Results of Three Life-Span Experimental Carcinogenicity and Anticarcinogenicity Studies on Tamoxifen in Rats

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INTRODUCTION

Tamoxifen is a drug that is widely used in medical oncology as an antiestrogen. This effect is due to its competitive action on estrogen receptors, but other mechanisms can be implied. Most likely, tamoxifen may also act via the hypophysis by lowering the production of ovarian estrogens.

The use of tamoxifen in oncology started in 1971,[1] and it has been progressively and gradually expanding. Up to the present day it seems that over 5 million women have undergone treatment with this drug. Ordinarily, tamoxifen is administered at the daily dose of 20 mg, but sometimes 30 or 40 mg are prescribed.

Tamoxifen has been found efficacious, and is therefore used in primary hormonotherapy for female and male mammary carcinoma and for endometrial cancer. Its use has also been proposed in other tumors, mainly melanomas.[2] Its therapeutic effect on mammary cancer has been proved with experimental animal models.[3]

Nowadays, tamoxifen is widely used in postsurgical adjuvant therapy for mammary carcinoma in women. There are at present 14 clinical trials on this use,[4–19] and the updated results seem to show an advantageous effect of the drug on disease-free survival time and on overall survival.

Tamoxifen has been shown to have chemopreventive effects on mammary cancers experimentally induced in rats, or in a strain of mice that develop mammary tumors spontaneously at a high incidence,[3,20–26] and on the spontaneous mammary cancers of the colony of Sprague-Dawley rats used in the Cancer Research Center at the Castle of Bentivoglio (BT) of the European Ramazzini Foundation.[27–39]

The results obtained on spontaneous mammary carcinomas in female Sprague-Dawley rats show a sharp chemopreventive effect of tamoxifen, and they are particu-

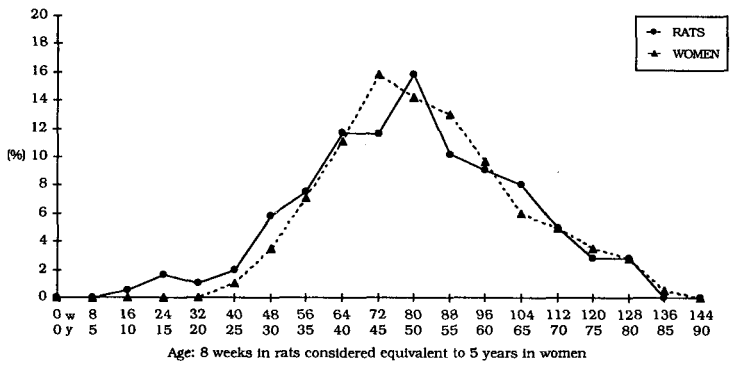

FIGURE 1. Comparative distribution by equivalent age of 232 mammary carcinomas observed among 2,000 untreated female Sprague-Dawley rats of the colony used at the CRC/ERF, and of 1,264 mammary carcinomas detected among 130,000 Bologna women under screening.

larly relevant for clinical extrapolation since this animal model must be considered human equivalent in its histological pattern, biological behavior, global incidence, and age-equivalent distribution of these tumors (FIG. 1).

The chemopreventive effect of tamoxifen on mammary carcinoma is also supported by the observation in mastectomized women of a protective effect of the drug on the contralateral mammary tumors, in the trials evaluating the effect of tamoxifen in adjuvant therapy. Of a total of 30,000 women included in those trials (180,000 woman-years), 379 cases of contralateral mammary carcinomas were observed in the control group, vs. 276 cases of these tumors in the tamoxifen-treated group, with an odds reduction of 35% (2P = 0.00001) (personal communication).

These experimental and clinical observations prompted three chemopreventive clinic trials, one in the United States on 16,000 women,[40-42] one in Italy on 20,000 women[43] and one in the United Kingdom on 15,000 women.[44,45] The daily dose employed in these trials is 20 mg/day.

Much is known about short- and middle-term wanted and unwanted effects of tamoxifen in treated women.[34,46-53] Much less is known of its long-term carcinogenic effects. Information on the carcinogenic potential of tamoxifen is, on the contrary, of primary relevance, because of the use of tamoxifen in adjuvant therapy, involving large groups of women who must be considered already cured by surgery alone, and because of the chemopreventive trials, which are now ongoing and whose results may eventually open the door to the adoption of tamoxifen treatment for chemoprevention of mammary cancer on large groups of women all over the world.

Careful pioneering observation in the Swedish adjuvant trial showed, even in 1989, an increase in endometrial carcinomas in women treated with tamoxifen at 40 mg daily.[54] The effect has now been confirmed also in women treated with the daily dose of 20 mg (the dose currently used).[55] In the total of 30,000 women of the ongoing adjuvant trials, at present 78 cases of endometrial carcinoma have been observed in treated women, vs. 21 in the control group (2P < 0.00001) (personal communication).

Five experimental studies in rats of different strains were performed to evaluate the carcinogenic effect of tamoxifen. The results, summarized in TABLE 1,[56-60] indicate that tamoxifen is indeed a hepatocarcinogen at very high doses. The still effective lower dose is 5 mg/kg b.w., which corresponds to 15 times the current clinical dose (considering 60 kg to be the weight of a woman, the current dose of 20 mg/day corresponds to 0.33 mg/day). It must be pointed out, on the other hand, that the maximum duration of these experimental hepatocarcinogenicity studies was 24 months.

To date there are no available results of long-term carcinogenicity bioassays of the types currently performed for industrial carcinogens and that follow the Good Laboratory Practices (GLP) (required for this type of testing). In 1988, 1989, and 1991, respectively, we started three life span experiments to evaluate the potential carcinogenic and anticarcinogenic effects of tamoxifen in all tissues and organs, following the rules of the GLP. The results of the three bioassays are herein presented. These three experiments are part of a wider project of 13 experimental studies, aimed at assessing the chemopreventive effects and carcinogenic risks of the drug, which was started in 1986.

MATERIALS AND METHODS

The tamoxifen tested is the one marketed by Zeneca, under the commercial name of Nolvadex®.

The tested animals were male and female Sprague-Dawley rats of the colony, which has been used for 25 years in the laboratories of the Cancer Research Center of the European Ramazzini Foundation of Oncology and Environmental Sciences, for which there is extensive information on expected nonneoplastic and neoplastic pathology available for about 10,000 controls.

In this strain, the incidence of mammary tumors is of the same order of that observed in women in industrial countries: mammary cancer arises in about 10% of the females (range 7-12%), and the number of mammary cancers per 100 animals usually ranges from 9 to 13 (since the same animal can bear more than one mammary malignancy). The distribution by equivalent ages in this animal model and in women overlaps (FIG. 1). The mammary cancers show all the various morphological and biological patterns that characterize the human types and subtypes.

For the purpose of the present studies, data are presented on selected tumors observed in 2 groups of untreated rats, respectively for 1,000 males and 1,000 females, born in 1988 (that is, at the same time as the animals of the herein-presented experiments), kept under control for their life span, and submitted to complete necropsy and systematic histopathological examination (TABLES 2 and 3).

The plans of the three experiments are presented in TABLE 4.

Tamoxifen was administered by stomach tube in water suspension; controls were gavaged with water alone.

The animals were submitted daily to observation, and weighed and clinically controlled periodically (weekly within the first 13 weeks of experiment, and then every 2 weeks).

