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Cervical Screening and General Physical Examination Behaviors of Women Exposed In Utero to Diethylstilbestrol

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■ Abstract

Objective. To estimate whether women exposed in utero to diethylstilbestrol (DES) report receiving more cervical and general physical examinations compared to unexposed women.

Materials and Methods. 1994 Diethylstilbestrol Adenosis cohort data are used to assess the degree of recommended compliance of cervical screenings found in 3,140 DES-exposed and 826 unexposed women. Participants were enrolled at 4 sites: Houston, Boston, Rochester, and Los Angeles. Logistic regression modeling was used to analyze mailed questionnaire data, which included reported frequency over the preceding 5 years (1990–1994) of Papanicolaou smears and general physical examinations.

Results. Diethylstilbestrol-exposed women exceeded the recommended frequency of Papanicolaou smear screenings [adjusted odds ratio (aOR) = 2.15, 95% CI (confidence interval) = 1.60–2.88] compared to the unexposed. This association held among those without a history of cervical intraepithelial neoplasia (aOR = 1.88, 95% CI = 1.35–2.62). Diethylstilbestrol-exposed women exceeded annual recommendations for physical examinations (aOR = 2.27, 95% CI = 1.16–4.43) among women without a history of chronic disease when compared to unexposed women.

Conclusions. Most DES-exposed women are receiving cervical cancer screening at least at recommended intervals, but one third of the women are not receiving annual Papanicolaou smear examinations. ■

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Key Words: diethylstilbestrol, physical examination, vaginal smears

In 1971, a strong association was found between in utero exposure to diethylstilbestrol (DES) and the development of clear cell vaginal and cervical adenocarcinoma

[1]. Within the same year, DES use was discontinued and no longer prescribed to maintain pregnancies [2]. Shortly thereafter, the National Cancer Institute (NCI) awarded contracts to 4 geographically separated institutions (Houston, Boston, Rochester, and Los Angeles) to study in utero DES-exposed offspring, leading to the creation of the Diethylstilbestrol Adenosis (DESAD) Project [3, 4]. Several studies have focused on cervical and vaginal changes in this exposed population [3, 5, 6]. This current study examines whether DES-exposed women relative to unexposed women are more likely to receive screening for cervical cancer and other health problems at recommended intervals.

MATERIALS AND METHODS

Patient recruitment has previously been described [3, 4]. Briefly, DES-exposed women were recruited through record review, physician referral, or walk-ins. The unexposed women were recruited from available medical records and from siblings of exposed women, matched on exposed women's ages within 6 months and on mothers' ages during pregnancy within 5 years. At the start of 1975 through 1983, both exposed and unexposed women were examined annually and then followed yearly with a questionnaire from 1984 to 1989 [6, 7]. Again in 1994, self-administered questionnaires were mailed to previous DESAD participants [7]. This study has been reviewed and approved by institutional review boards at each participating study site.

Information describing screening behaviors was obtained from the 1994 questionnaire, including the number of Papanicolaou smears and the number of general physical examinations (GPEs).

Women reported the frequency of Papanicolaou smear screening in the past 5 years in the following ordinal categories: none, once, 2 to 3 times, 4 to 5 times, and more than 5 times. The Department of Health, Education, and Welfare in 1978, the NCI in 1980, and the American College of Obstetricians and Gynecologists in 1994 recommended annual gynecological examinations for DES-exposed women [8–10]. The recommendation for Papanicolaou smear screening for asymptomatic DES-exposed women includes not only the cervical cytology examination but also an extensive vaginal examination, with screening beginning at age 14, 4 years earlier than the recommendation age for unexposed women [8, 10].

Compliance was defined as receiving 4 to 5 Papanicolaou smears in the past 5 years, whereas receiving

more than 5 was defined as exceeding recommendations. These 2 groups were compared with those with fewer than 4 Papanicolaou smears in the past 5 years, which was considered noncompliant. Women with hysterectomies were excluded from the Papanicolaou smear analysis.

