ORIGINAL ARTICLE

Adverse Health Outcomes in Women Exposed In Utero to Diethylstilbestrol

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ABSTRACT

BACKGROUND

Before 1971, several million women were exposed in utero to diethylstilbestrol (DES) given to their mothers to prevent pregnancy complications. Several adverse outcomes have been linked to such exposure, but their cumulative effects are not well understood.

METHODS

We combined data from three studies initiated in the 1970s with continued long-term follow-up of 4653 women exposed in utero to DES and 1927 unexposed controls. We assessed the risks of 12 adverse outcomes linked to DES exposure, including cumulative risks to 45 years of age for reproductive outcomes and to 55 years of age for other outcomes, and their relationships to the baseline presence or absence of vaginal epithelial changes, which are correlated with a higher dose of, and earlier exposure to, DES in utero.

RESULTS

Cumulative risks in women exposed to DES, as compared with those not exposed, were as follows: for infertility, 33.3% vs. 15.5% (hazard ratio, 2.37; 95% confidence interval [CI], 2.05 to 2.75); spontaneous abortion, 50.3% vs. 38.6% (hazard ratio, 1.64; 95% CI, 1.42 to 1.88); preterm delivery, 53.3% vs. 17.8% (hazard ratio, 4.68; 95% CI, 3.74 to 5.86); loss of second-trimester pregnancy, 16.4% vs. 1.7% (hazard ratio, 3.77; 95% CI, 2.56 to 5.54); ectopic pregnancy, 14.6% vs. 2.9% (hazard ratio, 3.72; 95% CI, 2.58 to 5.38); preeclampsia, 26.4% vs. 13.7% (hazard ratio 1.42; 95% CI, 1.07 to 1.89); stillbirth, 8.9% vs. 2.6% (hazard ratio, 2.45; 95% CI, 1.33 to 4.54); early menopause, 5.1% vs. 1.7% (hazard ratio, 2.35; 95% CI, 1.67 to 3.31); grade 2 or higher cervical intraepithelial neoplasia, 6.9% vs. 3.4% (hazard ratio, 2.28; 95% CI, 1.59 to 3.27); and breast cancer at 40 years of age or older, 3.9% vs. 2.2% (hazard ratio, 1.82; 95% CI, 1.04 to 3.18). For most outcomes, the risks among exposed women were higher for those with vaginal epithelial changes than for those without such changes.

CONCLUSIONS

In utero exposure of women to DES is associated with a high lifetime risk of a broad spectrum of adverse health outcomes. (Funded by the National Cancer Institute.)

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Soon after the first synthetic estrogen, diethylstilbestrol (DES), was developed in 1938,[1] it was used clinically to prevent complications of pregnancy.[2] In the early 1950s, four clinical trials revealed no evidence of efficacy, and DES use declined.[3-6] In the late 1960s, an unusual cluster of cases of clear-cell adenocarcinoma of the vagina and cervix in adolescent girls and young women was observed at one hospital.[7] The clinicians involved, working with the mothers of these women,[8] discovered a strong association between this cancer and in utero exposure to DES.[9]

Subsequent clinical studies of women exposed to DES in utero showed developmental defects of the genital tract along with several complications of pregnancy.[10,11] The significance and magnitude of such risks remained unclear, and concerns were expressed that other adverse effects might develop, prompting longer-term studies of some women. In the early 1990s, we combined three cohort studies, initially developed in the mid-1970s and including documentation of DES exposure, and participants were recontacted and enrolled in a systematic assessment and follow-up study, the results of which are reported here.

METHODS

STUDY OVERSIGHT

Institutional review boards at each field center and the National Cancer Institute approved the study, and all participants provided written informed consent.