At death, all animals were submitted to systematic necropsy. Specimens for histopathology include mammary glands, mammary tumors, brain, pituitary gland,

TABLE 1. Incidence of Hepatocarcinomas in Various Rat Strains Submitted to Long-term Treatment with Tamoxifen

Strain of Rats	Duration of Experiment (months)	Daily Dose (mg/kg b.w.)	No. of Animals		Hepatocarcinoma (Bearing Animals) (%)	Reference
			At Start	Corrected		
Sprague-Dawley	15	2.8	57	22	0	56
	15	11.3	57	11	45	
	12	45.2	55	4	75	
Wistar	24	5.0	52	51	16	57
	24	20.0	52	51	64	
	24	35.0	52	51	64	
Sprague-Dawley	12	11.3	84	36	44	58
	12	22.6	75	24	100	
Sprague-Dawley	15	11.3	5	5	60	59
	15	45.0	8	6	83	
Fischer F344	15	12.5	20	8	0	60

TABLE 2. Spontaneous Incidence of Selected Tumors in a Group of 1,000 Randomized Control Male Sprague-Dawley Rats

Type of Tumor	Animals Bearing Tumors		Incidence of Tumors	
	No.	%	No.	Per 100 Animals
Mammary				
Benign[a]	26	2.6	27	2.7
Malignant[b]	5	0.5	5	0.5
Hepatocarcinomas	11	1.1		
Testicular Leydig cell tumors	61	6.1		

[a] Fibromas and fibroadenomas.
[b] Carcinomas and sarcomas.

TABLE 3. Spontaneous Incidence of Selected Tumors in a Group of 1,000 Randomized Control Female Sprague-Dawley Rats

Type of Tumor	Animals Bearing Tumors		Incidence of Tumors	
	No.	%	No.	Per 100 Animals
Mammary				
Benign[a]	407	40.7	549	54.9
Malignant[b]	84	8.4	99	9.9
Hepatocarcinomas	0	–		
Uterine				
Carcinomas	16[c]	1.6		
Sarcomas	23	2.3		
Total malignant tumors	39	3.9		

[a] The great majority fibroadenomas and some fibromas.
[b] The great majority carcinomas and a few cases of sarcoma.
[c] Eleven adenocarcinomas and five squamous cell carcinomas.

TABLE 4. Plan of Three Experimental Studies

Experiment	1 (BT 5T)	2 (BT 8T)	3 (BT 12T)
Sex	Males and females	Females	Females
Age at start (weeks)	8	12	56
Route of administration	Oral[a]	Oral[a]	Oral[a]
Administered dose (mg/kg b.w.)	3.3	3.3	3.3
Schedule of treatment	6 days weekly, life span	8 days every 8 weeks, life span	6 days weekly, for 40 weeks
Duration of the experiment	Life span	Life span	Life span
Number of rats per group (treated and control)	100	150	139
Total number of animals	400	300	278
Duration of life span	167	166	143

[a] By stomach tube in water suspension.

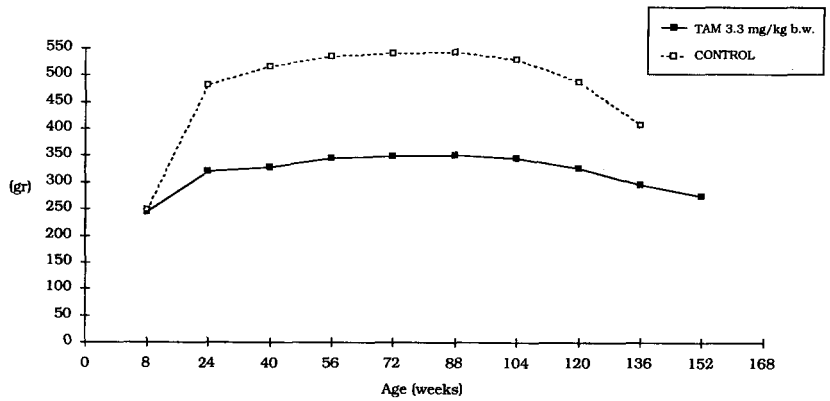

FIGURE 2. Mean body weight of males in experiment 1 (BT 5T).

Zymbal glands, salivary glands, Harderian glands, head (with oral and nasal cavities and external and internal ear ducts) (5 sections), tongue, thyroid and parathyroids, pharynx, larynx, thymus and mediastinal lymph nodes, trachea, lung and mainstem bronchi, heart, diaphragm, liver, spleen, pancreas, kidneys and adrenal glands, esophagus, stomach (fore and glandular), intestine (4 levels), bladder, prostate, uterus, vagina, gonads, interscapular fat pad, subcutaneous and mesenteric lymph nodes, femur, and any other organs and tissues with pathological lesions. All organs and tissues were preserved in 70% ethyl alcohol, except bones, which were fixed in 10% formalin and then decalcified with 10% formaldehyde and 20% formic acid in water solution. The normal specimens were trimmed, following the standard procedures of the BT laboratory: i.e., parenchymal organs were dissected through the hilus to expose the widest surface, and hollow organs were sectioned across the greatest diameter(s). The pathological tissue was trimmed through the largest surface, including normal adjacent tissues. The trimmed specimens were processed as paraffin blocks, and 3-5-micron sections of every specimen were obtained. Sections were routinely stained with hematoxylin-eosin. Specific stainings were performed when needed. The histological slides were examined independently by two pathologists, and then reviewed by a third pathologist.

RESULTS

Body Weight. In the animals treated with tamoxifen a reduction in body weight was observed: such reduction parallels the intensity of treatment (FIGS. 2-5). In the animals treated six times weekly since six weeks of age and for their life span (exp. 1/BT5T), a reduction of size among tamoxifen-treated animals of both sexes was observed.

Survival. In all three experiments, a moderate increase in the survival rate was observed in tamoxifen-treated groups with respect to control groups (FIG. 6-9).

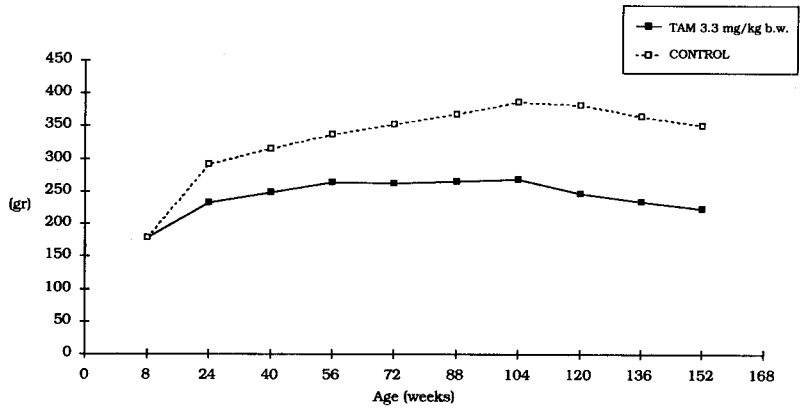

FIGURE 3. Mean body weight of females in experiment 1 (BT 5T).

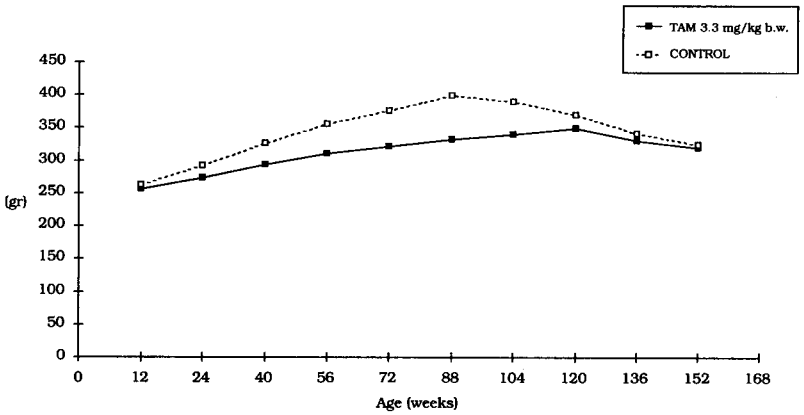

FIGURE 4. Mean body weight of females in experiment 2 (BT 8T).

