Prenatal Diethylstilbestrol Exposure and Risk of Breast Cancer

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Abstract

It has been hypothesized that breast cancer risk is influenced by prenatal hormone levels. Diethylstilbestrol (DES), a synthetic estrogen, was widely used by pregnant women in the 1950s and 1960s. Women who took the drug have an increased risk of breast cancer, but whether risk is also increased in the daughters who were exposed *in utero* is less clear. We assessed the relation of prenatal DES exposure to risk of breast cancer in a cohort of DES-exposed and unexposed women followed since the 1970s by mailed questionnaires. Eighty percent of both exposed and unexposed women completed the most recent questionnaire. Self-reports of breast cancer were confirmed by pathology reports. Cox proportional hazards regression was used to compute incidence rate ratios (IRR) for prenatal DES exposure relative to no exposure. During follow-up, 102 incident cases of invasive breast cancer occurred, with 76 among DES-exposed women (98,591 person-years) and 26 among unexposed women (35,046 person-years). The overall age-adjusted IRR was 1.40 [95% confidence interval (95% CI), 0.89-2.22]. For breast cancer occurring at ages ≥40 years, the IRR was 1.91 (95% CI, 1.09-3.33) and for cancers occurring at ages ≥50 years, it was 3.00 (95% CI, 1.01-8.98). Control for calendar year, parity, age at first birth, and other factors did not alter the results. These results, from the first prospective study on the subject, suggest that women with prenatal exposure to DES have an increased risk of breast cancer after age 40 years. The findings support the hypothesis that prenatal hormone levels influence breast cancer risk. (Cancer Epidemiol Biomarkers Prev 2006;15(8):1509–14)

Introduction

Trichopoulos and Lipman (1) and Trichopoulos et al. (2) have hypothesized that *in utero* exposure to high levels of estrogens increases future risk of breast cancer by increasing the number of breast stem cells at birth and, therefore, the number at risk of malignant transformation. Epidemiologists have used factors such as birthweight (3-10), maternal preeclampsia (7, 8, 11), and twin pregnancy (4, 8, 12), which might be related to prenatal hormone levels, as surrogate exposure measures to assess the hypothesis. The results to date are inconclusive (13).

Diethylstilbestrol (DES) is an orally active synthetic estrogen that was first synthesized in 1938 and frequently prescribed to pregnant women in the 1940s to 1960s (14). Early studies suggested that the drug might prevent spontaneous abortion (15), but later, better-controlled studies showed no benefit (16). Although no definitive data are available, reports using pharmacy records and complete review of sets of prenatal records suggest that at least 1 million and probably as many as 2 million women were exposed to the drug before birth (17).

In 1971, *in utero* exposure was found to be associated with a greatly increased risk of clear cell carcinoma of the vagina and cervix (18). Subsequently, DES use was found to be associated with an increased risk of breast cancer in women who took the drug (19, 20), raising concerns about the possibility of an increased risk of breast cancer in daughters who were exposed *in utero*.

The DES tragedy offers a rare opportunity for a direct assessment of the hypothesis that prenatal exposure to high levels of estrogens increases future breast cancer risk. Simultaneously, such an investigation may provide important information on risk for those 1 to 2 million women who were exposed to DES. We previously reported that follow-up of a DES cohort showed little or no association between exposure and breast cancer risk overall (21). However, a statistically significant 2.5-fold risk was observed among women ages ≥40 years (21). At that time, most of the cohort was still young and the results were based on only 27 exposed and 7 unexposed cases occurring at ages ≥40 years. With an additional 4 to 5 years of follow-up, the total number of cases ages ≥40 years has more than doubled, allowing for a more definitive analysis.