STUDY PARTICIPANTS AND EARLY FOLLOW-UP

Three cohort studies were included in this investigation of daughters of DES-exposed women, one part of the National Cancer Institute's Combined Cohort Study of DES Exposure: the national cooperative Diethylstilbestrol Adenosis (DESAD) study, the Dieckmann study, and the Women's Health Study (WHS). Detailed descriptions of the designs, methods, and study populations are provided in the original reports[12-14] and summarized in the Supplementary Appendix (available with the full text of this article at NEJM.org). The Dieckmann study was a clinical trial of DES administration during pregnancy in the early 1950s. Beginning in 1975, 338 (83%) of the DES-exposed female infants and 298 (77%) of the unexposed female infants born alive were successfully contacted and agreed to undergo an initial clinical examination and complete periodic questionnaires specific to the Dieckmann cohort, assessing clinical and lifestyle information. The DESAD study, also begun in 1975, included women from five major medical centers for whom there was documentation of the presence or absence of in utero DES exposure (4015 and 1034 women, respectively); these women underwent five annual examinations and subsequently completed periodic questionnaires specific to the DESAD cohort, assessing clinical and lifestyle information. The WHS was initially a study of women who were given DES during their pregnancies, from the period of 1940 to 1960, at three medical centers and one private obstetric practice; more than 83% of the women were located and responded to one to three questionnaires in the 1980s. A partial cohort of their daughters (327 exposed and 716 unexposed) was identified and invited in 1994 to participate in the current follow-up study.

COMBINED COHORT FOLLOW-UP

Of the 4301 DES-exposed and 1955 unexposed women from the original cohorts who were successfully contacted and invited to participate in the Combined Cohort Study, 4001 (93%) and 1683 (86%), respectively, responded to one or more of the three questionnaires specific to the Combined Cohort Study (one each administered in 1994, 1997, and 2001). The average age at last follow-up was 48 years. For an additional 652 DES-exposed women (578 in the DESAD cohort and 74 in the Dieckmann cohort) and 244 unexposed women (170 in the DESAD cohort and 74 in the Dieckmann cohort) who could not be located or had not responded to any of the questionnaires, the original studies had systematic follow-up data regarding grade 2 or higher cervical intraepithelial neoplasia (CIN 2+) and any type of cancer, with an average age at last follow-up of 31 years; these data were included in the analyses of the CIN 2+ and cancer end points. Of the 4653 exposed and 1927 unexposed women, 4015 and 1034, respectively, were from the DESAD study; 363 and 326, respectively, were from the Dieckmann study; and 275 and 567, respectively, were from the WHS.

OUTCOMES

We assessed 12 adverse health outcomes that were significantly associated with DES exposure in previous analyses of the combined cohort: infertility (attempting but failing to conceive over a period of ≥12 months), spontaneous abortion (at <14 weeks' gestation), ectopic pregnancy, loss of preg-

Table 1. Baseline Characteristics of Women with and Those without In Utero Exposure to Diethylstilbestrol (DES).*

Characteristic	Exposed Women (N=3796)	Unexposed Women (N=1659)
	percentage	
Year of birth†		
Before 1950	18	27
1950–1954	45	45
1955–1959	25	24
1960 or later	12	3
Age at last follow-up‡		
<40 yr	20	14
40–44 yr	19	16
45–50 yr	34	35
≥50 yr	27	35
Education		
High school or less	14	21
Some college	24	27
College	35	30
Graduate school	28	23
Cigarette use§		
Never	58	50
Ever	42	50
Body-mass index¶		
<20.0	15	14
20.0–24.9	52	50
25.0–29.9	20	23
≥30.0	13	13
Age at menarche		
<12 yr	17	19
12–13 yr	58	58
≥14 yr	25	23
Oral-contraceptive use		
Never	19	17
Ever	81	83
No. of sexual partners§		
0 or 1	24	22
2–4	28	29
5–9	23	25
≥10	25	24
No. of pregnancies§		
0	26	17
1	17	15
2	27	32
≥3	31	36

Table 1. (Continued.)

Characteristic	Exposed Women (N=3796)	Unexposed Women (N=1659)
	percentage	
Age at birth of first child§		
<25 yr	34	46
25–29 yr	37	32
≥30 yr	28	22
No. of general physical examinations in previous 5 yr		
0	16	14
1	25	23
2 or 3	33	34
≥4	26	29
No. of Papanicolaou smears in previous 5 yr§		
0	3	4
1	7	7
2 or 3	22	28
≥4	68	61
No. of mammograms in previous 5 yr		
0	28	22
1	29	29
2 or 3	31	34
≥4	12	16

* Characteristics of the study participants were ascertained on the basis of responses to a 1994 questionnaire. There were no significant differences between the two study groups unless otherwise indicated.
† P<0.01 for the comparison between exposed and unexposed participants.
‡ Age at last follow-up is based on the total analysis cohort, including subjects who participated only in the original studies.
§ P<0.05 for the comparison between exposed and unexposed participants, adjusted for year of birth.
¶ The body-mass index is the weight in kilograms divided by the square of the height in meters.