Nononcological Changes. No evident behavioral changes were observed in tamoxifen-treated animals. In female rats, atrophic changes in cervical mucosa were observed at the histological examination, following continuous treatment with tamoxifen, started at a young age.

Carcinogenic and Anticarcinogenic Effects. Multiple tumors of the same site (monolateral and bilateral organs) and type were plotted only once, apart from the mammary and adrenal tumors of the same type, whose multiplicity has been taken into account.

Experiment 1 (BT5T)

The overall results are shown in TABLES 5 and 6. In the tamoxifen-treated groups there was a sharply decreased incidence of total benign tumors (TABLE 7), while no

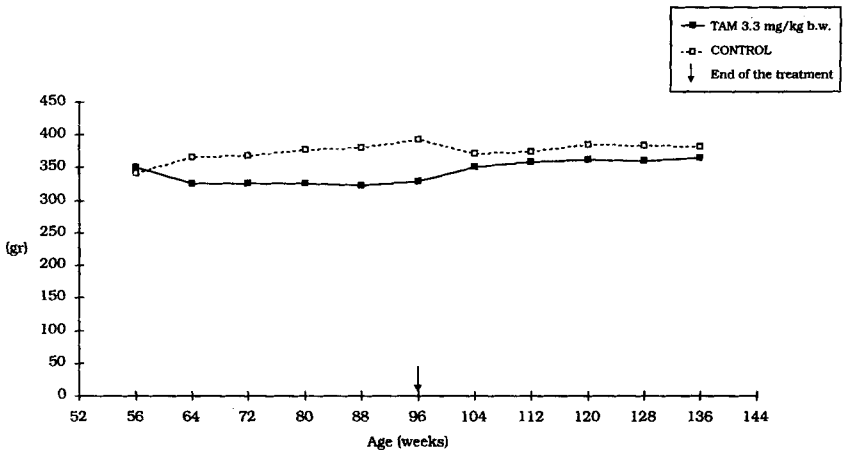

FIGURE 5. Mean body weight of females in experiment 3 (BT 12T).

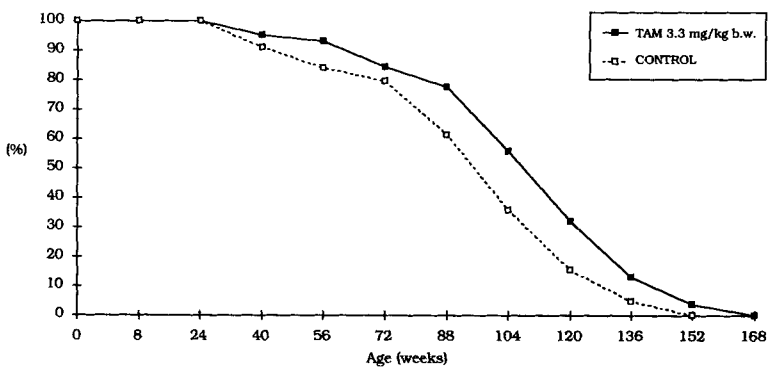

FIGURE 6. Survival of males of experiment 1 (BT 5T).

remarkable difference in the incidence of total malignant tumors was observed between treated and control males and females (TABLE 8). With respect to single tumors, tamoxifen was found: (1) to increase benign and malignant mammary tumors in males, and sharply decrease/inhibit benign and malignant tumors in females (TABLES 9, 10); (2) to decrease the pituitary gland tumors in males and females (TABLE 11), the medullary adrenal pheochromocytomas in males and females (TABLE 12), the islet cell pancreatic tumors in males (TABLE 13), the Leydig cell testicular tumors (TABLE 14) and the polyps of the uterus (TABLE 15); and (3) to slightly increase tumors and correlated oncological lesions of the liver among males and females (TABLE 16), and tumors of the uterus and vagina (TABLE 17). One pheochromoblastoma was found among treated males and treated females, while none were observed among

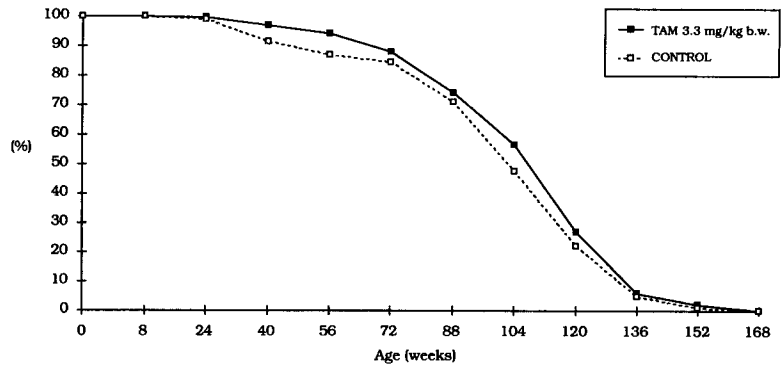

FIGURE 7. Survival of females of experiment 1 (BT 5T).

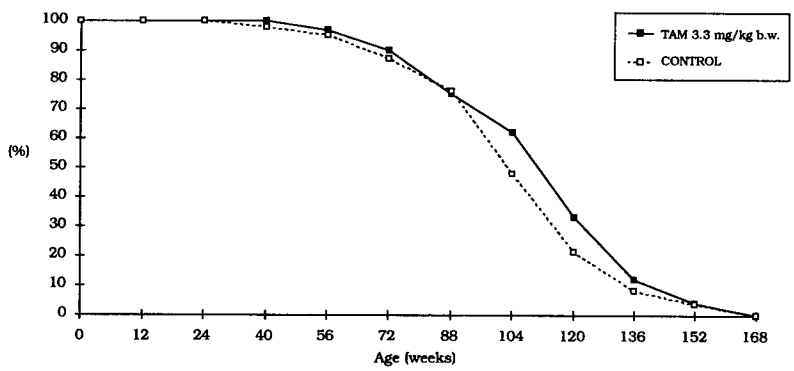

FIGURE 8. Survival of females of experiment 2 (BT 8T).

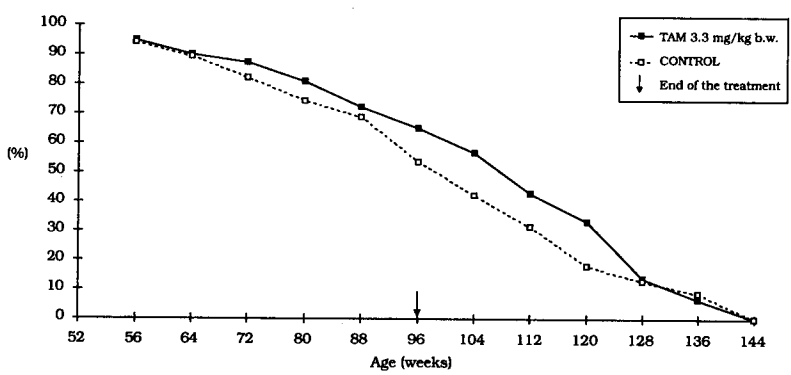

FIGURE 9. Survival of females of experiment 3 (BT 12T).

