

Cancer Risk in Women Exposed to Diethylstilbestrol In Utero

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Context.—The association between in utero exposure to diethylstilbestrol (DES) and clear cell adenocarcinoma (CCA) of the vagina and cervix is well known, yet there has been no systematic study of DES-exposed daughters to determine whether they have an increased risk of other cancers. As many as 3 million women in the United States may have been exposed to DES in utero.

Objective.—To determine whether women exposed to DES in utero have a higher risk of cancer after an average of 16 years of follow-up.

Design.—A cohort study with mailed questionnaires and medical record review of reported cancer outcomes.

Participants.—A cohort of 4536 DES-exposed daughters (of whom 81% responded) and 1544 unexposed daughters (of whom 79% responded) who were first identified in the mid-1970s.

Main Outcome Measures.—Cancer incidence in DES-exposed daughters compared with population-based rates and compared with cancer incidence in unexposed daughters.

Results.—To date, DES-exposed daughters have not experienced an increased risk for all cancers (rate ratio, 0.96; 95% confidence interval [CI], 0.58-1.56) or for individual cancer sites, except for CCA. Three cases of vaginal CCA occurred among the exposed daughters, resulting in a standardized incidence ratio of 40.7 (95% CI, 13.1-126.2) in comparison with population-based incidence rates. The rate ratio for breast cancer was 1.18 (95% CI, 0.56-2.49); adjustment for known risk factors did not alter this result.

Conclusions.—Thus far, DES-exposed daughters show no increased cancer risk, except for CCA. Nevertheless, because exposed daughters included in our study were, on average, only 38 years old at last follow-up, continued surveillance is warranted to determine whether any increases in cancer risk occur during the menopausal years.

occurrence of cancer, precursor lesions, and reproductive effects,⁵⁻⁷ but systematic follow-up of these cohorts had ceased by 1990. Concern has arisen that DES-exposed daughters may be at higher risk of breast cancer.⁸ Exposure to high levels of endogenous estrogen in utero has been hypothesized to increase the risk of breast cancer⁹ and DES is a potent estrogen. We conducted a study to ascertain the risk of breast and other cancers in women exposed to DES in utero by combining the previously identified cohorts, beginning follow-up in 1978 and extending it through 1994.

METHODS

Subjects

Three individual cohorts are included in this combined follow-up study. The largest cohort consists of 4936 women enrolled in the National Cooperative Diethylstilbestrol Adenosis (DESAD) study during the mid-1970s.⁵ Nearly half of the exposed subjects were identified by prenatal record review at 5 centers. The remainder were referred by physicians or were self-referrals but were required to have documented exposure to DES. Women not exposed to DES in utero were selected from the same record sources as the exposed subjects or were sisters of exposed subjects. Women were followed yearly with either clinical examinations (through 1980) or mailed questionnaires (from 1984 through 1989).

The second cohort (the Dieckmann cohort) includes 644 female offspring whose mothers participated in a randomized clinical trial of the efficacy of DES during pregnancy in the early 1950s.¹⁰ In 1974, attempts were made to trace all subjects in this cohort, and 83% of exposed and 77% of unexposed subjects responded to a questionnaire.¹¹ Follow-up of this cohort was episodic during the 1980s; subjects were last contacted in 1990.¹²

A third cohort (the Horne cohort) consists of 281 exposed daughters and 219 of their unexposed sisters whose mothers were treated with DES during preg-

DIETHYLSTILBESTROL (DES), a drug first synthesized in 1938,¹ was administered to several million pregnant

women in the United States and Europe for the prevention of spontaneous abortion and premature delivery.² In 1971, Herbst et al³ reported a strong association between DES use in pregnancy and the occurrence of vaginal clear cell adenocarcinoma (CCA) in exposed female offspring. Animal models have demonstrated a range of DES effects on offspring exposed in utero, including reproductive dysfunction, immune system changes, behavioral and sexual abnormalities, and increases in various reproductive cancers in males and females. However, the applicability of these experiments to humans and the mechanism of carcinogenesis are unclear.⁴ In the mid-1970s, several separate cohorts of DES-exposed daughters and unexposed comparison groups were followed for the

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Table 3.—Cancer Risk in Daughters Exposed or Unexposed to Diethylstilbestrol, Compared With SEER Incidence Rates, and Relative Risk of Cancer, Comparing Exposed With Unexposed Daughters*