Materials and Methods

Study Participants. In 1992, an effort was made to assemble all extant U.S. cohorts of DES-exposed persons that had an appropriate comparison group of unexposed persons and had medical record documentation of exposure or nonexposure (19, 22, 23). As previously described (24), the existing cohorts of daughters identified were from (*a*) the National Cooperative Diethylstilbestrol Adenosis Project (DESAD; ref. 22), (*b*) a randomized clinical trial of DES carried out at the University of Chicago in 1951-1952 (Dieckmann; ref. 23), and (*c*) a large private infertility practice in Massachusetts (Horne). In

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addition, female offspring of women who had participated in a study of health effects in mothers (Women's Health Study; ref. 19) were identified in 1994 through review of written information that had been abstracted from the mothers' prenatal records in the 1970s and were invited to participate in the current study. Review of the mother's prenatal record provided documentation of exposure for all exposed participants.

The unexposed cohort for the current study comprised unexposed women from the same four cohorts that provided the exposed subjects. In the DESAD study, unexposed subjects were either sisters of exposed participants (24%) or nonrelatives identified from the same record sources as the exposed (76%), most of whom were matched to the exposed on year of birth and mother's age at delivery. Dieckmann study unexposed subjects were the daughters of trial participants who were randomized to receive a placebo rather than DES. Horne cohort unexposed were those daughters who had no record of exposure (in prenatal records) and who were also identified as unexposed in interviews with their mothers. Women's Health Study unexposed daughters were identified through review of the prenatal and obstetric records of participants in the Women's Health Study.

As shown in Table 1, of the 7,439 daughters originally identified for inclusion in any of the four original cohorts, 549 were ineligible for the National Cancer Institute DES follow-up study for the following reasons: never located (n = 210), missing date of birth (n = 36), deceased before 1978 (n = 26), lost or refused before 1978 (n = 260), or cancer before entry in the study (n = 17). Therefore, a total of 4,817 exposed and 2,073 unexposed daughters comprised the cohort included in the National Cancer Institute study.

Follow-up. The start of follow-up was January 1, 1978 for all participants except those who were first enrolled in 1994/1995, for whom January 1, 1995 was taken as start of follow-up. Follow-up questionnaires were sent to participants in 1994, 1997, and 2001. The baseline questionnaire (1994) ascertained lifetime reproductive history, use of female hormones, cigarette smoking, alcohol intake, and body size; subsequent questionnaires updated information on reproductive and hormonal factors. Each questionnaire asked about occurrence of cancer and frequency of mammographic screening. The close of follow-up for the most recent questionnaire was June 2003, and that questionnaire was completed by 3,812 exposed daughters (80% of those still alive in 2001) and 1,637 unexposed daughters (also 80% of those still alive in 2001). A comparison of those who were and were not lost to follow-up since 1994 revealed no material differences with regard to breast cancer risk factors in both exposed and unexposed women (data not shown). Fifty-nine exposed and 18 unexposed women died during follow-up. The median age at start of follow-up was 24 years for exposed and 26 years for unexposed women, and the median number of years followed was 24 for exposed and 22 for unexposed. The majority of participants were from the DESAD study (68%), with 11% from the Dieckmann trial, 7% from the Horne cohort, and 14% from the Women's Health Study.

Table 1. Participation in National Cancer Institute DES follow-up study

	DES exposed	Unexposed
No. identified for the original cohorts	5,067	2,372
Ineligible for National Cancer Institute study		
Missing date of birth	21	15
Never located	56	154
Deceased before 1978	11	15
Lost or refused before 1978	154	106
Cancer before start of follow-up	8	9
Total eligible for National Cancer Institute study	4,817	2,073
Died during follow-up	59	18
Responded to 1994 questionnaire	3,932 (82%)	1,735 (84%)
Responded to 1997 questionnaire	3,946 (82%)	1,722 (83%)
Responded to 2001 questionnaire*	3,812 (80%)	1,637 (80%)

*Proportion of eligible subjects still alive in 2001.