TABLE 5. Results of Experiment 1 (BT 5T): Number and Percentage of Male Sprague-Dawley Rats Bearing Various Types of Benign and Malignant Tumors[a]

Site	Histotype	Groups			
		I: 3.3 mg/kg b.w.		II: 0 (control)	
		No.	%	No.	%
Skin	Keratoacanthoma	0	–	1	1.0
Subcutaneous tissue	Fibroma	0	–	2	2.0
	Rhabdomyosarcoma	1	1.0	0	–
	Angiosarcoma	0	–	2	2.0
	Osteosarcoma	0	–	1	1.0
Mammary gland[b]	Fibroma and fibroadenoma	6	6.0	1	1.0
	Adenocarcinoma	2 (3)	2.0	0	–
Zymbal glands	Carcinoma	1	1.0	0	–
Ear ducts	Carcinoma	2	2.0	2	2.0
Nasal cavities	Olfactory neuroblastoma	1	1.0	0	–
Larynx	Squamous cell carcinoma	1	1.0	1	1.0
Trachea	Squamous cell carcinoma	0	–	1	1.0
Intestine	Leiomyoma	1	1.0	1	1.0
Liver[c]	Hepatoadenoma	1	1.0	0	–
	Hepatocarcinoma	2	2.0	0	–
Pancreas[d]	Islet cell adenoma	1	1.0	7	7.0
	Islet cell adenocarcinoma	0	–	1	1.0
Kidneys	Adenoma	2	2.0	0	–
Testes[e]	Leydig cell tumor	0	–	4	4.0
Peritoneum	Mesothelioma	1	1.0	0	–
Pituitary gland[f]	Adenoma	5	5.0	11	11.0
Thyroid gland	C-cell carcinoma	1	1.0	0	–
Adrenal glands[g]	Cortical adenoma	0	–	1	1.0
	Pheochromocytoma	16 (17)	16.0	19 (27)	19.0
	Pheochromoblastoma	1	1.0	0	–

Bones					
Cranium	Osteosarcoma	3	3.0	1	1.0
Soft tissues	Fibrosarcoma	0	–	1	1.0
Spleen	Fibroangioma	4	4.0	1	1.0
Hemolymphoreticular tissues[h]	Lymphomas and leukemias	11	11.0	14	14.0

[a] Numbers in parentheses indicate the number of tumors (one animal can bear more than one tumor).
[b] See TABLES 9, 10.
[c] See TABLE 16.
[d] See TABLE 13.
[e] See TABLE 14.
[f] See TABLE 11.
[g] See TABLE 12.
[h] Including spleen.

TABLE 6. Results of Experiment 1 (BT 5T): Number and Percentage of Female Sprague-Dawley Rats Bearing Various Types of Benign and Malignant Tumors[a]

		Groups			
		I: 3.3 mg/kg b.w.		II: 0 (Control)	
Site	Histotype	No.	%	No.	%
Skin	Dermatofibroma	1	1.0	0	–
	Sebaceous gland adenoma	1	1.0	0	–
	Fibrosarcoma	0	–	1	1.0
Subcutaneous tissue	Fibrosarcoma	1	1.0	0	–
	Liposarcoma	1	1.0	0	–
Mammary gland[b]	Fibroma and fibroadenoma	0	–	37 (55)	37.0
	Adenocarcinoma	0	–	8 (12)	8.0
	Fibrosarcoma	0	–	1	1.0
Zymbal glands	Carcinoma	1	1.0	1	1.0
Ear ducts	Carcinoma	2	2.0	3	3.0
Oral cavity, lips and tongue	Carcinoma	1	1.0	1	1.0
Larynx	Squamous cell carcinoma	0	–	1	1.0
Intestine	Adenocarcinoma	1	1.0	0	–
Liver[c]	Hepatoadenoma	1	1.0	0	–
	Cholangioma	0	—	2	2.0
	Hepatocarcinoma	3	3.0	0	–
Pancreas[d]	Islet cell adenocarcinoma	0	–	1	1.0
Bladder	Rhabdomyosarcoma	1	1.0	0	–
Ovaries	Fibroangioma	1	1.0	0	–
Uterus[e]	Polyp	0	–	13	13.0
	Fibroma	2	2.0	0	–
	Fibroangioma	1	1.0	0	–
	Angioma	0	–	1	1.0
	Adenocarcinoma	0	–	1	1.0

	Squamous cell carcinoma	1	1.0	0	–
	Sarcoma	3	3.0	2	2.0
Vagina[e]	Squamous cell carcinoma	1	1.0	0	–
Peritoneum	Mesothelioma	1	1.0	0	–
Pituitary gland[f]	Adenoma	2	2.0	16	16.0
Thyroid gland	Papillary adenocarcinoma	1	1.0	1	1.0
	C-cell carcinoma	0	–	1	1.0
Adrenal glands[g]	Cortical adenoma	5	5.0	6	6.0
	Pheochromocytoma	12 (19)	12.0	17 (25)	17.0
	Cortical adenocarcinoma	1	1.0	0	–
	Pheochromoblastoma	1	1.0	0	–
Major peripheral nerves	Malignant Schwannoma	1	1.0	0	–
Bones					
Cranium	Osteoma	1	1.0	0	–
	Osteosarcoma	1	1.0	1	1.0
Thymus	Squamous cell carcinoma	0	–	1	1.0
Spleen	Fibroangioma	1	1.0	0	–
	Angiosarcoma	1	1.0	0	–
Hemolymphoreticular tissues[h]	Lymphomas and leukemias	11	11.0	9	9.0

[a] Numbers in parentheses indicate the number of tumors (one animal can bear more than one tumor).
[b] See TABLES 9, 10.
[c] See TABLE 16.
[d] See TABLE 13.
[e] See TABLES 15, 17.
[f] See TABLE 11.
[g] See TABLE 12.
[h] Including thymus and spleen.

TABLE 7. Results of Experiment 1 (BT 5T): Incidence of Total Benign Tumors in Males and Females

Group No.	Dose (mg/kg b.w.)	Animals		Benign Tumors			
				Animals Bearing Tumors		Tumors	
		Sex	No.	No.	%	No.	Per 100 Animals
I	3.3	M	100	29	29.0	37	37.0
		F	100	26	26.0	35	35.0
II	0	M	100	33	33.0	56	56.0
		F	100	57	57.0	118	118.0

TABLE 8. Results of Experiment 1 (BT 5T): Incidence of Total Malignant Tumors in Males and Females

Group No.	Dose (mg/kg b.w.)	Animals		Malignant Tumors			
				Animals Bearing Tumors		Tumors	
		Sex	No.	No.	%	No.	Per 100 Animals
I	3.3	M	100	26	26.0	28	28.0
		F	100	31	31.0	34	34.0
II	0	M	100	24	24.0	24	24.0
		F	100	27	27.0	37	37.0

TABLE 9. Results of Experiment 1 (BT 5T): Incidence of Benign Mammary Tumors in Males and Females

Group No.	Dose (mg/kg b.w.)	Animals		Benign Mammary Tumors			
				Animals Bearing Tumors		Tumors	
		Sex	No.	No.	%	No.	Per 100 Animals
I	3.3	M	100	6	6.0	6	6.0
		F	100	0	–	0	–
II	0	M	100	1	1.0	1	1.0
		F	100	36	36.0	55	55.0

TABLE 10. Results of Experiment 1 (BT 5T): Incidence of Malignant Mammary Tumors in Males and Females

Group No.	Dose (mg/kg b.w.)	Animals		Malignant Mammary Tumors			
				Animals Bearing Tumors		Tumors	
		Sex	No.	No.	%	No.	Per 100 Animals
I	3.3	M	100	2	2.0	3	3.0
		F	100	0	–	0	–
II	0	M	100	0	–	0	–
		F	100	9	9.0	13	13.0

