Epidemiologic investigation of breast cancer incidence in a cohort of female workers with high exposure to PCDD/F and HCH

D. Flesch-Janys[1], H. Becher[2], J. Berger[3], A. Manz[4], I. Morgenstern[4], S. Nagel[5], K. Steindorf[6]

[1]Epidemiology Working Group, Ministry of Work, Health and Social Affairs and Institute for Mathematics and Computer Science in Medicine, University Hospital Eppendorf, Hamburg, Germany, Lagerstr. 36, 20357 Hamburg
[2]Department of Tropical Hygiene and Public Health, University of Heidelberg
[3]Institute for Mathematics and Computer Science in Medicine, University Hospital Eppendorf, Hamburg, Germany
[4]Medical Center for Chemical Workers` Health, Hamburg
[5]Occupational Health Service, Hamburg
[6]Knoll AG, Ludwigshafen

Introduction

An increase in the incidence of breast cancer over the last decades was observed in many countries, though recent data from different countries including the U.S., The Netherlands and Britain indicate no further increases in the incidence and decreases in mortality since the beginning of the 90´s. This increase cannot totally be explained with changes in known risk factors and improvements in early detection by mass screening programs (Feuer et al. 1992[1]). It was hypothesized that environmental exposure to chemicals with estrogenic properties (i.e. DDT, HCH, some PCBs etc.) may have contributed to this trend (Davis et al. 1993[2]). However, several human studies conducted so far showed conflicting results (Adami et al. 1995[3]).

We earlier reported an increase in breast cancer mortality in a cohort of female workers of a pesticide producing plant in Hamburg (SMR 2.5) with high exposure to HCH and PCDD/F, however the number of observed cases (n=11) were small (Manz et al. 1991[4]). The objective of the present epidemiologic study was to confirm the finding of an increased risk in breast cancer from the mortality study by an incidence study and to analyze whether breast cancer risk varied with exposure to polychlorinated dibenzo-p-dioxins and furans (PCDD/F) and/or exposure to hexachlorocyclohexane (HCH). Additional information with respect to occupational health implications can be found in Knecht et al. (1999)[5].

Materials and Methods

The cohort consists of n=398 female workers of a former chemical plant in Hamburg (Manz et al. 1991[4]). The plant had produced different herbicides and insecticides (2,4,5-T, HCH) in the time period 1952-1984. Detailed working histories in 22 departments were extracted from company records. Incidence follow-up covered the time period 1952-1995. Female employees known to be alive in 1995 were interviewed by a mailed questionnaire. In case a woman reported that cancer had been diagnosed within the period mentioned medical records were obtained to verify the dia

gnoses. For deceased death records were used and date of diagnosis was set to date at death. Exposure to PCDD/F, especially 2,3,7,8-TCDD, and ß-HCH was assessed by blood levels in a subgroup. Production department specific dose rate estimates were derived from the analysis of all available blood levels (males and females) under the assumption of a first order elimination kinetic using half life estimates from an elimination study (Flesch-Janys et al. 1996)[6]. Using these dose rates an exposure indicator reflecting the cumulative exposure until the end of follow-up (area under the curve; in ng/kg (blood fat x years) for PCDD/F; in µg/l (blood x years for ß-HCH)) was estimated for every woman [7].

Standardized incidence ratios were calculated for all cancer sites with 2 or more observed cases using reference incidence data from the cancer registry of the Saarland for the years 1970-1992 (data were extrapolated for the interval 1960-1969 and 1993-1995). In the analysis all who did not respond to the questionnaire were treated as non-cancer cases. Overall SIR was also calculated excluding non-responders. In order to assess dose-response relationships the cohort was divided in tertiles of PCDD/F and ß-HCH exposure. In addition, time-dependent proportional hazard models (internal comparison) stratified by birth year were calculated using the lowest tertile of exposure indicator as reference. Relative risks for different combinations of TCDD/ß-HCH and TEQ/ß-HCH were calculated to separate effects.