Table 2. Characteristics of study participants at baseline in 1994 by prenatal DES exposure

Characteristic	Exposed (N = 4,817)	Unexposed (N = 2,073)
	N (%)	N (%)
Study cohort		
DESAD	3,914 (81)	1,004 (49)
Dieckmann	354 (7)	319 (15)
New Kids	264 (6)	542 (26)
Horne	285 (6)	208 (10)
Year of birth		
<1950	745 (15)	479 (23)
1950-1954	2,067 (43)	896 (43)
1955-1959	1,212 (25)	478 (23)
≥1960	793 (16)	220 (11)
Race		
White	4,593 (98)	1,899 (97)
Nonwhite	95 (2)	54 (3)
Marital status		
Ever married or living as married	3,720 (89)	1,594 (89)
Never married	448 (11)	204 (11)
Years of education		
≤12	548 (14)	370 (21)
13-15	912 (23)	441 (25)
16	1,423 (36)	552 (31)
≥17	1,098 (27)	408 (23)
Ever smoked		
Yes	1,899 (45)	946 (51)
No	2,334 (55)	898 (49)
Mother smoked during pregnancy		
Yes	1,457 (36)	421 (35)
No	2,344 (58)	603 (51)
Don't know	268 (6)	167 (14)
Ever used oral contraceptives		
Yes	3,573 (76)	1,557 (79)
No	1,128 (24)	413 (21)
Ever used menopausal hormones		
Yes	343 (19)	193 (11)
No	3,649 (91)	1,585 (89)
Birthweight, g		
<3,000	1,748 (39)	447 (26)
3,000-3,499	1,677 (37)	701 (41)
3,500+	1,046 (23)	543 (32)
Body mass index, kg/m^2		
<20	625 (16)	275 (16)
20-24	2,088 (53)	893 (51)
25-29	754 (19)	374 (21)
30+	479 (12)	210 (12)
Age at menarche, y		
<12	744 (16)	330 (17)
12-13	2,848 (61)	1,155 (59)
14+	1,108 (24)	485 (25)
Parity		
0	1,560 (36)	497 (26)
1	831 (19)	303 (16)
2	1,313 (30)	674 (36)
3+	648 (15)	408 (22)
Age at first birth (among parous), y		
<25	862 (31)	581 (42)
25-29	1,019 (36)	442 (32)
30-34	656 (23)	257 (19)
35+	254 (9)	105 (8)
No. mammograms in previous 5-y period		
0	1,198 (30)	458 (26)
1	1,116 (28)	479 (27)
2 or 3	1,170 (30)	554 (32)
≥4	441 (11)	257 (15)

NOTE: Missing values for each covariate are excluded.

Table 3. Prenatal DES exposure in relation to risk of invasive breast cancer

	Exposed		Unexposed		Age-adjusted IRR* (95% CI)	Multivariable IRR† (95% CI)
	Person-years of follow-up	Cases	Person-years of follow-up	Cases		
Entire cohort	98,591	76	35,046	26	1.40 (0.89-2.22)	1.40 (0.86-2.29)
Age <40 y	69,243	16	21,988	9	0.61 (0.27-1.38)	0.57 (0.24-1.34)
Age ≥40 y	29,348	60	13,058	17	1.91 (1.09-3.33)	2.05 (1.12-3.76)
Age 40-49 y	26,433	46	10,843	12	1.60 (0.85-3.02)	1.62 (0.83-3.18)
Age ≥50 y	2,915	14	2,215	5	3.00 (1.01-8.98)	3.85 (1.06-14.0)

*IRR for breast cancer incidence in exposed women relative to unexposed.
†Adjusted for age, years of education, number of births, age at 1st birth, age at menarche, use of female hormone supplements, use of oral contraceptives, family history of breast cancer, birthweight, and cohort.

Incident cases of breast cancer were identified through self-reports on the study questionnaires. Searches of the National Death Index identified breast cancer in participants who had died or been lost to follow-up. Pathology reports, death certificates, or cause of death from National Death Index Plus were obtained for all but 10 of the reported cases of breast cancer. Review of these records confirmed the diagnosis of breast cancer in all but one instance, and that woman was excluded. Because the confirmation rate was high, participants whose records could not be obtained were included as cases. In total, there were 102 cases of incident invasive breast cancer. Data on exact date of diagnosis, histologic type, tumor size and spread, and estrogen and progesterone receptor status were abstracted from the pathology reports, which had been obtained for 87% of cases.