nancy in second trimester (at 14 to 27 weeks' gestation), preeclampsia (according to a physician's diagnosis), preterm delivery (at <37 weeks' gestation), stillbirth (at >27 weeks' gestation), neonatal death (within the first month of life), early menopause (onset of natural menopause before 45 years of age), CIN 2+, invasive breast cancer at 40 years of age or older, and clear-cell adenocarcinoma. Induced abortions, which are unrelated to DES exposure,[15] were excluded from all analyses. Specific questions, methods, and data relating to each outcome are described in detail in reports on the individual outcomes.[15-20]

The reproductive outcomes were assessed by means of self-reported, standardized responses to one or more of the three Combined Cohort Study questionnaires. Other studies,[21,22] including one involving a subgroup of mothers of the DESAD study participants,[23] have shown that self-reports of the types of pregnancy outcomes assessed in this study are generally concordant with the data obtained from medical records.

Histories of cancer diagnoses and all biopsies of the cervix or vagina were also obtained by means of self-report in each of the three Combined Cohort questionnaires, and pathological reports were sought for validation. Investigators for the original cohorts assessed and validated these neoplastic events in an identical manner, by obtaining pathology reports for these conditions, and data from both sources were combined for these outcomes.

Eighty-two cases of invasive breast cancer diagnosed at an age of 40 years or older were reported. Pathological reports were obtained for 75 of these cases, all of which confirmed the reported diagnosis. Because of the reporting accuracy, we included the 7 cases for which we could not ob-

tain the relevant pathological records. In the Combined Cohort Study questionnaires, pathological reports during follow-up of women who underwent biopsy resulted in a diagnosis of CIN 2+ in 149 DES-exposed women and 27 unexposed women. Representative slides for these cases were reviewed by one of us, without knowledge of exposure status, who confirmed 137 cases in the exposed group and 23 cases in the unexposed group. These were combined with 88 previous cases (71 in DES-exposed women and 17 in unexposed women) confirmed by means of pathological review in the original cohorts, for a total of 248 cases of CIN 2+ for analysis.

STATISTICAL ANALYSIS

Hazard ratios and their 95% confidence intervals were computed with the use of the Cox proportional-hazards model, with age as the underlying time metric,[24] and cumulative risks were estimated by means of the Breslow estimator, based on the empirical cumulative hazard function.[25] The Q statistic was used to assess the heterogeneity of hazard ratios among cohorts.[26] The excess risk, or the excess hazard of disease in the DES-exposed group that was attributable to the exposure, was calculated as the difference in cumulative risk between the exposed and unexposed groups. All analyses were performed with the use of SAS statistical software (version 9.2).[27] Covariates were assessed as potential confounders by adding them individually to the models and retaining them if the hazard ratio changed by 10% or more. Because year of birth, gravidity or parity (depending on the timing of the outcome), and original cohort met this criterion, all estimated hazard ratios and cumulative risks were adjusted for these variables.

For both the hazard ratio and cumulative risk analyses, the time period covered depended on the outcome (Table 1 in the Supplementary Appendix). In general, risk was evaluated from birth or from age at first pregnancy or first delivery. Analyses of spontaneous abortion, ectopic pregnancy, and loss of pregnancy in the second trimester were limited to gravid women (those who have ever been pregnant), and analyses of preeclampsia, stillbirth, preterm delivery, and neonatal death were limited to parous women. Follow-up continued to 45 years of age for the reproductive outcomes and to 55 years of age for the other outcomes.

The Dieckmann and DESAD studies incorporated a comprehensive gynecologic examination around the time of recruitment that systematically identified vaginal epithelial changes by means of colposcopy or iodine staining.[12,28] Vaginal epithelial changes were defined as vaginal epithelium that was glandular in nature (adenosis) or metaplastic squamous epithelium, which develops as adenosis undergoes physiologic healing. These changes were initially linked to women exposed to DES early in pregnancy who also had large cumulative doses by the end of pregnancy.[29] The changes were subsequently determined to be independently related to both early exposure and total dose.[30] In these two cohorts, analyses were carried out with the absence or presence of vaginal epithelial changes as surrogates for the DES dose. Tests of significance were conducted in the DES-exposed group for the difference in risk of outcomes between women with vaginal epithelial changes and those without such changes.[24,27]

RESULTS

STUDY PARTICIPANTS

As compared with their unexposed peers at the time of the first Combined Cohort questionnaire, DES-exposed women were somewhat younger, were less likely to have smoked, had fewer pregnancies, were older at first delivery, had slightly fewer sexual partners, and had more Papanicolaou smears (Table 1).