Results

Out of n=398 females 4 were lost of follow-up. For 334 (83.4%) women cancer incidence could be assessed. A total of 61 cancer cases (57 confirmed by medical records) were identified (34 deceased, 31 alive), including 23 (11 deceased, 12 alive; all confirmed by medical records) breast cancer cases. Tab. 1 shows the standardized incidence ratios for selected cancer sites. Total cancer (excluding ICD 173) was slightly elevated, but the 95% confidence interval (CI) included one. Breast cancer showed a SIR of 1.55 (95%CI 0.98,2.32) under the assumption that all non-responder had been non-breast-cancer-cases. Excluding non-responder from the analysis yielded a SIR of 1.84 (1.17,2.67). Cancers of corpus uteri and ovary (ICD 182,183) were also elevated. The significant increase in ill defined cancer of the genital tract (ICD 184) was based on three cases, however all were self-reported and no medical documents were available.

Tab. 1 Standardized incidence ratios

Localization	ICD-9	Pers.yr.	Obs.ss.	Exp.	SIR	95%CI
All (\ICD 173)	140-208	11704	57	52.0	1.10	0.83-1.42
Digestive	150-159	12016	6	13.8	0.43	0.16-0.95
Breast	174	11910	23	14.9	1.55	0.98-2.32
Uterus	182	11983	5	3.8	1.31	0.42-3.05
Ovary	183	12016	4	2.6	1.55	0.42-3.96
Other genital	184	11963	3	0.6	5.45	1.12-15.9
Bladder	188	11996	2	1.1	1.81	0.22-6.55
Kidney	189	12016	2	1.2	1.71	0.21-6.17
Lymphohematopoietic	200-208	12016	4	2.8	1.44	0.39-3.68

* Reference data 1970-1974 were used for 1960-1969, 1991-1992 for1993-1995

Table 2 shows the descriptive parameters for PCDD/F for the subgroup of women with available blood levels. The arithmetic mean and median for both measured and back-calculated levels indicate substantial exposure of the cohort for these substances.

Table 2 Mean, median, minimum and maximum of PCDD/F blood levels (ng/kg blood lipid)

	Mean	Median	Minimum	Maximum	N
2,3,7,8-TCDD (measured levels)	71,9	13,0	2,4	1439,0	65
2,3,7,8-TCDD (end of employment, backcalculated)	506,8	125,8	2,4	6397,4	65
I-TEQ (measured levels)	123,2	53,2	19,3	1634,8	64
I-TEQ (end of employment, backcalculated)	811,2	172,8	19,3	6789,1	64

The SIRs for the tertiles of I-TEQ and ß-HCH and breast cancer are shown in table 3. TCDD (not shown), I-TEQ and ß-HCH indicators all showed a dose related effect on breast cancer incidence. For all indicators a significant increase in risk in the highest tertile was observed. The univariate Cox-regression models using the lowest tertiles of the respective exposure indicators as reference showed basically the same results (not shown). Results of the Cox regression model simultaneously including I-TEQ and ß-HCH are shown in table 4. Dose-response relationship for I-TEQ persisted after inclusion of ß-HCH, however, due to high correlation of both exposure variables the standard errors became large. SIR analysis of combinations of I-TEQ and ß-HCH dichotomized at the median showed no conclusive results either (not shown).

Table 3 Standardized Incidence Ratios for Tertiles of I-TEQ and ß-HCH

I-TEQ(ng/kg Blood fat*year)	**RR**	**95%CI**	**ß-HCH**(µg/l Blood*year)	**RR**	**95%CI**
0 – 1900.9	0.99	0.4-2.05	0 - 70.9	1.36	0.55-2.81
1901.0-2823.9	1.51	0.55-3.28	71.0 - 233.9	0.80	0.22-2.05
> 2824.0	2.56	1.23-4.71	> 234	2.53	1.31-4.42

Table 4 Cox Regression Model including I-TEQ and ß-HCH simultaneously (Relative risks)

