feeding of retinol acetate (33). It is not evident what effect of RA could account for an increase in hemangiomas. RA is not known to be genotoxic (40). Therefore, until the present finding is confirmed and the biological nature of hemangiomas is better understood, no hazard of RA for humans should be inferred.

The retinoids are a family of fat-soluble molecules each with a varying effect on growth, differentiation, and tumor inhibition (41–46). The toxicity of the compounds also varies (45,47), with many new synthetic compounds having a superior anticarcinogenicity-to-toxicity ratio (44). The compound used in this study, RA, accumulates in the liver (12,45) and, when compared with synthetic compounds, is more toxic. Studies of the type performed here, but use other retinoids, could provide more promising information for the use of vitamin A for human cancer prevention.

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