For the physical examination component, compliance was defined as having a GPEs 4 to 5 times in the past 5 years, and more than 5 was defined as exceeding recommendations. The reference group was fewer than 4 to 5 examinations in the past 5 years. Annual examinations were categorized as compliant, even though periodic examinations (ranging from once to every 4 years based on age and gender) are recommended by the American College of Physicians and the American Medical Association [11]. However, the reviewed literature at this time has shown that patients expect a complete annual examination, and physicians comply at such a request [12]. Furthermore, setting the compliance level at a yearly examination allowed for more straightforward comparisons across ages in the study population.

The analysis addressed the association between DES exposure and reported frequency of cervical cancer screening and GPEs. Because a personal history of cervical intraepithelial neoplasms (CIN) may result in more frequent Papanicolaou smear screening, the analyses were stratified to assess whether such a history modified the association between DES exposure and frequency of Papanicolaou smear screening. Similarly, women with a chronic disease may be more likely to receive more frequent physical examinations, so the association between DES exposure and frequency of physical examinations was conducted separately by those who did and did not have 1 or more of the specified chronic diseases listed in Table 1. All statistical evaluation was performed using SPSS 11.0 statistical software (SPSS, Inc., Chicago, IL) and EpiInfo 6.04d (Geneva, Switzerland).

Although the parent study used a prospective cohort design, odds ratios (OR) were chosen as the relevant measure of association between DES exposure status and screening frequency in the past 5 years. The dependent outcome variables had 3 frequency levels. Separate binary (i.e., compliant vs. noncompliant and exceeding recommendations vs. noncompliant) logistic regression models were used to estimate the ORs and 95% confidence intervals (CI) for each of the 2 outcome categories that met or exceeded recommendations compared to the reference category [13].

Table 1. Comparison of Exposed and Unexposed Women From the 1994 DESAD Cohort Study in Demographic and Other Factors Associated With Gynecological Screening and Physician Visits

	DES Exposed (n = 3,140)		DES Unexposed (n = 826)	
	No.	%	No.	%
Age, y				
25–29	50	2	0	0
30–34	354	11	30	4
35–39	877	28	263	32
40–44	1,296	41	301	36
45–49	533	17	200	24
50–55	30	1	32	4
Education				
Less than high school and post-high school	402	13	152	18
Junior college	724	23	197	24
4-Year college	1,125	36	257	31
Graduate school	880	28	217	26
Missing	9	0.3	3	0.4
Marital status				
Single	410	13	113	14
Married	2,261	72	591	72
Widowed/divorced/separated	425	14	105	13
Missing	44	1	17	2
Site				
Boston	921	29	321	39
Mayo	588	19	186	23
California	803	26	172	21
Baylor	828	26	147	18
History of CIN ^a				
Yes	672	21	64	8
No	2,058	66	661	80
Missing	410	13	101	12
History of an abnormal Pap smear ^a				
Yes	1,162	37	178	22
No	1,588	51	535	65
Missing	390	12	113	14
History of diagnosis (ever) with a sexually transmitted infection ^b				
Yes	713	23	158	19
No	2,427	77	668	81
History of chronic disease ^c				
Yes	890	28	233	28
No	2,250	72	593	72

DESAD, Diethylstilbestrol Adenosis; DES, diethylstilbestrol; CIN, cervical intraepithelial neoplasms.

^aWomen with hysterectomies were excluded from this comparison (N = 415; exposed = 322 and unexposed = 93); the Yates 2-sided *p* value comparing the prevalence of hysterectomy in exposed and unexposed is 0.44.

^bSexually transmitted infections include a diagnosis of any of the following: herpes, HIV, chlamydia, genital warts, or syphilis.

^cChronic disease includes a diagnosis of any of the following: lupus erythematosus, scleroderma, rheumatoid arthritis, multiple sclerosis, chronic ulcerative colitis, regional enteritis, insulin-dependent diabetes mellitus, thyrotoxicosis, thyroiditis, hyperthyroidism, pernicious anemia, idiopathic thrombocytopenic purpura, Addison disease, Behçet syndrome, temporal arteritis, optic neuritis, asthma, chronic fatigue syndrome, congenital abnormalities (spine/skeleton), or a diagnosis/treatment for depression/mental illness.