Approvals for the study were obtained from the human investigation committees at the five field centers and the National Cancer Institute. Participants indicated their informed consent by filling out and returning questionnaires or taking part in a telephone interview. Signed medical record releases were obtained for review of medical records.

Statistical Analysis. Person-years at risk were computed from the start of follow-up until the earliest of the following: date of breast cancer diagnosis, date of response to the most recent questionnaire, date of death, or date of last known follow-up. Cox proportional hazards regression (25) was used to compute incidence rate ratios (IRR), with stratification on individual year of age. Parity, age at first birth, age at menarche, age at menopause, family history of breast cancer, use of oral contraceptives, use of female hormone supplements, calendar year at risk, years of education, cigarette smoking, birthweight, and body mass index were considered as potential confounders by examining models that controlled for age and each other variable separately and a model that included terms for all potential confounders. Parity, age at first birth, age at menopause, use of oral contraceptives, and use of female hormone supplements were treated as time-dependent covariates. None of the factors except age changed the IRRs by >10%. We estimated IRRs for the association of prenatal DES exposure with risk of invasive breast cancer overall, within age strata, and within strata of breast cancer risk factors. To examine whether the association between DES exposure and breast cancer was modified by other covariates (e.g., age, use of female hormones), we conducted likelihood ratio tests that compared models with and without cross-product terms between exposure and these covariates. Departure from the proportional hazards assumption was tested by the likelihood ratio test comparing models with and without cross-product terms between exposure and age (<40 versus 40+ years).

Data on gestational week of first use of DES were available for 75% of exposed women, permitting an analysis of timing of first use in relation to breast cancer risk. Cumulative dose of DES exposure was available for only 38% of exposed daughters. The study cohorts included women from several regions of the United States with varying DES prescribing practices. We characterized the various exposed cohorts as ''high-dose'' or ''low-dose'' based on knowledge about regional practices. Women from the University of Chicago randomized trial, from the Boston cohorts, and from the California cohort of the DESAD project were grouped together as a high-dose cohort. Among participants with complete information on cumulative dose, the median doses were 12,442, 8,675, and 7,550 mg for the Chicago, Boston, and California cohorts, respectively. Women from the Texas, Minnesota, and Wisconsin cohorts of the DESAD project were grouped together as a low-dose cohort. Among those whose cumulative dose was known, the median doses were 2,572, 1,520, and 3,175 mg for the Texas, Minnesota, and Wisconsin cohorts, respectively. Thus, the available dose data supported our classification of cohorts. Women's Health Study daughters who were not from Boston were excluded from this analysis due to a lack of information on usual DES prescribing practices for other regions.

Risk among the exposed was also compared with that of the general population. Expected numbers of cancers and standardized incidence ratios were calculated for the exposed cohort using cancer incidence rates for white women from the Surveillance, Epidemiology, and End Results Program (26). The standardized incidence ratios and their 95% confidence intervals (95% CI) were computed assuming a Poisson distribution for the observed number of cancers (25).

Results

Exposed and unexposed women were similar with regard to most factors, with a few exceptions (Table 2). Exposed women were younger, less likely to be parous, had an older age at first

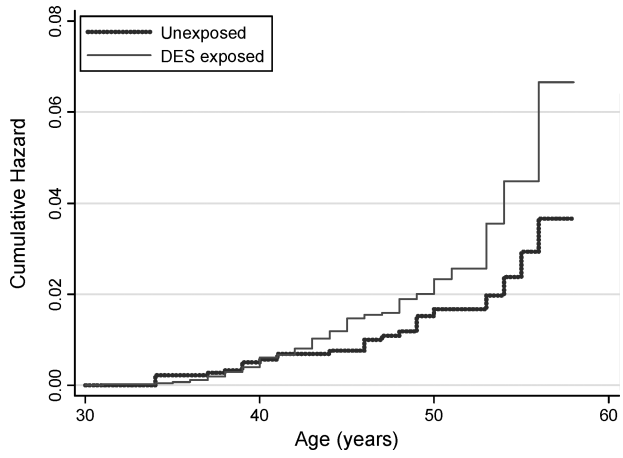

Figure 1. Cumulative hazard plots for prenatal DES exposure in relation to risk of breast cancer.