I-TEQ(ng/kg Blood fat*year)	**RR**	**95%CI**	**ß-HCH**(µg/l Blood*year)	**RR**	**95%CI**
0 – 1900.9	1		0 - 70.9	1	
1901.0-2823.9	2.11	0.53-8.41	71.0 - 233.9	0.51	0.14-1.90
> 2824.0	2.94	0.61-14.11	> 234	1.04	0.26-4.09

Discussion

This cohort of female workers is one of those with the highest exposure to PCDD/F and ß-HCH worldwide, confirmed by measurements of blood levels in a subgroup. The data allowed for the construction of an exposure indicator to obtain an estimate of the potential dose related effect on breast cancer.
The estimated SIR are considered to be appropriately estimated using the Saarland incidence data. Comparing the incidence for Hamburg in 1991 (since incidence data are available) with the Saar-

land (1990-1993) showed incidence rates of 86.3/100000 vs. 83.4/100000 (standardized by Europe population standard) for breast cancer. In addition, the Cox-regression models without using external reference data yielded comparable dose-response results as those from SIR analysis.
There are several restrictions of this study complicating the interpretation of the findings. First, the cohort is small, thus the power of the study is low to detect small increases in risk near background levels. Second, adjustment for known risk factors for breast cancer was not possible due to the lack of complete data, however there is no strong indication that any of these factors should be strongly related to the exposure indicators. Finally, due to the high correlation of exposure to PCDD/Fs and ß-HCH the respective contributions of ß-HCH and PCDD/F to elevated breast cancer risk could not be separated.
In conclusion, breast cancer incidence was elevated within the cohort, confirming the finding of the mortality study. There is an increase of breast cancer risk in the groups with the highest estimates of PCDD/F and ß-HCH exposure, however no definite conclusions on the individual contributions to the elevated risk of these substances can be drawn. An extension of the follow up including additional determinations of blood levels is warranted.

Acknowledgement
This study was supported in part by a grant from the Hamburgische Krebsgesellschaft. We gratefully acknowledge the support of the Hamburg and Saarland cancer registry

References

1. Feuer EJ, Wun L-M. How much of the recent rise in breast cancer can be explained by increases in mammography utilization? A dynamic population model approach. *Am.J.Epidemiol.* 1992;**136**:1423-1436.
2. Davis DL, Bradlow HL, Wolff M, Woodruff T, Hoel DG, Antonculver H. Medical hypothesis - xenoestrogens as preventable causes of breast cancer. *Environ.Health.Perspect.* 1993;**101**:372-377.
3. Adami HO, Lipworth L, Titus-Ernstoff L, et al. Organochlorine compounds and estrogen-related cancers in women. *Ca.Cau.Con.* 1995;**6**:551-566.
4. Manz A, Berger J, Dwyer JH, Flesch-Janys D, Nagel S, Waltsgott H. Cancer mortality among workers in a chemical plant contaminated with dioxin. *Lancet* 1991;**338**:959-964.
5. Knecht U, Manz A, Walter D, Woitowitz H-J. Arbeitsbedingte Gefährdung durch halogenierte Dioxine und Furane - Untersuchungen zur Belastungssituation in der Arbeitswelt und zur Mortalität und Morbidität exponierter Chemiearbeiter. *Schriftenreihe derBundesanstalt für Arbeitsschutz (in press)* 1999.
6. Flesch-Janys D, Becher H, Gurn P, et al. Elimination of polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/F) in occupationally exposed persons. *J.Toxicol.Environ.Health.* 1996;**47**:363-378.
7. Flesch-Janys D, Steindorf K, Gurn P, Becher H. Estimation of cumulative exposure to polychlorinated dibenzo-p-dioxins/furans occupationally exposed cohort and standardized mortality ratio analysis of cancer mortality by dose in an occupationally exposed cohort. *Environ.Health.Perspect.* 1998;**106**:655-662.