Concentrations and Profiles of PCDDs and PCDFs in Human Mammary Carcinoma Tissue

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Introduction

Lately, there have been unreviewed claims that polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) might play a causative role in human mammary carcinomas. Further, it has been stated that PCDDs and PCDFs would accumulate in mammary carcinomas possibly exerting local immunosuppressive effects leading to promotion and tumor progression.
Factually, dioxins are generally accepted as potent tumor promotors although they seem to lack initiating mutational capacity. Dioxins are able to interfere with steroid receptors exerting antiandrogenic and antiestrogenic effects[1]. Preliminary own results indicate that dioxins in subtoxic concentrations are able to augment estrogen production in cultured throphoblastic cells[2]. Estrogens are intimately involved in the carcinogenesis of mammary carcinomas. Therefore, it was of particular clinical interest to investigate whether dioxins would in fact accumulate in mammary carcinoma tissue beyond background tissue burden.

Materials and Methods

Fresh tissue sections of axillary adipose tissue and primary mammary carcinomas not needed for histological evaluation or staging were obtained after surgical excision at the University Women's Hospital, Tübingen. Normal breast tissue was obtained from autopsy material of patients deceased from causes other than mammary carcinomas. Tissue samples were frozen at -20 °C until processed. The samples were freeze-dried and, after addition of all 2,3,7,8-substituted PCDD/F congeners as $^{13}C_{12}$-labeled standards, Soxhlet-extraction with n-heptane was performed. Following determination of the fat weight a clean-up with three or four steps was carried out. Finally, the determination of PCDDs and PCDFs was performed by HRGC/HRMS.

Results

The PCDD/PCDF concentrations (in pg/g extractable fat) of seven mammary carcinoma tissue samples and two normal breast tissue samples are shown in Table 1. Figure 1 shows the profiles of the ten homologue groups of tetra- to octachlorinated PCDDs/PCDFs found in the mammary carcinoma and the normal breast tissue samples, in human adipose tissue[3] and in mothers' milk samples from Germany[4]. The diagrams in Figure 1 are based on the means of n analytical samples. For the calculation of the arithmetic means all our analytical data were normalized to the total sum of PCDDs + PCDFs = 1000. In case of human adipose tissue and mothers' milk the arithmetic means of the single homologue groups were normalized.

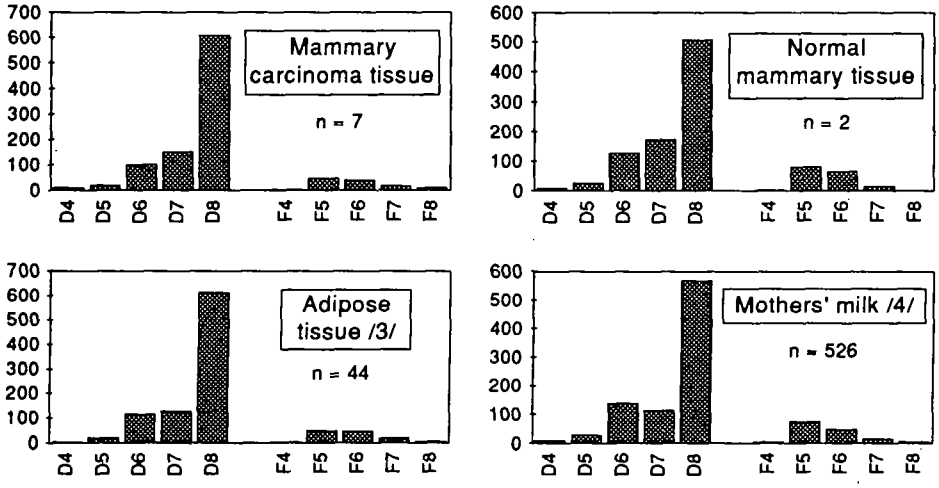

Figure 1: Comparison of the PCDD/F homologue profiles in mammary carcinoma tissue with that in normal breast tissue, adipose tissue and mothers' milk

The analytical data show the following results:

1) The PCDD/PCDF concentrations in human mammary carcinoma and normal breast tissue are very similar. The I-TEQ values seem to confirm the expected tendency towards higher concentrations with increasing age.