OUTCOMES

The observed hazard ratios associated with DES exposure (vs. no exposure) ranged from 1.42 for preeclampsia to more than 3.70 for ectopic pregnancy, loss of second-trimester pregnancy, preterm delivery, and neonatal death (Table 2). Although preeclampsia and preterm delivery can occur during the same pregnancy, the risk of preterm delivery was increased even among women without preeclampsia (hazard ratio, 4.84; 95% confidence interval [CI], 3.75 to 6.24). The majority of deaths of neonates (85% of such deaths in the DES-exposed group and 77% in the unexposed group) occurred in association with preterm delivery. The risk of neonatal death was also elevated in the absence of preterm delivery, but there were only 2 such deaths in the unexposed group and 10 in the exposed group. Three cases of clear-cell adenocarcinoma of the vagina and one case of clear-cell adenocarcinoma of the cervix were diagnosed, all in the exposed

Table 2. Hazard Ratios for Adverse Health Outcomes in Women with and Those without Diethylstilbestrol (DES) Exposure.*

Adverse Outcome	Exposed Women	Unexposed Women	Hazard Ratio (95% CI)†
	no./total no.		
Infertility	1144/3769	252/1654	2.37 (2.05 to 2.75)
Spontaneous abortion‡	916/2690	328/1291	1.64 (1.42 to 1.88)
Ectopic pregnancy‡	255/2692	36/1293	3.72 (2.58 to 5.38)
Loss of second-trimester pregnancy‡	201/2692	35/1293	3.77 (2.56 to 5.54)
Preterm delivery§	624/2385	100/1238	4.68 (3.74 to 5.86)
Preeclampsia§	216/2412	80/1159	1.42 (1.07 to 1.89)
Stillbirth§	54/2385	16/1239	2.45 (1.33 to 4.54)
Neonatal death§	57/2383	7/1238	8.12 (3.53 to 18.65)
Early menopause	181/3993	49/1682	2.35 (1.67 to 3.31)
Cervical intraepithelial neoplasia, grade ≥2	208/4120	40/1785	2.28 (1.59 to 3.27)
Breast cancer at ≥40 yr	61/3693	21/1647	1.82 (1.04 to 3.18)
Clear-cell adenocarcinoma	4/4652	0/1926	∞ (0.37 to ∞)

* Total numbers of women vary among outcomes, primarily reflecting whether all, gravid, or parous women were included in the analyses, but also owing to some missing responses to the questionnaires ascertaining the outcome and to missing covariates. CI denotes confidence interval.
† Hazard ratios were calculated with age as the time metric and adjustment for date of birth and cohort.
‡ The analysis was restricted to gravid women and adjusted for number of pregnancies.
§ The analysis was restricted to parous women and adjusted for number of births.

group. The number of cases of clear-cell adenocarcinoma of the vagina or cervix expected on the basis of age-specific rates in the U.S. population was 0.102, for an observed-to-expected ratio of 39 (95% CI, 15 to 104). Associations between DES exposure and adverse outcomes were similar among the three cohorts, except for ectopic pregnancy, for which the hazard ratios in WHS, the DESAD study, and the Dieckmann study were 1.91, 4.28, and 9.44, respectively ($P<0.05$ for heterogeneity).

Hazard ratios for the various outcomes associated with DES exposure were not materially altered by adjustment for other potential confounders (Table 3 in the Supplementary Appendix). Some outcomes reported by the study participants occurred before they were first enrolled in the original follow-up studies, whereas others occurred throughout the subsequent follow-up period. For outcomes with sufficient numbers of cases for assessment, hazard ratios were similar for outcomes occurring before and those occurring after recruitment for the original cohorts, as well as for outcomes assessed before and those assessed after the start of the follow-up period for the Combined Cohort Study (Table 4 in the Supplementary Appendix).