TABLE 11. Results of Experiment 1 (BT 5T): Incidence of Pituitary Gland Tumors in Males and Females

Group No.	Dose (mg/kg b.w.)	Animals		Animals Bearing Pituitary Gland Adenomas	
		Sex	No.	No.	%
I	3.3	M	100	5	5.0
		F	100	2	2.0
II	0	M	100	11	11.0
		F	100	16	16.0

TABLE 12. Results of Experiment 1 (BT 5T): Incidence of Adrenal Glands Pheochromocytomas and Pheochromoblastomas in Males and Females

Group No.	Dose (mg/kg b.w.)	Animals		Pheochromocytomas				Pheochromoblastomas			
				Animals Bearing Tumors		Tumors		Animals Bearing Tumors		Tumors	
		Sex	No.	No.	%	No.	Per 100 Animals[a]	No.	%	No.	Per 100 Animals
I	3.3	M	100	16	16.0	17	17.0	1	1.0	1	1.0
		F	100	12	12.0	19	19.0	1	1.0	1	1.0
II	0	M	100	19	19.0	27	27.0	0	–	0	–
		F	100	17	17.0	25	25.0	0	–	0	–

[a] In several animals pheochromocytomas were observed in both adrenal glands.

TABLE 13. Results of Experiment 1 (BT 5T): Incidence of Islet Cell Pancreatic Tumors in Males and Females

Group No.	Dose (mg/kg b.w.)	Animals		Animals Bearing Tumors			
				Islet Cell Adenomas		Islet Cell Adenocarcinoma	
		Sex	No.	No.	%	No.	%
I	3.3	M	100	1	1.0	0	–
		F	100	0	–	0	–
II	0	M	100	7	7.0	1	1.0
		F	100	0	–	1	1.0

TABLE 14. Results of Experiment 1 (BT 5T): Incidence of Leydig Cell Testicular Tumors

Group No.	Dose (mg/kg b.w.)	Animals		Animals Bearing Leydig Cell Tumors	
		Sex	No.	No.	%
I	3.3	M	100	0	–
II	0	M	100	4	4.0

TABLE 15. Results of Experiment 1 (BT 5T): Incidence of Polyps of the Uterus

Group No.	Dose (mg/kg b.w.)	Animals		Animals Bearing Tumors	
		Sex	No.	No.	%
I	3.3	F	100	0	–
II	0	F	100	13	13.0

TABLE 16. Results of Experiment 1 (BT 5T): Incidence of Tumors and Other Lesions of Oncological Interest of the Liver in Males and Females

Group No.	Dose (mg/kg b.w.)	Animals		Animals Bearing Liver Changes							
				Nodular Hyperplasias		Nodular Dysplasias		Hepatoadenomas		Hepatocarcinomas[a]	
		Sex	No.	No.	%	No.	%	No.	%	No.	%
I	3.3	M	100	9	9.0	2	2.0	1	1.0	2	2.0
		F	100	6	6.0	1	1.0	1	1.0	3	3.0
II	0	M	100	4	4.0	0	–	0	–	0	–
		F	100	6	6.0	0	–	0	–	0	–

[a] All with small deviation (low grade).

TABLE 17. Results of Experiment 1 (BT 5T): Incidence of Malignant Tumors of the Uterus and Vagina

Group No.	Treatment (mg/kg b.w.)	Animals		Animals Bearing Tumors											
				Uterus				Vagina				Total			
				Carcinomas		Sarcomas		Carcinomas		Sarcomas		Carcinomas		Sarcomas	
		Sex	No.	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
I	3.3	F	100	1	1.0	3	3.0	1	1.0	0	–	2	2.0	3	3.0
II	0	F	100	1	1.0	2	2.0	0	–	0	–	1	1.0	2	2.0

control animals (TABLE 12). No relevant changes were found in the incidence of the other detected tumors as a whole (TABLES 18, 19).

Experiment 2 (BT8T)

The overall results are shown in TABLE 20. In the tamoxifen-treated group there was again a clearly decreased incidence of total benign tumors (TABLE 21), while only a slight and not remarkable difference in the incidence of total malignant tumors was observed (TABLE 22). With respect to single tumors, tamoxifen was found: (1) to markedly decrease benign and malignant mammary tumors (TABLES 23, 24) (2) to decrease the pituitary gland tumors (TABLE 25), the medullary adrenal tumors (TABLE 26), the islet cell pancreatic tumors (TABLE 27), and the polyps of the uterus (TABLE 28) (3) not to affect the incidence of tumors and oncological lesions of the liver (TABLE 29); and (4) to increase the uterine-vagina sarcomas (TABLE 30). No relevant changes were found in the incidence of the other detected tumors as a whole (TABLES 31, 32).

Experiment 3 (BT12T)

The overall results are shown in the TABLE 33. In the tamoxifen-treated group there was again a clearly decreased incidence of total benign tumors (TABLE 34) and a slight and not remarkable decrease of total malignant tumors (TABLE 35). In the tamoxifen-treated group a reduction in benign mammary tumors was observed, both at the end of the treatment and thereafter (TABLE 36). After 40 weeks of treatment, complete protection against mammary cancer was observed; the protective effect also lasted after stopping the treatment (TABLE 37). A reduction in the incidence of pituitary gland tumors (TABLE 38), of the islet cell pancreatic tumors (TABLE 39), and of the polyps of the uterus (TABLE 40) was also observed. No decreased incidence of adrenal gland pheochromocytomas was detected (TABLE 41). No carcinogenic effect of tamoxifen was found on the liver (TABLE 42) and the uterus and vagina (TABLE 43). No relevant changes were found in the incidence of the other detected tumors as a whole among treated and control animals (TABLE 44, 45).

CONCLUSIONS

Under the tested experimental conditions, the results of our three experiments show that:

1. tamoxifen has a strong inhibiting (chemopreventive) effect on mammary cancer in females;
2. such chemopreventive effect also lasts when the treatment is stopped;
3. tamoxifen reduces the incidence of other tumors (including pituitary, medullary adrenal, islet cell pancreatic and Leydig cell testicular tumors, and polyps of the uterus);

TABLE 18. Results of Experiment 1 (BT 5T): Incidence of Benign Tumors Not Including the Ones Decreased[a] or Increased[b] by Tamoxifen Treatment

Group No.	Dose (mg/kg b.w.)	Animals		Benign Tumors			
				Animals Bearing Tumors		Tumors	
		Sex	No.	No.	%	No.	Per 100 Animals
I	3.3	M	100	7	7.0	7	7.0
		F	100	13	13.0	13	13.0
II	0	M	100	6	6.0	6	6.0
		F	100	8	8.0	9	9.0

[a] Decreased benign tumors: mammary tumors in females, pituitary gland adenomas, pheochromocytomas, islet cell pancreatic tumors, Leydig cell testicular tumors, polyps of the uterus (see TABLES 9-15).

[b] Increased benign tumors: mammary tumors in males, liver hepatoadenomas (see TABLES 9 and 16).

TABLE 19. Results of Experiment 1 (BT 5T): Incidence of Malignant Tumors Not Including the Ones Decreased[a] or Increased[b] by Tamoxifen Treatment

Group No.	Dose (mg/kg b.w.)	Animals		Malignant Tumors			
				Animals Bearing Tumors		Tumors	
		Sex	No.	No.	%	No.	Per 100 Animals
I	3.3	M	100	22	22.0	22	22.0
		F	100	24	24.0	25	25.0
II	0	M	100	23	23.0	23	23.0
		F	100	18	18.0	20	20.0

[a] Decreased malignant tumors: mammary tumors in females, islet cell pancreatic tumors (see TABLES 10 and 13).