2) The concentrations in both tissues are in good agreement with data from human adipose tissue of 44 adults[3].

3) The homologue profiles in human carcinoma and normal mammary tissue show no significant variation. Both are consistent with those in human adipose tissue[3] and mothers' milk[4]. A comparison of the congener profiles of the 17 2,3,7,8-substituted PCDDs/PCDFs found in carcinoma and normal mammary tissue also show a good agreement with the profile found in mothers' milk[4] (data not shown).

4) The internal comparison of mammary tumor tissue with corresponding axillary adipose tissue (data not shown) reveals a mere tendency towards slightly higher

PCDD/PCDF concentrations in tumor tissue (based on extractable fat). Regarding the congener profiles no significant difference between the two groups of samples can be detected.

Discussion

The few human studies published hitherto suggest that dioxins possess a carcinogenic potential. Interestingly, one study on female workers occupationally exposed to 2,3,7,8-TCDD elicited that the "Standardized mortality ratios (SMR)" were raised for breast cancer (SRM = 2.15)[5]. On the other hand, a ten year follow-up study of the consequences of the Seveso accident revealed an increased incidence of certain forms of cancer, but liver and breast cancer mortality tended to be below expectations[6]. Other authors could demonstrate in one case that a pancreatic tumor is able to accumulate dioxins beyond the concentrations found in blood fat. However, this was a patient with a high accidental dioxin contamination[7].

Our data from women not occupationally exposed to PCDDs and PCDFs do not show any significant accumulation of PCDD or PCDF congeners or homologue groups in human mammary carcinoma tissue.

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Tissue	Mammary carcinoma tissue								Adip. tissue /3/	Normal mammary tissue	
Sample	1	2	3	4	5	6	7	Mean	n = 44	1	2
Age (years)	44	63	64	73	75	80	81	68.6	57.7	70	40
Fat content (%)	11.8	22.1	45.3	48.2	16.3	43.2	20.0	29.6		83.8	39.5
2,3,7,8-TetraCDD	5.1	11.7	10.4	6.8	6.2	8.6	6.1	7.8	3.2	3.7	3.9
1,2,3,7,8-PentaCDD	11.4	12.5	16.5	15.9	13.4	19.4	26.2	16.5	19.5	12.4	9.9
Total HexaCDDs	40.9	66.7	80.9	124	59.7	112	121	86.5	122	78.4	45.7
1,2,3,4,6,7,8-HeptaCDD	72.3	95.6	176	138	75.2	183	154	128	132	124	54.5
OctaCDD	186	390	511	936	296	1361	579	608	642	373	157
2,3,7,8-TetraCDF	1.1	(<5.4)	3.1	1.2	4.9	7.0	5.0	3.2	3.1	0.9	1.3
1,2,3,7,8-PentaCDF	(<1.6)	(<5.9)	1.6	(<1.5)	(<1.9)	4.1	3.6	1.3		0.9	0.8
2,3,4,7,8-PentaCDF	19.5	43.7	31.4	22.5	25.4	73.8	58.5	39.3	50,1*	51.4	26.9
Total HexaCDFs	16.8	37.1	33.1	27.9	23.2	52.3	43.8	33.5	48.8	58.6	14.0
1,2,3,4,6,7,8-HeptaCDF	6.1	19.3	11.9	16.7	8.4	23.8	14.4	14.4	21.4	9.5	5.9
OctaCDF	5.3	11.2	2.9	8.1	7.9	13.8	7.7	8.1	5.4	0.9	(<1.8)
I-TEQ (NATO/CCMS)	27.4	51.7	48.6	43.8	35.6	76.0	67.9	**50.1**	**57.6**	**51.1**	**29.1**

* Total of both PentaCDFs

Table 1: PCDD and PCDF concentrations in pg/g extractable fat in human mammary carcinoma and normal mammary tissue compared with those in human adipose tissue /3/