Serum Dioxin Concentrations and Breast Cancer Risk in the Seveso Women's Health Study

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2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD or dioxin), a widespread environmental contaminant, has been shown to disrupt multiple endocrine pathways. The International Agency for Research on Cancer classified TCDD as a known human carcinogen, primarily based on occupational studies of increased mortality from all cancers combined. Using data from the Seveso Women's Health Study (SWHS), we examined the association between individual serum TCDD levels and breast cancer risk in women residing around Seveso, Italy, in 1976, at the time of an industrial explosion that resulted in the highest known population exposure to TCDD. The SWHS cohort comprises 981 women who were infants to 40 years old in 1976, resided in the most contaminated areas at the time of the explosion, and had archived sera that was collected soon after the explosion. For each woman, serum TCDD exposure was measured by high-resolution mass spectrometry. Cancer cases were identified during interview and confirmed by medical record. At interview, 15 women (1.5%) had been diagnosed with breast cancer and serum TCDD levels for cases ranged from 13 to 1,960 ppt. Cox proportional hazards modeling showed that the hazard ratio for breast cancer associated with a 10-fold increase in serum TCDD levels ($\log_{10}$ TCDD) was significantly increased to 2.1 (95% confidence interval, 1.0–4.6). Covariate-adjusted results were not different. Individual serum TCDD is significantly related with breast cancer incidence among women in the SWHS cohort. Continued follow-up of the cohort will help shed light on the possible role of TCDD in the pathogenesis of breast cancer. *Key words:* breast neoplasms, dioxin, epidemiology, tetrachlorodibenzo-*p*-dioxin. *Environ Health Perspect* 110:625–628 (2002). [Online 15 May 2002]

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The compound 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD or dioxin) is the most toxic member of a class of planar, halogenated aromatic hydrocarbons (*1,2*). TCDD is a widespread environmental contaminant produced by various chemical reactions and combustion processes (*3*). It is highly lipophilic and extremely stable and thus accumulates in the food chain (*2*). TCDD has a half-life of 7–9 years in humans (*4*). In animals, TCDD is a potent carcinogen and has been shown to disrupt multiple endocrine pathways (*1,2,5*). The International Agency for Research on Cancer has classified TCDD as a known human carcinogen, primarily on the basis of occupational studies of increased mortality from all cancers combined, but no particular cancer sites were predominant (*5*).

The few epidemiologic studies that have examined the relationship between TCDD exposure and breast cancer risk are limited by small sample size and lack of individual exposure data. Breast cancer mortality (*6,7*) and incidence (*8*) increased in female workers employed in the production of TCDD-contaminated phenoxyherbicides. Significantly increased mortality from breast cancer was reported in a Russian town with a chemical plant known to be a source of TCDD (*9*). However, a hospital-based breast cancer case–control study found no difference in breast tissue concentration of TCDD between women with breast cancer and women with benign breast disease, but the level of exposure was low (1.0–7.9 ppt, lipid-adjusted) (*10*).

On 10 July 1976, an explosion at a trichlorophenol manufacturing plant near Seveso, Italy, resulted in the highest TCDD levels known in human residential populations (*11*). Up to 30 kg of TCDD were deposited over the surrounding area (~18 km^2) (*12*), which was divided into exposure zones (A, B, R, non-ABR) based on TCDD measurements in soil. Ten- and 15-year follow-up studies of the Seveso population found no increased risk for breast cancer incidence (*13,14*) or mortality (*15–17*). However, after 20 years of follow-up, a statistically nonsignificant increased risk for breast cancer mortality emerged among women who resided in zones A or B, the most heavily contaminated areas, and who were younger than 55 years at death [relative risk (RR) = 1.2, 95% confidence interval (CI), 0.6–2.2], but not in those who were older (*18*). Exposure estimates were based on zone of residence, so the study lacked individual-level exposure data. Furthermore, recent analyses of individual serum TCDD measurements for 601 Seveso women suggest a wide range of individual TCDD exposure within zones (*19*).

Using data from the Seveso Women's Health Study (SWHS) (*20*), a historical cohort study of the female population residing around Seveso at the time of the explosion in 1976, we examined the association between breast cancer risk and individual-level TCDD exposure, measured in archived serum collected soon after the explosion (*21*).