Table 4. Prenatal DES exposure in relation to risk of invasive breast cancer among women ages ≥40 years according to parity, family history of breast cancer, use of female hormone supplements, use of oral contraceptives, and menopausal status

	Exposed		Unexposed		Age-adjusted IRR (95% CI)
	Person-years of follow-up	Cases*	Person-years of follow-up	Cases*	
Parous	19,290	43	9,941	14	1.98 (1.06-3.71)
Nulliparous	9,901	17	3,100	3	1.72 (0.50-5.86)
Family history	3,938	18	1,771	4	2.26 (0.74-6.91)
No family history	24,899	42	11,156	13	1.83 (0.96-3.51)
Ever FH use	6,677	20	3,137	8	1.69 (0.70-4.08)
Never FH use	22,083	39	9,752	9	1.98 (0.96-4.10)
Never OC use	6,088	12	2,468	1	—
Ever OC use	23,073	48	10,461	16	1.63 (0.91-2.94)
Premenopausal	20,587	39	8,989	8	2.20 (1.02-4.72)
Postmenopausal	6,383	17	2,974	7	1.87 (0.72-4.83)

Abbreviations: FH, female hormone supplement; OC, oral contraceptives.
*Case numbers do not sum to total because of missing data on covariates.

birth, had a lower birthweight, and were more educated than unexposed women.

There were 98,591 person-years of follow-up among the exposed daughters and 35,046 person-years among the unexposed. Seventy-six cases of invasive breast cancer occurred among the exposed and 26 among the unexposed for an age-adjusted IRR of 1.40 (95% CI, 0.89-2.22) comparing DES-exposed to unexposed women (Table 3). As shown in Fig. 1, results differed by age: the IRR for women ages <40 years was 0.61 (95% CI, 0.27-1.38) whereas the IRR for ages ≥40 years was 1.91 (95% CI, 1.09-3.33), and the interaction was statistically significant ($P = 0.03$). There was a further increase for women ages ≥50 years, among whom the IRR was 3.00 (95% CI, 1.01-8.98), but this IRR was not statistically different from the IRR for ages 40 to 49 years. The IRRs from multivariable models were closely similar to those from the age-adjusted models, as shown in Table 3, and for the remaining analyses we present IRRs from age-adjusted models only. Comparison of exposed cases to those expected based on rates in the general population yielded a similar pattern by age, with standardized incidence ratios of 0.93 (95% CI, 0.57-1.52), 1.13 (95% CI, 0.84-1.50), and 1.77 (95% CI, 1.05-3.00) for ages <40, 40-49, and 50+ years, respectively. Because the breast cancer risk factor profiles for the exposed and unexposed cohorts are different from those of the general population, subsequent analyses were limited to IRRs. Furthermore, because there was a statistically significant age-interaction for ages <40 and ≥40 years, all further analyses were confined to women ages ≥40 years, among whom the majority of breast cancer cases (77 of 102) arose.

A positive association of prenatal DES exposure with risk of breast cancer in women ages ≥40 years was present across strata of important breast cancer risk factors (Table 4). The IRRs were 2.20 among premenopausal women and 1.87 among postmenopausal women. Among postmenopausal women ages ≥50 years, the IRR was 2.47 (95% CI, 0.80-7.61; data not shown).

As shown in Table 5, the IRR for the low-dose exposure cohort relative to unexposed cohort was 1.63 (95% CI, 0.87-3.08) and the IRR for the high-dose cohort relative to unexposed cohort was 2.16 (95% CI, 1.18-3.96; $P_{trend} = 0.01$).