In analyses assessing outcomes according to DES exposure and, within the DES-exposed group, according to the presence or absence of vaginal epithelial changes (as a biologic marker of dose and timing of exposure), hazard ratios for 9 of the 12 outcomes in the DES-exposed group were higher among study participants with vaginal epithelial changes than among those without vaginal epithelial changes; risks were significantly greater for 7 of the outcomes (Fig. 1, and Table 5 in the Supplementary Appendix).

The cumulative risk of clear-cell adenocarcinoma among the DES-exposed women was 0.1% (95% CI, 0.0 to 0.3%). Table 3 provides the estimated cumulative risks of exposed and unexposed women in whom the study outcomes developed by 45 or 55 years of age, depending on outcome, along with the excess risks (the estimated percentage of all exposed women in whom the outcome developed, most likely as a result of their exposure). The excess risks among the exposed women ranged from 1.7% for a breast-cancer diagnosis at an age of 40 years or older to 35.4% for preterm delivery (among parous women only). DES-exposed women who also had vaginal epithelial changes had substantially higher cumulative and excess

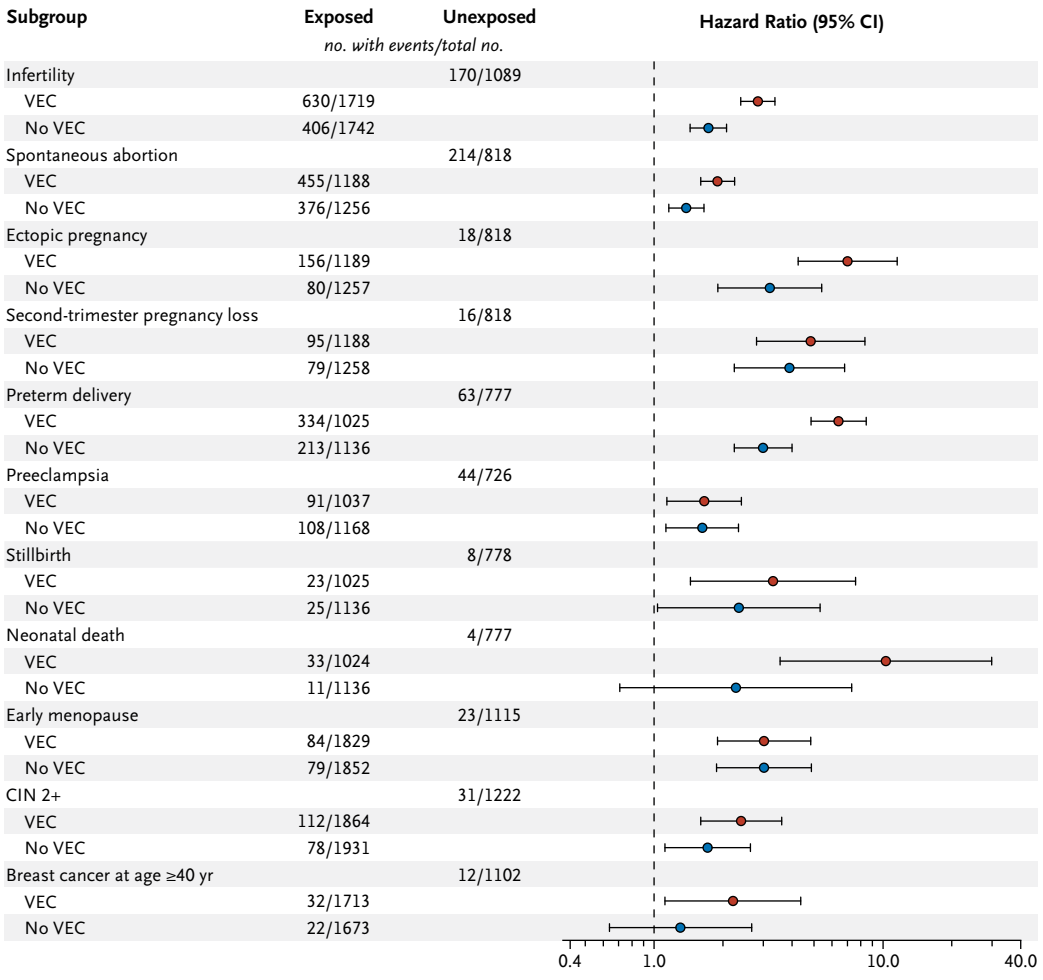

Figure 1. Hazard Ratios for Adverse Health Outcomes in the DESAD and Dieckmann Cohorts, According to Diethylstilbestrol (DES) Exposure Status and, in the DES-Exposure Group, the Presence or Absence of Vaginal Epithelial Changes (VEC) at Entry Examination.