Materials and Methods

Study population. Women eligible for the SWHS were infants to 40 years old in 1976, had resided in one of the most highly contaminated zones, A or B, and had adequate stored sera collected soon after the explosion (*20*). Enrollment began in March 1996 and was completed in July 1998. Of 1,271 eligible women, 17 (1.3%) could not be located or contacted, 21 (1.6%) had died, and 12 (1%) were too ill to participate. Of the 96.1% of eligible women who could be contacted, 981 (80%) participated.

Procedure. Details of the study procedure are presented elsewhere (*20*). Briefly, participation included obtaining informed consent, drawing blood, and conducting personal interviews and, for a subset of women, a gynecologic examination and transvaginal ultrasound. The interview was conducted by a trained nurse-interviewer who was blinded to serum TCDD levels and zone of residence. At interview each woman

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was asked if she had ever been diagnosed with cancer. If she said yes, medical records were obtained and were reviewed by a cancer pathologist who was blinded to the woman's exposure. This study was approved by the Institutional Review Boards of the participating institutions.

Laboratory analyses. For each participant, we selected the first serum sample collected between 1976 and 1981 of adequate volume (> 0.5 mL) for analysis. We measured the TCDD concentration in these samples, which had been stored at –20°C at Desio Hospital, by high-resolution mass spectrometry (*22*). Values were reported on a lipid-weight basis in parts per trillion (*23*). We measured TCDD in sera collected in 1976 or 1977 for 899 women (92%), from 1978 through 1981 for 54 women (5%), and in 1996 or 1997 for 28 women (3%) whose earlier samples had become concentrated by dessication.

For four women whose post-1977 TCDD values were detectable but ≤ 10 ppt, the measured value was used. For 42 women whose post-1977 TCDD levels were > 10 ppt and who were more than 16 years old in 1976, the serum TCDD level was back-extrapolated to 1976 using the first-order kinetic model, assuming a 9-year half-life (*4*). For 27 women whose post-1977 TCDD levels were > 10 ppt, and who were 16 years old or younger in 1976, the Filser toxicokinetic model was used for back-extrapolation (*24*). For the 96 women with nondetectable values, a serum TCDD level equal to one-half the detection limit was assigned (*25*). For the lipid-adjusted study median serum sample weight of 0.65 g, the median limit of detection was 18.8 ppt.

Statistical analyses. We analyzed serum TCDD both as a continuous ($\log_{10}$ TCDD) and as a categorical variable. Serum TCDD was categorized as < 20.0 ppt, 20.1–44 ppt, 44.1–100 ppt, and > 100 ppt. The lowest cut point was set at 20 ppt (body burden ~4 ng/kg) because the median value was between 15 and 20 ppt for 11 pooled serum samples collected from women residing in an unexposed zone, non-ABR, at the time of the explosion (*26*). The highest cut point was set at 100 ppt (body burden ~20 ng/kg) because previous studies in Seveso reported an effect of TCDD at about this level (*27,28*). The middle cutpoint was set at 44 ppt (body burden ~8.8 ng/kg) to make the middle groups comparable in size.

Statistical analyses were performed using STATA 7.0 (*29*). We used Cox proportional hazards modeling for the main analysis. The response variable was age at breast cancer diagnosis or age at interview for non-cases, and each subject entered the analysis at her age on the explosion date, 10 July 1976. We report the measure of effect as the hazard ratio (HR) and 95% CI. We examined the effect of potential confounders and effect modifiers identified in the breast cancer literature (*30,31*). Confounders included gravidity, parity, age at first pregnancy, age at last pregnancy, lactation, family history of breast cancer, age at menarche, current body mass index, oral contraceptive use, menarcheal status at explosion, menopause status at diagnosis, weight, height, smoking, and alcohol consumption. Because of the small number of cases, these variables were entered into the models one at a time.

Results

Table 1 presents the distribution of selected characteristics of the SWHS cohort at the time of interview (1996–1998). On 10 July 1976, 232 women (24%) were younger than 10 years old, and 283 (29%) were premenarcheal. The average age of the cohort at interview was 40.8 (SD = 11.7) years, and 264 women (27%) were nulliparous. The mean age at first pregnancy for the 717 parous women was 24.2 years, and 626 (87%) had ever lactated. Seventy-five women (8%) reported a family history of breast cancer.