DES exposure that began before the 9th week of gestation was not associated with a greater increase of breast cancer risk in women ages ≥40 years than was exposure that began later in the pregnancy: the IRRs were 1.48 for the earliest exposure, 2.04 for exposure that began in the 9th to 12th week of pregnancy, and 2.01 for exposure that began after the first trimester.

The association of DES exposure with breast cancer was present for both estrogen receptor–positive and estrogen receptor–negative tumors and for both progesterone receptor–positive and progesterone receptor–negative tumors (Table 6). Only three of the tumors with known histology did not have a ductal component, and therefore it was not possible to evaluate the association for other histologic types. The IRR was 1.64 (95% CI, 0.75-3.59) for tumors <2 cm in diameter and 3.25 (95% CI, 1.03-10.2) for larger tumors. IRRs for cases with no positive lymph nodes were similar to those for cases with one or more positive nodes.

Discussion

The present results suggest that prenatal exposure to DES may increase risk of breast cancer. DES-exposed women ages ≥40 years were estimated to have 1.9 times the risk of unexposed women of the same ages. For women ages ≥50 years, the estimated relative risk was even higher, but the relatively small number of cases makes the age gradient imprecise. The association was present within all strata of the breast cancer risk factors that were examined and did not differ by receptor status of the tumor, tumor size, or lymph node involvement. Furthermore, the highest relative risk was observed for the cohorts receiving the highest cumulative dose of DES exposure.

Table 5. Timing of first exposure to DES and characteristic dose of DES in relation to breast cancer among women ages ≥40 years

	Person-years of follow-up	No. cases	Age-adjusted IRR (95% CI)
Unexposed	13,058	17	Reference
Weeks of gestation of first exposure			
≤8 wk	7,731	12	1.48 (0.69-3.16)
9-12 wk	6,511	14	2.04 (0.99-4.23)
≥13 wk	8,272	19	2.01 (1.03-3.90)
Characteristic dose in cohort*			
Low dose	12,215	22	1.63 (0.86-3.11)
High dose	16,160	36	2.17 (1.18-3.97)
Unknown	973	2	1.75 (0.40-7.65)

*Low-dose cohort includes participants from hospitals in Texas, Minnesota, and Wisconsin. High-dose cohort includes participants from hospitals in Boston, Chicago, and California. Unknown includes participants from hospitals in New Hampshire and Maine.

Table 6. DES exposure in relation to risk of breast cancer among women ages ≥40 years according to tumor characteristics

	No. cases		Age-adjusted rate ratio (95% CI)
	Exposed	Unexposed	
Estrogen receptor			
Positive	43	13	1.92 (1.00-3.67)
Negative	8	2	1.76 (0.37-8.32)
Progesterone receptor			
Positive	35	10	2.06 (0.98-4.34)
Negative	13	3	2.12 (0.60-7.52)
Histology			
Ductal	49	14	1.94 (1.04-3.61)
Lobular	2	1	—
Both	3	0	—
Tumor size			
<2 cm	26	9	1.64 (0.75-3.59)
≥2 cm	21	4	3.25 (1.03-10.2)
Positive nodes			
None	27	8	2.20 (0.95-5.11)
≥1	22	5	2.10 (0.79-5.60)