Hazard ratios (on a $\log_{10}$ scale) differed significantly between VEC-positive and VEC-negative subgroups of the DES-exposed group for infertility, spontaneous abortion, ectopic pregnancy, preterm delivery, and neonatal death ($P<0.001$), as well as for grade 2 or higher cervical intraepithelial neoplasia (CIN 2+) ($P=0.02$) and invasive breast cancer at an age of 40 years or older ($P=0.05$). Hazard ratios for clear-cell adenocarcinoma are ∞ for both subgroups and therefore are not included. Total numbers of women vary among outcomes, primarily reflecting whether all, gravid, or parous women were included in the analysis, but also owing to some missing responses to the questionnaires ascertaining the outcome and to missing covariates. VEC status was not available for the WHS cohort. All outcomes were computed with age as the time metric and with adjustment for date of birth and cohort. Data for spontaneous abortion, ectopic pregnancy, and loss of second-trimester pregnancy were restricted to gravid women and adjusted for number of pregnancies. Data for preterm delivery, preeclampsia, stillbirth, and neonatal death were restricted to parous women and adjusted for number of births.

risks for most outcomes than DES-exposed women without these vaginal changes. The excess risks among DES-exposed women with vaginal epithelial changes versus women without DES exposure were 26% for infertility and 53% for preterm delivery (among parous women) (Fig. 2, and Table 6 in the Supplementary Appendix).

DISCUSSION

In this follow-up study of more than 4600 women with documented in utero exposure to DES, we found increased risks of clear-cell adenocarcinoma of the vagina and cervix and 11 other, more common adverse health outcomes, as compared

Table 3. Cumulative Risks of Adverse Health Outcomes in Women with and Those without Diethylstilbestrol (DES) Exposure and the Excess Risk Due to Exposure.*

Adverse Outcome	Exposed Women	Cumulative Risk†	Unexposed Women	Cumulative Risk†	Excess Risk (95% CI)‡
	no./total no.	*percent*	*no./total no.*	*percent*	
Infertility	1144/3769	33.3	252/1654	15.5	17.8 (14.5 to 20.9)
Spontaneous abortion§	916/2690	50.3	328/1291	38.6	11.7 (3.3 to 20.1)
Ectopic pregnancy§	255/2692	14.6	36/1293	2.9	11.7 (8.9 to 14.5)
Loss of second-trimester pregnancy§	201/2692	16.4	35/1293	1.7	14.7 (8.5 to 20.9)
Preterm delivery¶	590/2268	53.3	89/1140	17.8	35.4 (27.3 to 43.6)
Preeclampsia¶	209/2299	26.4	77/1072	13.7	12.7 (4.5 to 20.9)
Stillbirth¶	54/2385	8.9	16/1239	2.6	6.3 (−0.8 to 13.3)
Neonatal death¶	57/2383	7.8	7/1238	0.6	7.2 (1.9 to 12.5)
Early menopause	181/3993	5.1	49/1682	1.7	3.4 (2.1 to 4.7)
Cervical intraepithelial neoplasia, grade ≥2	208/4120	6.9	40/1785	3.4	3.5 (1.5 to 5.4)
Breast cancer at ≥40 yr	59/3693	3.9	20/1647	2.2	1.7 (−1.4 to 4.7)

* Total numbers of women vary among outcomes, primarily reflecting whether all, gravid, or parous women were included in the analyses, but also owing to some missing responses to the questionnaires ascertaining the outcome and to missing covariates.
† Cumulative risks were calculated with age as the time metric and adjustment for date of birth and cohort.
‡ Excess risk was not computed for clear-cell adenocarcinoma because there were no cases in unexposed women. The cumulative risk for exposed women was 0.1% (95% CI, 0.0 to 0.3).
§ The analysis was restricted to gravid women and adjusted for number of pregnancies.
¶ The analysis was restricted to parous women and adjusted for number of births.