Potential confounders for exposure–outcome associations assessed in this study included age (in 5-year categories), marital status (single, married, or widowed/divorced/separated), education (high school and post-high school, junior college, full college, and graduate

school), and study site. All of these were included in the final models as their inclusion resulted in a 10% or greater change between the crude and adjusted estimates for the exposure–outcome association when comparing the crude and adjusted associations [14]. The Breslow–Day test for homogeneity was used to determine whether the association between DES exposure and screening behaviors differed by history of CIN or chronic disease. A 2-sided *p* value of .25 or less was considered evidence of effect-measure modification [13].

The Yates 2-sided *p* value was used to test differences in screening frequency between exposed and unexposed women. Unconditional logistic regression was used to estimate adjusted prevalence ORs for DES and the categories of screening frequency levels. The ordinal variable indicating screening frequency was included in logistic models to assess whether DES exposure was associated with a trend toward increased screening frequency; the Wald 2-sided *p* value test was presented [15].

RESULTS

Response rates for the 1994 questionnaire were high for all centers: 96% of the exposed and 98% of the unexposed women at the Boston Center, 96% of both exposed and unexposed women at the Rochester Center, 84% of the exposed and 91% of the unexposed at the California Center, and 89% of the exposed and 83% of the unexposed women at the Baylor Center.

The total number of study participants who responded to the 1994 questionnaire included 3,140 exposed women and 826 unexposed women, 98% of whom were Caucasian. Among the exposed women who responded to the 1994 questionnaire, 46% were originally recruited into the cohort through record review, 33% through physician referral, and 21% were walk-ins. In the unexposed population, 75% were recruited through record review and 25% were siblings of exposed women.

Diethylstilbestrol-exposed women were similar to unexposed women on study variables with the following exceptions (Table 1): unexposed women were older (unexposed mean age = 42 years, and DES-exposed mean age = 40 years; Yates 2-sided *p* < .0001), whereas DES-exposed women were more highly educated (*p* < .0001) than unexposed women (those whose education did not exceed high school, including nongraduates, and those with post-high school vocational training were compared to those with the higher levels of junior college through graduate school). There was no significant difference between exposed and unexposed women

Table 2. Adjusted Odds Ratios and 95% Confidence Interval for Pap Smear Visits in the Past 5 Years (1990–1994) for DESAD Exposed and Unexposed Women With Intact Uteri

	DES Exposed (n = 2,818)		DES Unexposed (n = 733)		Adjusted OR ^b	95% CI	p for trend ^c
	No.	%	No.	%			
No. of Pap smear visits in past 5 years ^a							
Missing ^d	7	0.2	8	1			
None	60	2	17	2			
Once	167	6	52	7			
2–3 times ^e	601	21	186	25	1.00	REF	
4–5 times ^f	1,381	49	393	54	1.05	0.87–1.27	
>5 times ^g	602	21	77	11	2.15	1.60–2.88	<0.001
Reported history of CIN (n = 732)							
	DES exposed (n = 668)		DES unexposed (n = 64)				
None	7	1	0	0			
Once	31	5	1	2			
2–3 times ^e	102	15	9	14	1.00	REF	
4–5 times ^f	296	44	36	56	0.48	0.22–1.02	
>5 times ^g	232	35	18	28	0.75	0.32–1.77	0.33
Reported no history of CIN (n = 2,709)							
	DES exposed (n = 2,056)		DES unexposed (n = 653)				
None	52	3	16	3			
Once	133	7	51	8			
2–3 times ^e	485	24	175	27	1.00	REF	
4–5 times ^f	1,040	51	353	54	1.05	0.86–1.29	
>5 times ^g	346	17	58	9	1.88	1.35–2.62	0.002

DESAD, Diethylstilbestrol Adenosis; DES, diethylstilbestrol; OR, odds ratio; CI, confidence interval; CIN, cervical intraepithelial neoplasia; REF, reference group.