Cancer Site	Exposed (n=4536)†			Unexposed (n = 1544)§			Rate Ratio (95% CI)¶
	Observed	Expected	SIR (95% CI)‡	Observed	Expected	SIR (95% CI)‡	
All cancer¶¶	61	56.7	1.08 (0.82-1.38)	22	20.6	1.07 (0.67-1.62)	0.96 (0.58-1.56)
Breast	29	24.3	1.19 (0.83-1.72)	9	9.2	0.98 (0.51-1.88)	1.18 (0.56-2.49)
Clear cell adenocarcinoma	3	0.07	40.7 (13.1-126.2)	0	0.02	0 (0-149.8)	∞ (0.08-∞)
Ovary	5	4.1	1.21 (0.50-2.90)	1	1.5	0.69 (0.10-4.87)	1.54 (0.18-13.22)
Endometrium, uterus or not otherwise specified	3	2.4	1.26 (0.41-3.92)	3	0.9	3.29 (1.06-10.19)	0.34 (0.07-1.69)
Thyroid	4	6.2	0.64 (0.24-1.71)	0	2.1	0 (0-1.43)	∞ (0.15-∞)
Digestive system	2	3.7	0.54 (0.14-2.17)	2	1.4	1.44 (0.36-5.77)	0.35 (0.05-2.46)
Lung	1	2.2	0.46 (0.06-3.26)	1	0.9	1.15 (0.16-8.14)	0.29 (0.02-4.67)
Brain	3	2.0	1.48 (0.48-4.58)	0	0.7	0 (0-4.28)	∞ (0.10-∞)
Leukemia/lymphoma	9	6.7	1.34 (0.70-2.58)	3	2.3	1.33 (0.43-4.12)	0.86 (0.23-3.21)
Hodgkin	5	2.7	1.84 (0.77-4.42)	0	0.8	0 (0-3.75)	∞ (0.18-∞)
Leukemia	2	1.6	1.22 (0.30-4.88)	2	0.6	3.44 (0.86-13.74)	0.33 (0.04-2.45)

*SEER indicates Surveillance, Epidemiology, and End Results; CI, confidence interval.

†68 110 Person-years.

‡Standardized incidence ratio (SIR) using age and calendar-year SEER rates to obtain expected values.

§22 599 Person-years.

¶Age-adjusted rate ratio, comparing exposed with unexposed daughters.

¶¶All cancers excluding cancer of the cervix and melanoma.

3 cases occurred among the 29 111 person-years accumulated by the cohort up through 29 years of age. There were no cases in the 38 999 person-years accumulated after 30 years of age. If we apply this rate of 1 per 10 000 cases per year to the 15-year time span when the vast majority of cases are diagnosed (from age 15 through 29 years), then our estimate of the cumulative incidence rate becomes 1.5 per 1000 exposed women. This is at the upper end of the range of 1 per 1000 to 1 per 10 000 estimated in 1979 and remarkably close to the rate of 1 per 1000 through 34 years of age estimated from population data in 1987.¹⁷ Thus, DES exposure leads to a large relative increase in the risk of CCA, but it affects only a small proportion of all exposed women. The lack of any cases in the cohort thus far older than 30 years is encouraging. However, several cases of primary CCA in exposed women in their 40s have been reported recently to the Registry for Research on Hormonal Transplacental Carcinogenesis (Arthur L. Herbst, MD, oral communication, November 10, 1997), and there is major interest in evaluating risk when the cohort reaches their 50s and 60s, when CCA is most common in unexposed women.

The effect of DES exposure on male offspring is still unknown. Animal studies have suggested an increased risk of testicular cancer and several case-control studies have attempted to assess this association, but results have been inconsistent.¹⁸ Diethylstilbestrol has been associated with a small increase in breast cancer risk in mothers exposed during pregnancy,¹⁹⁻²³ although the studies are not entirely consistent.^{7,24} Because of the multiple lines of evidence linking estrogen to breast cancer risk, perhaps the most attention and concern

Table 4.—Cancer Risk in Daughters Exposed to Diethylstilbestrol by Original Cohort and by Time Since Exposure*