[b] Increased malignant tumors: mammary tumors in males, pheochromoblastomas, hepatocarcinomas, tumors of the uterus and vagina (see TABLES 10, 12, 16, and 17).

TABLE 20. Results of Experiment 2 (BT 8T): Number and Percentage of Female Sprague-Dawley Rats Bearing Various Types of Benign and Malignant Tumors[a]

Site	Histotype	Groups			
		I: 3.3 mg/kg b.w.		II: 0 (Control)	
		No.	%	No.	%
Subcutaneous tissue	Lipoma	1	0.7	1	0.7
Mammary gland[b]	Fibroma and fibroadenoma	41 (55)	27.3	68 (93)	45.3
	Fibrolipoma	1	0.7	0	–
	Adenocarcinoma	5	3.3	12 (13)	8.0
	Fibrosarcoma	0	–	2	1.3
	Fibrohistiocytosarcoma	0	–	1 (2)	0.7
Zymbal glands	Carcinoma	1	0.7	1	0.7
Ear ducts	Carcinoma	7	4.7	3	2.0
Lung	Osteosarcoma	0	–	1	0.7
Stomach					
Glandular stomach	Adenoma	0	–	1	0.7
	Adenocarcinoma	0	–	1	0.7
Intestine	Adenocarcinoma	0	–	1	0.7
Liver[c]	Hepatocarcinoma	0	–	1	0.7
Pancreas[d]	Islet cell adenoma	1	0.7	6	4.0
Ovaries	Fibroma	0	–	1	0.7
	Fibroangioma	1	0.7	4	2.7
Uterus[e]	Polyp	3	2.0	13	8.7
	Fibroma	1	0.7	2	1.3
	Fibroangioma	0	–	1	0.7
	Squamous cell carcinoma	1	0.7	0	–
	Sarcoma	5	3.3	1	0.7
Vagina[e]	Squamous cell carcinoma	1	0.7	1	0.7
	Sarcoma	2	1.3	0	–
Peritoneum	Mesothelioma	1	0.7	1	0.7

Pituitary gland[f]	Adenoma	22	14.7	45	30.0
Thyroid gland	C-cell adenoma	3	2.0	2	1.3
	C-cell carcinoma	0	–	1	0.7
Adrenal glands[g]	Cortical adenoma	8	5.3	9	6.0
	Pheochromocytoma	8	5.3	18 (20)	12.0
	Cortical adenocarcinoma	4	2.7	1	0.7
	Pheochromoblastoma	1	0.7	1	0.7
Central nervous system					
Brain	Ependimoma	1	0.7	0	–
Meninges	Meningioma	2	1.3	0	–
Major peripheral nerves	Malignant Schwannoma	1	0.7	0	–
Bones					
Cranium	Osteosarcoma	2	1.3	1	0.7
Other	Osteosarcoma	0	–	2	1.3
Soft tissues	Fibrosarcoma	0	–	1	0.7
Spleen	Fibroangioma	0	–	3	2.0
Hemolymphoreticular tissues[h]	Lymphomas and leukemias	11	7.3	13	8.7

[a] Numbers in parentheses indicate the number of tumors (one animal can bear more than one tumor).
[b] See TABLES 23, 24.
[c] See TABLE 29.
[d] See TABLE 27.
[e] See TABLE 28, 30.
[f] See TABLE 25.
[g] See TABLE 26.
[h] Including spleen.

TABLE 21. Results of Experiment 2 (BT 8T): Incidence of Total Benign Tumors

Group No.	Dose (mg/kg b.w.)	Animals		Benign Tumors			
				Animals Bearing Tumors		Tumors	
		Sex	No.	No.	%	No.	Per 100 Animals
I	3.3	F	150	66	44.0	106	70.6
II	0	F	150	108	72.7	201	134.0

TABLE 22. Results of Experiment 2 (BT 8T): Incidence of Total Malignant Tumors

Group No.	Dose (mg/kg b.w.)	Animals		Malignant Tumors			
				Animals Bearing Tumors		Tumors	
		Sex	No.	No.	%	No.	Per 100 Animals
I	3.3	F	150	40	26.7	43	28.7
II	0	F	150	38	25.3	48	32.0

TABLE 23. Results of Experiment 2 (BT 8T): Incidence of Benign Mammary Tumors

Group No.	Dose (mg/kg b.w.)	Animals		Benign Mammary Tumors			
				Animals Bearing Tumors		Tumors	
		Sex	No.	No.	%	No.	Per 100 Animals
I	3.3	F	150	42	28.0	55	36.7
II	0	F	150	68	45.3	93	62.0

TABLE 24. Results of Experiment 2 (BT 8T): Incidence of Malignant Mammary Tumors

Group No.	Dose (mg/kg b.w.)	Animals		Malignant Mammary Tumors			
				Animals Bearing Tumors		Tumors	
		Sex	No.	No.	%	No.	Per 100 Animals
I	3.3	F	150	5	3.3	5	3.3
II	0	F	150	15	10.0	17	11.3

TABLE 25. Results of Experiment 2 (BT 8T): Incidence of Pituitary Gland Tumors

Group No.	Dose (mg/kg b.w.)	Animals		Animals Bearing Pituitary Gland Adenomas	
		Sex	No.	No.	%
I	3.3	F	150	22	14.7
II	0	F	150	45	30.0

TABLE 26. Results of Experiment 2 (BT 8T): Incidence of Adrenal Gland Pheochromocytomas and Pheochromoblastomas

Group No.	Dose (mg/kg b.w.)	Animals		Pheochromocytomas				Pheochromoblastomas			
				Animals Bearing Tumors		Tumors		Animals Bearing Tumors		Tumors	
		Sex	No.	No.	%	No.	Per 100 Animals	No.	%	No.	Per 100 Animals
I	3.3	F	150	8	5.3	8	5.3	1	0.7	1	0.7
II	0	F	150	18	12.0	20	13.3	1	0.7	1	0.7

TABLE 27. Results of Experiment 2 (BT 8T): Incidence of Islet Cell Pancreatic Tumors

Group No.	Dose (mg/kg b.w.)	Animals		Animals Bearing Tumors			
				Islet Cell Adenomas		Islet Cell Adenocarcinoma	
		Sex	No.	No.	%	No.	%
I	3.3	F	150	1	0.7	0	–
II	0	F	150	6	4.0	0	–

TABLE 28. Results of Experiment 2 (BT 8T): Incidence of Polyps of the Uterus

Group No.	Dose (mg/kg b.w.)	Animals		Animals Bearing Tumors	
		Sex	No.	No.	%
I	3.3	F	150	3	2.0
II	0	F	150	13	8.7

TABLE 29. Results of Experiment 2 (BT 8T): Incidence of Tumors and Other Lesions of Oncological Interest of the Liver

Group No.	Dose (mg/kg b.w.)	Animals		Animals Bearing Liver Changes							
				Nodular Hyperplasias		Nodular Dysplasias		Hepatoadenomas		Hepatocarcinomas	
		Sex	No.	No.	%	No.	%	No.	%	No.	%
I	3.3	F	150	10	6.7	0	–	0	–	0	–
II	0	F	150	6	4.0	1	0.7	0	–	1	0.7

TABLE 30. Results of Experiment 2 (BT 8T): Incidence of Malignant Tumors of the Uterus and Vagina

Group No.	Treatment (mg/kg b.w.)	Animals		Animals Bearing Tumors											
				Uterus				Vagina				Total			
				Carcinomas		Sarcomas		Carcinomas		Sarcomas		Carcinomas		Sarcomas	
		Sex	No.	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
I	3.3	F	150	1	0.7	5	3.4	1	0.7	2	1.3	2	1.3	7	4.7
II	0	F	150	0	–	1	0.7	1	0.7	0	–	1	0.7	1	0.7

TABLE 31. Results of Experiment 2 (BT 8T): Incidence of Benign Tumors Not Including the Ones Decreased[a] by Tamoxifen Treatment

Group No.	Dose (mg/kg b.w.)	Animals		Benign Tumors			
				Animals Bearing Tumors		Tumors	
		Sex	No.	No.	%	No.	Per 100 Animals
I	3.3	F	150	16	10.7	16	10.7
II	0	F	150	23	15.3	24	16.0

[a] Decreased benign tumors: mammary tumors, pituitary gland adenomas, pheochromocytomas, islet cell pancreatic tumors, polyps of the uterus (see TABLES 23-28).