with women without DES exposure, with hazard ratios ranging from 1.4 to 8.1. We also calculated the cumulative percentages of exposed and unexposed women in whom these outcomes developed through 45 years of age (for reproductive outcomes) or 55 years of age and found that the percentages of exposed women in whom outcomes could be attributed to DES (i.e., the excess risk) ranged from 1.7% for breast cancer to 35.4% (among exposed parous women) for preterm delivery. For most outcomes, among women exposed to DES, those with clinical evidence of vaginal epithelial changes at a young age, a marker of high DES dose and exposure early in gestation, had significantly higher risks than those without vaginal epithelial changes.

Our study has several strengths, including documentation of exposure status, clinical examinations, high rates of follow-up among both exposed and unexposed women, and the ascertainment of multiple outcomes. Previous studies using data from these cohorts provided estimates of hazard ratios for these outcomes. Our study extends these observations, including assessments of risk on the basis of the presence of vaginal epithelial changes as a biomarker of timing and dose of DES exposure, estimates of lifetime absolute risks of the outcomes among the exposed women, and the percentage of exposed women with adverse outcomes that were likely to be attributable to the exposure. A limitation of our study is that outcomes other than cancer and CIN 2+ were assessed by means of self-report. However, the major reproductive outcomes documented in medical records have been shown to be reasonably accurately reported by affected women, including mothers in the DESAD study.[21,23] In addition, our record retrieval and review of most reported cancers indicated more than 90% agreement between the clinical records and the participants' reports, with similar rates of agreement among exposed and unexposed women.[31] The hazard ratios for outcomes reported to have occurred before the women were made aware of their exposure status were similar to those that occurred after the women were made aware. Also, as we previously reported, rates of a self-reported diagnosis of depression or anxiety — outcomes that are likely to be more susceptible to reporting biases — were similar among the exposed women and the unexposed women.[32] Our observation that, among exposed women, hazard ratios for most adverse outcomes associated with DES were higher for women with