^aWomen with previous hysterectomies were removed from the analysis (N = 415; exposed = 322, unexposed = 93).

^bAdjusted for age (continuous variable), education, marital status, and study site.

^cThe p value (2-sided) for trend included all 5 outcome frequency categories; none of the frequency categories were combined for the trend test.

^dMissing values indicate a nonresponse to the question regarding number of Pap smear visits in the past 5 years.

^eCategories (none, once, and 2–3 times) were combined to form the reference category.

^fThe category 4–5 times was compared with the reference group and defined as compliant for annual Pap smear screening.

^gThe category more than 5 times was compared with the reference group and defined as exceeding recommendations for annual Pap smear screening.

regarding marital status ($p = .98$). However, DES-exposed women were more likely to report having a history of CIN ($p < .0001$) than unexposed women, history of an abnormal Papanicolaou smear ($p < .0001$), and a diagnosis of a sexually transmitted infection (e.g., herpes, HIV, chlamydia, genital warts, or syphilis) ($p = .03$). There was no significant difference between exposed and unexposed women regarding a history of chronic disease ($p = .97$), BBD ($p = .94$), and hysterectomies ($p = .44$).

Table 2 presents the association between DES exposure and Papanicolaou smear screening frequency. Diethylstilbestrol-exposed women were more likely to exceed recommendations for annual Papanicolaou smear screening [adjusted odds ratio (aOR) = 2.15, 95% CI = 1.60–2.88]. Among women without a reported history of CIN, DES-exposed women were more likely than unexposed women to exceed recommendations for

Papanicolaou smears (aOR = 1.88, 95% CI = 1.35–2.62; p value for trend = .002), whereas among women with a history of CIN, this was not observed.

Among all women, DES exposure was not associated with receiving more general physical visits. However, among women with no history of chronic disease, DES exposure was positively associated with reporting more than 5 visits in the past 5 years (aOR = 2.27, 95% CI = 1.16–4.43; p value for trend = .07) (Table 3), yet DES exposure was not associated with an increased frequency of GPEs among women with a reported history of a chronic disease.

The analysis was also repeated, removing the women who had never had a screening examination within the past 5 years from the noncompliant group, under the assumption that these women maybe fundamentally different than women who have had at least 1 screening

Table 3. Adjusted ORs and 95% Confidence Intervals for General Physical Examinations in the Past 5 Years (1990–1994) in DESAD Exposed and Unexposed Women

	DES Exposed (n = 3,140)		DES Unexposed (n = 826)		Adjusted OR ^a	95% CI	p for trend ^b
	No.	%	No.	%			
No. of physical exams in the past 5 years							
Missing ^c	64	2	23	3			
None	491	16	113	14			
Once	780	25	211	26			
2–3 times ^d	1,005	32	266	32	1.00	REF	
4–5 times ^e	641	20	183	22	0.96	0.79–1.17	
>5 times ^f	159	5	30	4	1.30	0.87–1.96	0.58
Reported history of chronic disease ^g (n = 1,105)							
	DES exposed (n = 878)		DES unexposed (n = 227)				
None	97	11	27	12			
Once	184	21	43	19			
2–3 times ^d	310	35	78	34	1.00	REF	
4–5 times ^e	224	25	59	25	1.03	0.72–1.46	
>5 times ^f	63	7	20	9	0.81	0.47–1.40	0.81
Reported no history of chronic disease ^g (n = 2,764)							
	DES exposed (n = 2,198)		DES unexposed (n = 576)				
None	394	18	86	15			
Once	596	27	168	28			
2–3 times ^d	695	31	188	32	1.00	REF	
4–5 times ^e	417	19	124	21	0.93	0.73–1.17	
>5 times ^f	96	4	10	2	2.27	1.16–4.43	0.07

DESAD, Diethylstilbestrol Adenosis; DES, diethylstilbestrol; OR, odds ratio; CI, confidence interval; REF, reference group.