A total of 21 women (2.1%) in the SWHS cohort reported that they had been diagnosed with cancer. Fifteen women (1.5%) had been diagnosed with breast cancer

Table 1. Characteristics of breast cancer cases (*n* = 15) and full SWHS cohort (*n* = 981), Italy, 1996–1998.

Characteristic	No. cases	No. full cohort (%)
Age at explosion (years)		
0–10	0	232 (23.6)
11–20	2	279 (28.4)
21–30	3	241 (24.6)
31–40	10	229 (23.3)
Menarche status at explosion[a]		
Premenarche	1	283 (28.8)
Postmenarche	14	697 (71.0)
Age at interview (years)		
20–29	0	191 (19.5)
30–39	2	284 (29.0)
40–49	2	244 (24.9)
≥ 50	11	262 (26.7)
Parity		
0	3	264 (26.9)
1–2	8	551 (56.2)
≥ 3	4	166 (16.9)
Age at first full-term pregnancy (years)		
< 20	1	117 (11.9)
20–25	4	357 (36.4)
> 25	7	243 (24.8)
Nulliparous	3	264 (26.9)
Lactation		
Never	2	91 (12.7)
Ever	10	626 (87.3)
Family history of breast cancer[a]		
No	13	900 (91.8)
Yes	2	75 (7.6)
Oral contraceptive use		
Never	9	456 (46.5)
Former	6	377 (38.4)
Current	0	148 (15.1)
Cigarette smoking		
Never	10	638 (65.0)
Former	4	141 (14.4)
Current	1	202 (20.6)

[a]Numbers do not add to 100% because of missing data.

Table 2. Characteristics of breast cancer cases, SWHS, Italy.

Breast cancer cases	Serum TCDD (ppt)	Age at exposure (years)	Age at diagnosis (years)	Years from exposure to diagnosis[a]	Pathologic confirmation	Menopausal at diagnosis	Estrogen receptor status	Progesterone receptor status
1	13.1	31	52	21	Yes	No	+	+
2	27.2	23	34	11	Yes	No		
3	40.1	35	48	13	Yes	Yes		
4	47.3	30	41	11	Yes	No		
5	49.4	34	51	18	Yes	No	–	+
6	55.8	38	46	8	Yes	No	+	+
7	57.2	36	48	12	No	Yes	+	+
8	71.8	14	33	19	Yes	No	+	+
9	83.6	36	57	20	Yes	Yes		
10	85.2	39	49	11	Yes	No		
11	191.0	21	41	20	Yes	No	+	+
12	200.0	37	57	20	No	Yes		
13	220.0	14	31	18	Yes	No	+	+
14	1160.0	32	42	9	Yes	Yes		
15	1960.0	31	48	17	Yes	Yes		

[a]Rounded to nearest year.

[*International Classification of Diseases, 9th Revision* (ICD-9), 174.8, 174.9] (*32*). Other diagnosed cancers and their respective individual serum TCDD levels included thyroid (n = 3; ICD-9, 193.8, 193.9; serum TCDD levels: 6.6, 106.0, 476.0 ppt); kidney (ICD-9, 172.9; serum TCDD level: 30.0 ppt); melanoma (ICD-9, 189.9; serum TCDD level: 20.6 ppt); and nonspecified (ICD-9, 195.5; serum TCDD level: 174.0 ppt). Because of the small numbers of cases, we only examined the relation of serum TCDD levels to breast cancer and all cancers combined.

Table 2 presents selected characteristics of the 15 breast cancer cases. Of the 15 cases, 13 (87%) were confirmed by pathology; the other two (13%) were confirmed by surgery report alone. The serum TCDD levels of women with breast cancer ranged from 13.1 to 1,960.0 ppt (median = 71.8 ppt). The average age of women with breast cancer on the explosion date was 30.1 years, with a range of 14–39 years. The average age at diagnosis was 45.2 years, with a range of 31–57 years. Breast cancer was diagnosed, on average, 15.2 years after the explosion, with the shortest period being 8 years. At diagnosis, nine (60%) women were premenopausal and six (40%) were postmenopausal. For the seven women for whom receptor status of tumors was available, six (87%) were estrogen-receptor positive and seven (100%) were progesterone-receptor positive.