TABLE 32. Results of Experiment 2 (BT 8T): Incidence of Malignant Tumors Not Including the Ones Decreased[a] or Increased[b] by Tamoxifen Treatment

Group No.	Dose (mg/kg b.w.)	Animals		Malignant Tumors			
				Animals Bearing Tumors		Tumors	
		Sex	No.	No.	%	No.	Per 100 Animals
I	3.3	F	150	28	18.7	29	19.3
II	0	F	150	26	17.3	28	18.7

[a] Decreased malignant tumors: mammary tumors, hepatocarcinomas (see TABLES 23 and 29).
[b] Increased malignant tumors: tumors of the uterus and vagina (see TABLE 30).

TABLE 33. Results of Experiment 3 (BT 12T): Number and Percentage of Female Sprague-Dawley Rats Bearing Various Types of Benign And Malignant Tumors[a]

		Groups			
		I: 3.3 mg/kg b.w.		II: 0 (Control)	
Site	Histotype	No.	%	No.	%
Skin	Squamous cell carcinoma	0	–	1	0.7
Subcutaneous tissue	Fibrosarcoma	0	–	1	0.7
	Angiosarcoma	0	–	1	0.7
Mammary gland[b]	Fibroma and fibroadenoma	48 (65)	35.2	65 (100)	46.8
	Adenocarcinoma	2	1.4	10 (13)	7.2
	Fibrosarcoma	2	1.4	1	0.7
	Liposarcoma	0	–	1	0.7
Sebaceous gland	Adenocarcinoma	0	–	1	0.7
Zymbal glands	Squamous cell carcinoma	1	0.7	0	–
Ear ducts	Squamous cell carcinoma	3	2.1	7	5.0
Nasal cavities	Squamous cell carcinoma	1	0.7	0	–
Oral cavity	Squamous cell carcinoma	2	1.4	0	–
Larynx	Rhabdomyosarcoma	0	–	1	0.7
Lung	Adenocarcinoma	1	0.7	0	–
Liver[c]	Fibroangioma	1	0.7	0	–
	Cholangioma	0	–	1	0.7
Pancreas[d]	Islet cell adenoma	2	1.4	7	5.0
	Fibrosarcoma	1	0.7	0	–
Ovaries	Granulosa and theca cell tumors	3	2.1	1	0.7
	Adenocarcinoma	1	0.7	1	0.7
Uterus[e]	Polyp	7	5.0	14	10.1
	Fibroma	0	–	2	1.4
	Fibroangioma	1	0.7	2	1.4
	Adenocarcinoma	2	1.4	3	2.1
	Squamous cell carcinoma	3	2.1	0	–
	Sarcoma	5	3.6	6	4.3

Vagina[e]	Squamous cell carcinoma	0	–	1	0.7
Peritoneum	Fibrosarcoma	1	0.7	0	–
	Mesothelioma	0	–	1	0.7
Pituitary gland[f]	Adenoma	27	19.4	44	31.6
Thyroid gland	C-cell adenoma	0	–	1	0.7
	Follicular carcinoma	1	0.7	1	0.7
	C-cell carcinoma	2	1.4	1	0.7
Adrenal glands[g]	Cortical adenoma	7	5.0	8	5.7
	Pheochromocytoma	13 (15)	9.3	15 (16)	10.8
	Cortical adenocarcinoma	1	0.7	0	–
	Pheochromoblastoma	1	0.7	0	–
Central nervous system					
Brain	Oligodendroglioma	1	0.7	2	1.4
Meninges	Meningioma	2	1.4	0	–
Major peripheral nerves	Malignant Schwannoma	1	0.7	0	–
Bones					
Cranium	Osteosarcoma	3	2.1	2	1.4
Others	Osteosarcoma	0	–	1	0.7
Soft tissues	Fibrosarcoma	1	0.7	0	–
Spleen	Fibroangioma	0	–	3	2.1
	Angiosarcoma	0	–	1	0.7
Hemolymphoreticular tissues[h]	Lymphomas and leukemias	15	10.8	12	8.6

[a] Numbers in parentheses indicate the number of tumors (one animal can bear more than one tumor).
[b] See TABLES 36, 37.
[c] See TABLE 42.
[d] See TABLE 39.
[e] See TABLES 40, 43.
[f] See TABLE 38.
[g] See TABLE 41.
[h] Including spleen.

TABLE 34. Results of Experiment 3 (BT 12T): Incidence of Total Benign Tumors

Group No.	Dose (mg/kg b.w.)	Animals		Benign Tumors			
				Animals Bearing Tumors		Tumors	
		Sex	No.	No.	%	No.	Per 100 Animals
I	3.3	F	139	69	49.6	130	93.5
II	0	F	139	92	66.2	199	143.2

TABLE 35. Results of Experiment 3 (BT 12T): Incidence of Total Malignant Tumors

Group No.	Dose (mg/kg b.w.)	Animals		Malignant Tumors			
				Animals Bearing Tumors		Tumors	
		Sex	No.	No.	%	No.	Per 100 Animals
I	3.3	F	139	45	32.4	53	38.1
II	0	F	139	43	30.9	59	42.4

TABLE 36. Results of Experiment 3 (BT 12T): Incidence of Benign Mammary Tumors

Group No.	Dose (mg/kg b.w.)	Animals		Biophase (weeks)	Benign Mammary Tumors			
					Animals Bearing Tumors		Tumors	
		Sex	No.		No.	%	No.	Per 100 Animals
I	3.3	F	139	96[a]	21	15.1	28	20.1
				143[b]	48	35.2	65	46.8
II	0	F	139	96[a]	39	28.0	66	47.5
				143[b]	65	46.8	100	71.9

[a] End of tamoxifen treatment.
[b] Life span.

TABLE 37. Results of Experiment 3 (BT 12T): Incidence of Malignant Mammary Tumors

Group No.	Dose (mg/kg b.w.)	Animals		Biophase (weeks)	Malignant Mammary Tumors			
					Animals Bearing Tumors		Tumors	
		Sex	No.		No.	%	No.	Per 100 Animals
I	3.3	F	139	96[a]	0	–	0	–
				143[b]	4	2.8	4	2.8
II	0	F	139	96[a]	8	5.7	10	7.2
				143[b]	12	8.6	15	10.8

[a] End of tamoxifen treatment.
[b] Life span.

TABLE 38. Results of Experiment 3 (BT 12T): Incidence of Pituitary Gland Tumors

Group No.	Dose (mg/kg b.w.)	Animals		Biophase (weeks)	Animals Bearing Pituitary Gland Adenomas	
		Sex	No.		No.	%
I	3.3	F	139	143[a]	27	19.4
II	0	F	139	143[a]	44	31.6

[a] Life span.