Our findings are consistent with those reports that have identified an increased risk in females exposed to intrauterine factors associated with altered hormone levels. These studies have not been consistent, but there have been a number of positive studies supporting a role for prenatal factors (13). The majority of studies of birthweight have found a positive association with breast cancer risk (3-6, 10). Birthweight has been positively correlated with maternal pregnancy estrogen levels (27-29) but not with cord levels (29). Dizygotic twin pregnancy, which is associated with higher levels of pregnancy estrogens (30, 31), has also been linked with increased breast cancer risk in the offspring, but less consistently (3, 8, 12). Daughters of preeclamptic pregnancies have a lower breast cancer risk (7, 8, 11). Whether this association is related to pregnancy hormone levels is unclear, however, because well-designed prospective studies have not found lower levels of estrogens either in the cord blood of preeclamptic births or in maternal serum (32-34). On the other hand, there is some evidence that testosterone levels (33, 34) and progesterone levels (32) may be higher in preeclamptic pregnancies. Experimental studies have examined the effects of neonatal DES exposure on the mammary glands of rodents: in a recent study of mice, DES exposure exerted long-lasting effects on proliferation and differentiation of the mammary glands (35), and in a study of rats, exposure led to an increased number of mammary tumors (36). One possible molecular mechanism for the association observed in our study is the mammary gland cell hypothesis (1, 2), which postulates that altered prenatal hormone exposure could lead to an increase in the total number of ductal stem cells at risk of carcinogenic stimulation.

Our finding of an increased relative risk with increased age at diagnosis was unexpected and warrants further investigation. We did not observe a positive association among women ages <40 years; in fact, the relative risk estimate was <1.0. However, we had limited power to detect an increased risk in younger women.

Because the unexposed cohort was slightly older than the exposed cohort, we adjusted for age by individual year. DES-exposed women typically have a later first birth and are more likely to be nulliparous, and both factors can increase breast cancer risk. We controlled for age at first birth and number of births in a time-dependent model and found that results were unchanged. Furthermore, an analysis restricted to nulliparous women, among whom there would not be confounding by parity, yielded results consistent with a positive association.

Standardized incidence ratios derived using general population incidence rates in U.S. white women indicated a similar, albeit weaker, association of prenatal DES exposure with breast cancer risk. Both the exposed and unexposed women in this study had breast cancer risk factor profiles that were different from those of the general population, with perhaps the most notable being a profoundly lower prevalence of overweight and obesity. Thus, we believe that the IRRs give the most unbiased estimates of the magnitude of the risks involved.

Selection bias is unlikely to explain the present findings. Eighty percent of both exposed and unexposed subjects were followed through the 2001 questionnaire cycle. In addition, nonrespondents were similar to respondents with respect to age, reproductive factors, body mass index, smoking, and other factors among both exposed and unexposed.

Information on DES exposure was ascertained from the mothers' prenatal records and was recorded before the beginning of follow-up for all subjects. Thus, nondifferential misclassification of exposure is extremely unlikely. The prevalence of mammography use was similar for the exposed and unexposed groups, suggesting that detection bias is an unlikely explanation for our findings. In addition, the positive association with DES exposure was present for tumors ≥2 cm in size, which would have been likely to come to diagnosis regardless of frequency of mammographic screening.

There are two important clinical implications of our results. First, DES-exposed women should be encouraged to adhere to breast cancer screening guidelines. Whereas we have observed that many exposed daughters have concerns about their cancer risks in general, many others fail to have mammograms at appropriate intervals, or at all. A second important consideration for DES-exposed women is whether to take female hormone supplements. Our findings indicate no statistical interaction between prenatal DES exposure and use of hormone supplements. However, we had limited power to detect an interaction. Because the commonly used female hormone supplements have been shown to independently increase risk of breast cancer (37), it might be wise for exposed women to avoid such supplements whenever possible.

In summary, the present findings suggest that women who were exposed to DES *in utero* have an increased risk of breast cancer at the ages at which breast cancer becomes more common. This is unwelcome news for the 1 to 2 million women who were prenatally exposed to DES, and underscores the need for regular screening for breast tumors. Although the relative risk is modest compared with the greatly increased risk of vaginal cancer associated with DES exposure, the number of cases attributable to DES exposure, if there is a true causal relation, will be substantially larger because breast cancer is a commonly occurring cancer. In addition, some have speculated that the effects of fetal exposure to pharmacologic hormonal levels may serve as sentinels for the subtle effects of less dramatic, but more prevalent, hormonal perturbations resulting from lifestyle or environmental exposures. The present results suggest that such environmental exposures may deserve more serious consideration.

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