The cumulative distribution of serum TCDD levels is presented in Figure 1 for all women in the cohort and for only women with breast cancer. The median serum TCDD level for women with breast cancer (median = 71.8 ppt, interquartile range 47.3–200.0) was greater than for women without breast cancer (median = 55.1 ppt, interquartile range 27.8–153.0). Although the total number of cases is small, the TCDD levels for women with breast cancer appear to be shifted to the right at the low end of the cumulative distribution. At the high end of the distribution the shift is not apparent.

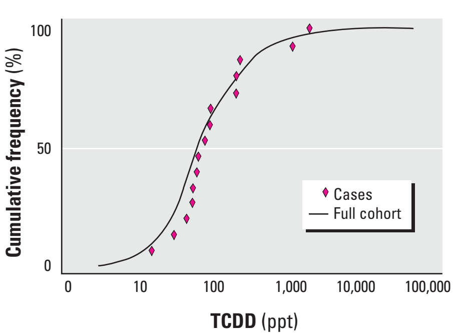

Figure 1. Cumulative distribution of 1976 serum TCDD levels for breast cancer cases (n = 15) versus full cohort (n = 981), SWHS, Italy.

In single-covariate Cox models, breast cancer risk was positively associated with younger age of menarche, lower gravidity, lower parity, never lactating, older age at first pregnancy, and family history of breast cancer. There was no association of breast cancer risk with age at explosion or menarche status (pre- or post-) on the date of the explosion (data not shown).

Table 3 presents the results of Cox proportional hazards modeling for the association between lipid-adjusted serum TCDD level and breast cancer risk. When TCDD was included as a continuous variable ($\log_{10}$ TCDD), the HR was significantly increased to 2.1 (95% CI, 1.0–4.6). That is, for a 10-fold increase in TCDD (e.g., from 10 to 100 ppt), a doubling of the hazard rate is predicted. The test for trend with continuous $\log_{10}$ TCDD was significant (p = 0.05). After adjusting for single covariates, no single variable was found to confound (i.e., change the TCDD parameter estimate by more than 10%) or to modify the TCDD–breast cancer association (data not shown). If the two cases that were diagnosed by surgery report alone were excluded from the analysis, the result was similar (HR = 2.1, 95% CI, 0.9–4.8).

When TCDD was considered as a categorical variable, there was some evidence of a dose–response trend, but it was not statistically significant (χ^2 = 3.3, df = 1, p = 0.07). Compared to the lowest exposure group (< 20 ppt), the HR (95% CI) for the three dose groups, 20.1–44 ppt, 44.1–100 ppt, and > 100 ppt, were 1.0 (0.1–10.8), 4.5 (0.6–36.8), and 3.3 (0.4–28.0), respectively. After adjustment for single covariates, including parity, the results were unchanged.

We also conducted Cox proportional hazards modeling for the association between serum TCDD level and risk for all cancers. The HR (95% CI) for all cancers associated with a 10-fold increase in exposure ($\log_{10}$ TCDD) was 1.7 (0.9–3.4). When TCDD was categorized, there was some evidence of a dose response, but it was not statistically significant (χ^2 = 2.9, df = 1, p = 0.09). Compared to the lowest exposure group (< 20 ppt), the HR (95% CI) for the three higher dose groups, 20.1–44 ppt, 44.1–100 ppt, and > 100 ppt, were 1.0 (0.2–5.5), 2.2 (0.5–10.8), and 2.5 (0.5–11.8), respectively.

Discussion

We observed a statistically significant, dose response–increased risk for breast cancer incidence with individual serum TCDD level among women in the Seveso Women's Health Study. We found more than a 2-fold increase in the hazard rate associated with a 10-fold increase in serum TCDD. This result should be considered an early finding because the SWHS cohort is relatively young, with an average age at interview of 40.8 years. Breast cancer incidence increases steadily with age, with the most rapid increase between ages 40 and 55 years (*30*). Moreover, the youngest women in the SWHS cohort were, in general, the most highly exposed (*19*). Of women who were 20–30 years of age at interview, 68% had serum TCDD levels > 100 ppt. Many of these women may not have had sufficient time for the effects of TCDD, if any, to become clinically manifest. Thus, it will be important to continue to follow the SWHS cohort.