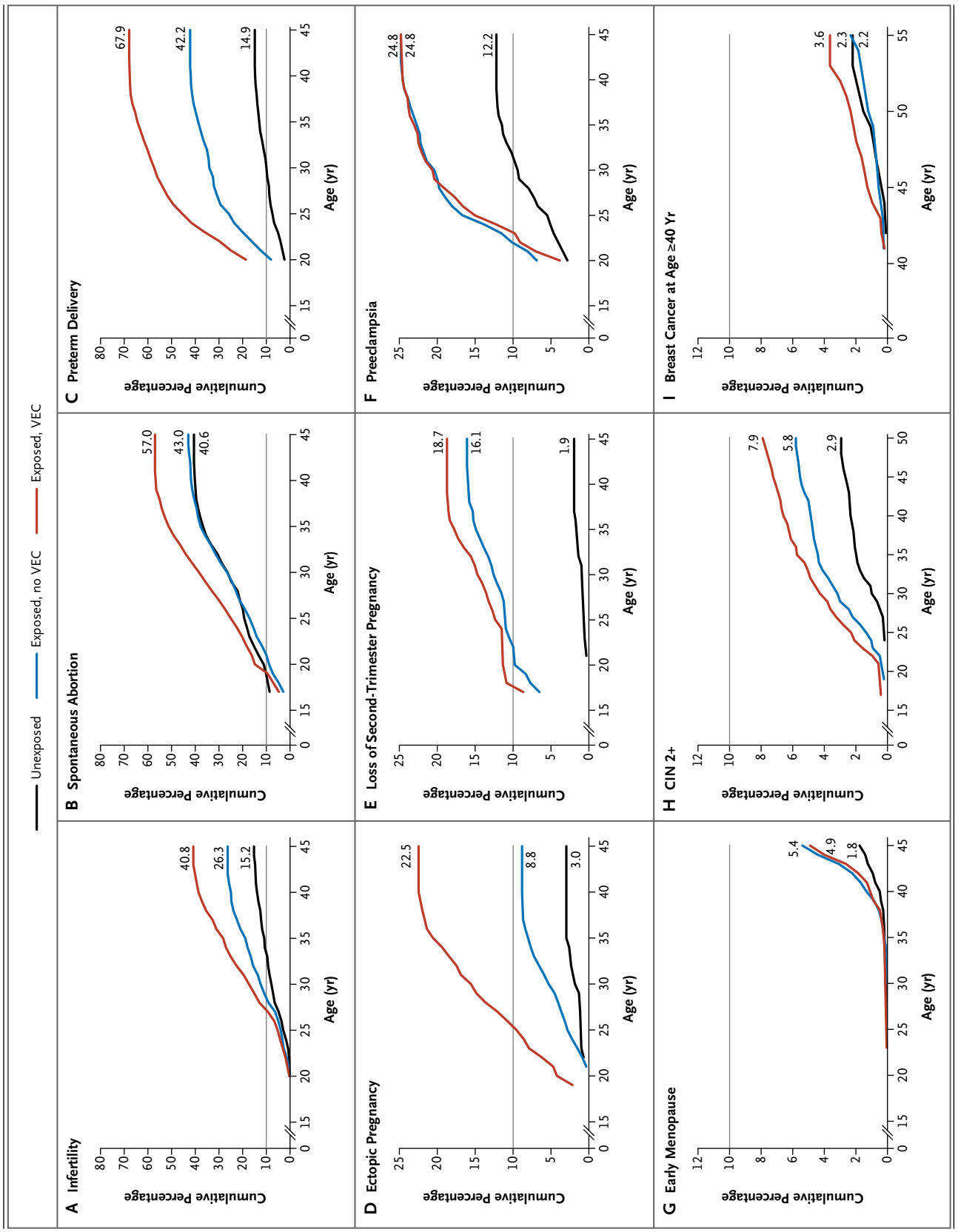

Figure 2 (facing page). Cumulative Risks of Adverse Health Outcomes in the DESAD and Dieckmann Cohorts, According to Diethylstilbestrol (DES) Exposure Status and, in the DES-Exposure Group, the Presence or Absence of Vaginal Epithelial Changes (VEC) at Entry Examination.

All analyses were adjusted for birth year and cohort. For the curves in Panels B, D, and E, data were limited to gravid women, with additional adjustment for the number of pregnancies. For the curves in Panels C and F, data were limited to parous women, with additional adjustment for the number of births. The horizontal line in each panel represents a cumulative percentage of 10% (for reference). VEC status was not available for the WHS cohort. Owing to small numbers of cases of stillbirth, neonatal death, and clear-cell adenocarcinoma, cumulative risks are unreliable and are not included.

vaginal epithelial changes than for women without such changes provides additional support for a causal relationship.

Other studies have assessed outcomes among women exposed to DES but, unlike our study, they did not have medical-record documentation of DES exposure status. Two studies showed an increased risk of uterine fibroids with DES exposure[33,34]; another showed increased risks of depression and endometriosis but not fibroids.[35,36] Our study did not assess the risks of these conditions in association with DES exposure, but we previously reported no significant increase in the risk of fibroids or the risk of depression among DES-exposed women as compared with the risk among unexposed women.[32,37] A recent study of cancer risk in a DES-exposed Dutch population reported no significant increase in the risk of breast cancer as compared with the risk in the general population.[38] The discrepancy between this observation and our findings could be related to differences in study design, chance, or possibly the DES dose; in our study, excess risk was seen primarily among women with vaginal epithelial changes, a condition not assessed in the Dutch study.

Reports of adverse outcomes in humans exposed to DES have stimulated a variety of mechanistic studies in laboratory animals that have shown a link between this exposure and specific structural anomalies, permanent epigenetic and other molecular changes, and compromised immune function. These findings suggest several teratogenic, molecular, and immunologic mechanisms that could underlie the range of pathologic effects observed in humans after in utero DES exposure.[39,40]

Our study linked 12 adverse health outcomes in women to their exposure to DES in utero, with most risks increased by a factor of more than two as compared with the risks among unexposed women, resulting in substantial percentages of the exposed women having outcomes attributable to their exposure. For most outcomes, risks were higher among women with vaginal epithelial changes, a histologic marker of high-dose DES exposure, than for women without this condition. Although DES has not been prescribed for pregnant women in the United States for 40 years, adverse outcomes continue to occur in women exposed in utero, and continued monitoring, as is ongoing in this cohort, for established and unexpected adverse outcomes seems prudent.

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