Cohort	All Cancer†		Breast Cancer	
	Cases, No.	Rate Ratio‡ (95% CI)	Cases, No.	Rate Ratio‡ (95% CI)
DESAD	67	1.17 (0.63-2.13)	32	1.33 (0.55-3.25)
Record review subjects	36	0.94 (0.47-1.89)	19	1.24 (0.48-3.28)
Dieckmann	13	0.57 (0.19-1.73)	6	0.91 (0.18-4.49)
Horne	3	1.14 (0.10-12.66)	0	...
Attained age, y (time since exposure)				
<40	54	0.79 (0.43-1.46)	20	0.66 (0.26-1.68)
≥40	29	1.22 (0.52-2.87)	18	3.17 (0.73-13.83)

*CI indicates confidence interval; DESAD, National Cooperative Diethylstilbestrol Adenosis Project.

†Excludes cancer of the cervix and melanoma.

‡Age-adjusted rate ratio, comparing exposed with unexposed daughters.

among those exposed to DES is focused on breast cancer. Indeed, several investigators have hypothesized that breast cancer risk in general may be associated with in utero exposure to elevated estrogen levels,^{9,25-27} and some associations have been reported for variables that may reflect endogenous in utero estrogen levels, such as maternal age, twin status, and preeclampsia during the index pregnancy. If the hypothesized relationship is due to estrogenicity itself, rather than to the chemical structure of the estrogen, then perhaps the best test of this hypothesis would be among women exposed in utero to the extraordinarily high levels achieved during DES treatment. Among the entire cohort, we found no evidence of an increased risk of breast cancer in women exposed to DES in utero. However, among women who were aged 40 years and older, there was a suggestion of a higher risk in the DES-exposed daughters compared with the unexposed daughters, but this result was not statistically significant and appeared to be due to a lower-than-ex-

pected rate of breast cancer among unexposed women in this age group.

Previous analysis of data from the DESAD study found no statistically significant difference in the prevalence of squamous cell lesions of the cervix in the DESAD cohort at their initial screening examination²⁸ but noted a 2-fold excess in the incidence of squamous cervical intraepithelial neoplasia (CIN) among exposed daughters at subsequent examinations.²⁹ The absence of an increased risk of invasive cervical cancer even in the presence of excess risks of CIN might not be surprising, since exposed daughters undergo frequent screening, with precursor lesions likely treated aggressively. An important limitation of our study is the absence of pathology reports for many of the cervical lesions reported on the questionnaires, due either to lack of response by hospital pathology departments or to subjects' lack of consent for retrieval of medical records. The pathology reports obtained showed poor agreement between the questionnaire and the pathologist's diagnosis. However, even when we

included those reported cases of cervical cancer for which we did not obtain pathology reports, the risk in exposed women was not significantly elevated, either compared with SEER rates or with unexposed daughters. The important remaining question is DES exposure in relation to risk of CIN subsequent to the last report from the DESAD project in 1984²⁹; we are currently collecting data to address this risk.

While the size of this group, the documentation of exposure, and the extent of data collection all make this a uniquely valuable cohort, it also has its limitations. For purposes of this analysis, follow-up began in 1978 shortly after assembly of the component cohorts and when the median age of the subjects was 24 years. Thus, there was no opportunity to assess the risks of childhood malignancies. We were also able to achieve complete follow-up on only 80% of the eligible study population. However, losses to follow-up were similar for exposed and nonexposed subjects. Also, when we extended the follow-up for lost subjects to the date of study completion, we found similar results to those that

used individual dates of last follow-up. The major limitation, however, relates to the relatively young age of cohort members, leading to a limited expected number of specific cancers. For example, our study has limited power (63%) to detect an RR of 2 for breast cancer, although it has high power (97%) to identify an RR of 3 ($\alpha = .05$, 1-sided test). Thus, while no statistically significant excess was noted for any site except CCA, the wide CIs indicate that we cannot rule out potentially important increases in risk for any site. With respect to breast cancer, the observations to date relate to cancers occurring at a young age. Any influence of DES on breast cancer may only become discernible among those cases that occur in the more usual age range of the disease.

This cohort study is the first to examine systematically the risk of all forms of cancer in a large group of DES-exposed daughters. The results should reassure the DES-exposed population, since they confirm previous estimates that CCA is an uncommon occurrence and they also reveal no major excesses in risk of other types of cancer. Since the majority of women in-

cluded in our study are currently younger than 50 years, it will be important to continue follow-up of the cohort to monitor cancer risk as the cohort ages.

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