The major limitation of our study is the small number of breast cancer cases. However, previous studies of occupational cohorts of TCDD-exposed women have had similar numbers, ranging from 9 to 23 cases, and have reported similar levels of risk (RR ~1.8–2.8) (*6–8*). These studies classified exposure based on job history, company production records, and, for a subset of workers, TCDD in serum or adipose measured many years after last exposure.

The results of the SWHS are consistent with those from the 20-year mortality study of the larger Seveso population, which reported a nonsignificant increased risk for mortality from breast cancer among women who were 54 years old or younger at death (*18*). However, the observations of the mortality study and SWHS are likely independent. The SWHS cohort included women who were infants to 40 years old in 1976, while the larger Seveso cohort included women who were 20–74 years old. In addition, we included incident cases diagnosed between 1976 and 1997, but not deaths (*18*). Of the 33 women who did not participate in the SWHS because they were dead or too ill, three had had breast cancer (deceased).

Table 3. Results of Cox proportional hazards model for association between lipid-adjusted serum TCDD levels and female breast cancer risk, SWHS, Italy.

Exposure	Cases/total	Crude hazard ratio (95% CI)	*p*-Value
$\log_{10}$ TCDD[a] (ppt)	15/981	2.1 (1.0–4.6)	0.05
TCDD (ppt)			
< 20	1/156	1.0	
20.1–44	2/241	1.0 (0.1–10.8)	
44.1–100	7/249	4.5 (0.6–36.8)	
> 100	5/335	3.3 (0.4–28.0)	0.07[b]

[a]Hazard ratio for 10-fold increase in serum TCDD concentration. [b]Test for trend.

The results of the SWHS are not consistent with the most recent cancer incidence study of the larger Seveso population (*13*). However, follow-up for that study was only through 1986, and most breast cancer cases in SWHS were diagnosed since then (13 of 15 cases). Using age-specific breast cancer rates for the region (1988–1992) (*33*), the expected number of cases is 11, whereas we report 15; the overall standardized incidence ratio for the 981 women is 1.36.

An advantage of the SWHS is that we were able to examine the relationship between serum TCDD concentration and breast cancer incidence, thus eliminating potential bias associated with disease survival. In addition, we were able to collect information during the interview, allowing consideration of potential confounding by known risk factors in the analysis. Finally, we were able to measure individual serum TCDD concentrations near the time of exposure, thus minimizing exposure misclassification.

In both animal and human studies, TCDD has been shown to be a multisite carcinogen (*5*). TCDD has been shown to induce antiestrogenic responses in rodent uterus and human breast cancer cells in culture (*34,35*). However, the finding of a significant positive association between TCDD exposure and breast cancer risk is supported by recent animal studies (*36–39*). These studies suggest that TCDD can modulate the risk of mammary cancer in different ways depending on the developmental stage at exposure. Postnatal TCDD exposure in female rats has been shown to suppress mammary gland development (*36*) and to inhibit progression of chemically induced mammary carcinoma (*37*). *In utero* and lactational TCDD exposure, however, has been shown to alter mammary gland differentiation by increasing the number of terminal end buds (*38,39*) and rendering the animals more susceptible to chemically induced carcinogenesis (*38*). It is not known whether prenatal or postnatal TCDD exposure differentially alters mammary gland differentiation in humans (*38,39*). The animal findings, however, suggest that we may not yet have observed the effect of TCDD on the most sensitive individuals in SWHS, those who were exposed *in utero* or before menarche at the time of the explosion.

In summary, we have shown that individual serum TCDD measurements are significantly related to breast cancer incidence among women in the SWHS cohort. This result should be considered an early finding because the number of cases is small and the cohort is relatively young. Continued follow-up of the SWHS cohort will help shed light on the possible role of TCDD in the pathogenesis of breast cancer.

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