TABLE 39. Results of Experiment 3 (BT 12T): Incidence of Islet Cell Pancreatic Tumors

Group No.	Dose (mg/kg b.w.)	Animals		Biophase (weeks)	Animals Bearing Tumors			
					Islet Cell Adenomas		Islet Cell Adenocarcinoma	
		Sex	No.		No.	%	No.	%
I	3.3	F	139	143[a]	2	1.4	0	–
II	0	F	139	143[a]	7	5.0	0	–

[a] Life span.

TABLE 40. Results of Experiment 3 (BT 12T): Incidence of Polyps of the Uterus

Group No.	Dose (mg/kg b.w.)	Animals		Biophase (weeks)	Animals Bearing Tumors	
		Sex	No.		No.	%
I	3.3	F	139	143[a]	7	5.0
II	0	F	139	143[a]	14	10.1

[a] Life span.

TABLE 41. Results of Experiment 3 (BT 12T): Incidence of Adrenal Gland Pheochromocytomas and Pheochromoblastomas

Group No.	Dose (mg/kg b.w.)	Animals		Biophase (weeks)	Pheochromocytomas				Pheochromoblastomas			
					Animals Bearing Tumors		Tumors		Animals Bearing Tumors		Tumors	
		Sex	No.		No.	%	No.	Per 100 Animals	No.	%	No.	Per 100 Animals
I	3.3	F	139	143[a]	13	9.3	15	10.8	1	0.7	1	0.7
II	0	F	139	143[a]	15	10.8	16	11.5	0	–	0	–

[a] Life span.

TABLE 42. Results of Experiment 3 (BT 12T): Incidence of Tumors and Other Lesions of Oncological Interest of the Liver

Group No.	Dose (mg/kg b.w.)	Animals		Biophase (weeks)	Animals Bearing Liver Changes							
					Nodular Hyperplasias		Nodular Dysplasias		Hepatoadenomas		Hepatocarcinomas	
		Sex	No.		No.	%	No.	%	No.	%	No.	%
I	3.3	F	139	143[a]	8	5.7	0	–	0	–	0	–
II	0	F	139	143[a]	8	5.7	0	–	0	–	0	–

[a] Life span.

TABLE 43. Results of Experiment 3 (BT 12T): Incidence of Malignant Tumors of the Uterus and Vagina

Group No.	Treatment (mg/kg b.w.)	Animals		Biophase (weeks)	Animals Bearing Tumors											
					Uterus				Vagina				Total			
					Carcinomas		Sarcomas		Carcinomas		Sarcomas		Carcinomas		Sarcomas	
		Sex	No.		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
I	3.3	F	139	143[a]	5	3.6	5	3.6	0	–	0	–	5	3.6	5	3.6
II	0	F	139	143[a]	3	1.2	6	4.3	1	0.7	0	–	4	2.9	6	4.3

[a] Life span.

TABLE 44. Results of Experiment 3 (BT 12T): Incidence of Benign Tumors Not Including the Ones Decreased[a] by Tamoxifen Treatment

Group No.	Dose (mg/kg b.w.)	Animals		Benign Tumors			
				Animals Bearing Tumors		Tumors	
		Sex	No.	No.	%	No.	Per 100 Animals
I	3.3	F	139	25	18.0	29	20.9
II	0	F	139	29	20.9	34	24.5

[a] Decreased benign tumors: mammary tumors, pituitary gland adenomas, islet cell pancreatic tumors, polyps of the uterus (see TABLES 36, 38, 39, and 40).

TABLE 45. Results of Experiment 3 (BT 12T): Incidence of Malignant Tumors Not Including the Ones Decreased[a] by Tamoxifen Treatment

Group No.	Dose (mg/kg b.w.)	Animals		Malignant Tumors			
				Animals Bearing Tumors		Tumors	
		Sex	No.	No.	%	No.	Per 100 Animals
I	3.3	F	139	40	28.8	47	33.8
II	0	F	139	36	25.9	44	31.6

[a] Decreased malignant tumors: mammary tumors (see TABLE 37).

4. when given at the dose of 3.3 mg/kg b.w., 10 times the ordinary dose in women, continuously for the life span, tamoxifen caused a slight increase in liver tumors. A borderline increase in malignancies of the uterus and vagina was also observed;
5. when the drug is given at the same dose, intermittently for the life span, an increase in uterine cancers (mainly sarcomas) was observed, but no carcinogenic effect on the liver was detected;
6. when the drug was given at the same dose, continuously but for a limited period of time, in adult female rats, no carcinogenic effect was detected; it must be pointed out that in this experiment, not only is the dose 10 times higher than the current clinical dose, but the length of treatment, with respect to the life span of the animal tested, is much longer than that considered in adjuvant therapy and in the chemoprevention of mammary cancer, with respect to the average age of women; and
7. tamoxifen increases the oncological pathology of the mammary gland in males.

On the basis of our data and of the experimental and clinical information from the scientific literature, the carcinogenic effects of tamoxifen on the liver and uterus appear to be related to the total dose. Such a dose relationship is clearly demonstrated for liver carcinogenesis in rats (TABLE 1) and, to some extent, also for uterine carcinogenesis in women: in fact, it is not by chance that the first evidence of endometrial uterine cancer was detected in the Swedish adjuvant therapy trial, in which tamoxifen was administered at the dose of 40 mg/day.

The chemopreventive effect of tamoxifen on mammary carcinoma is specifically effective in the control of breast cancer. However, even the carcinogenic side effects cannot be underestimated. As very often occurs in medical practice, the problem now is to assess whether there is a dose of the drug that is effective for chemoprevention, but that does not entail serious carcinogenic risks. There are two facts that support the expectation that such a dose may exist. Our data show that life-span treatment with tamoxifen at a dose 10 times higher than the one ordinarily employed in medical practice entails only marginal carcinogenic effects (Experiment 1), which, however, do not emerge in the experiment where the drug was given for a limited period, although still at a high dose and with continuous administration (Experiment 3). On the other hand, another series of experiments in our project (now ready for publication) have shown that 0.1 mg/kg b.w. of tamoxifen, corresponding to 6 mg daily in women, still completely inhibited the onset of spontaneous mammary cancer in our colony of rats, therefore demonstrating that doses much lower than 20 mg daily may still be effective in adjuvant therapy. The time has come to review the tamoxifen posology, in order to continue to benefit from its chemopreventive/therapeutic effect without creating risk situations.

SUMMARY

Tamoxifen was submitted to carcinogenicity bioassays on Sprague-Dawley rats (of the colony used at the Cancer Research Center in the Castle of Bentivoglio of

the European Ramazzini Foundation of Oncology and Environmental Sciences) at the dose of 3.3 mg/kg b.w., by stomach tube, in three experiments.

In the first experiment the drug was administered once daily, 6 days a week to male and female rats, 8 weeks old at start for their life span. In the second experiment, the drug was administered to female rats, 12 weeks old at start, once daily for 8 consecutive days every 8 weeks for their life span. In the third experiment the drug was administered to female rats, 56 weeks old at start, 6 times weekly for 40 weeks; and then the animals were kept alive for their life span.

In the first experiment, a mild increase in hepatocarcinomas with low grading was detected. In the first and second experiments, a borderline increase in uterine malignancies was found. No carcinogenic effect was observed in the third experiment.

In the three experiments, tamoxifen showed a strong, long-lasting chemopreventive effect on mammary benign tumors and cancers. The presented data also indicate that tamoxifen treatment reduces the incidence of other tumors: pituitary adenomas, adrenal pheochromocytomas, islet cell pancreatic tumors, Leydig cell testicular tumors, and polyps of the uterus.

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