^aAdjusted for age (continuous variable), education, marital status, and study site.

^bThe p value (2 sided) for trend included all 5 outcome frequency categories; none of the frequency categories were combined for the trend test.

^cMissing values indicate a nonresponse to the question regarding number of general physical examinations in the past 5 years.

^dCategories (none, once and 2–3 times) were combined to form the reference category.

^eThe category 4–5 times was compared to the reference group and defined as compliant for annual, general physical examinations.

^fThe category more than 5 times was compared to the reference group and defined as exceeding recommendations for annual, general physical examinations.

^gChronic disease includes a diagnosis of any of the following: lupus erythematosus, scleroderma, rheumatoid arthritis, multiple sclerosis, chronic ulcerative colitis, regional enteritis, insulin-dependent diabetes mellitus, thyrotoxicosis, thyroiditis, hyperthyroidism, pernicious anemia, idiopathic thrombocytopenic purpura, Addison's Disease, Behçet's Syndrome, temporal arteritis, optic neuritis, asthma, chronic fatigue syndrome, congenital abnormalities (spine/skeleton), or a diagnosis/treatment for depression /mental illness.

examination. This comparison analysis was no different from the original crude and adjusted ORs analysis previously discussed.

DISCUSSION

The results of this study showed that the behavior of women who knew they were exposed to DES in utero but had never had a report of CIN was associated with more than the recommended number of Papanicolaou smear screenings. Diethylstilbestrol exposure was also associated with more than annual physical examinations among those without a history of a chronic disease. It appears that women exposed to DES are aware of their increased risk of such conditions, and this possibly influences their increased rate of screening procedures.

A strength of the DESAD study was its efforts to address the problem of selection bias. To reduce selection bias that may result when study respondents disproportionately include volunteers compared with a more random population-based sample, medical records were linked with live birth data for exposed and unexposed women. Exposed women were then invited to participate in the study [4]. This strategy should have minimized a selection bias that can occur when more health-conscience volunteers are participating in the study, resulting in an OR moving away from the null. Another strength of the DESAD study was its efforts to reduce loss-to-follow-up. All study sites had an interview response rate of at least 80% from the study inception, and some cohorts exceeded a 90% response rate, which is rare in any large study continuing over a period of decades.

Study limitations included the potential for misclassification of the reported frequencies of cervical and physical examinations. Although the DESAD study had an established diagnosis verification system, in the data used for this analysis, screening examinations and health conditions were not verified by pathology or medical reports. Therefore, this study relied solely on self-report of screening and previous health conditions that were examined as potential effect-measure modifiers.

According to previous reports, women tend to overreport the frequency of cervical cancer screening [16–19]. There is no evidence to suggest that DES-exposed women were more likely than unexposed women to overreport the frequency of screening examinations. However, previous data showed that DES-exposed women were more likely than unexposed women to misreport their diagnoses [6]. If DES-exposed women overstated screening frequency to a greater extent than unexposed women, this would bias the OR away from the null; however, if such differential misclassification were the case, we would expect to observe positive associations for both cervical screening and GPEs, but this did not occur.

The lack of insurance information in this study may result in confounding by health-care access. If DES-exposed women were more likely than unexposed women to have insurance and therefore receive more frequent screening, then insurance status, rather than DES exposure, would be the factor that led to more frequent screening. Potential confounding could only be operating if insurance status led to more frequent screening and was more common in DES-exposed women. We attempted to address this issue of potential confounding by adjusting for education and marital status, which are highly correlated with receiving preventive care [20, 21] and being insured [22].

A total of 29% of DES-exposed women were not receiving annual Papanicolaou smear examinations (≤ 2 –3 examinations in the past 5 years) as recommended by the Department of Health, Education, and Welfare; NCI; and the American College of Obstetricians and Gynecologists [8–10]. Among the exposed women who did not meet these recommendations, 21% reported a history of CIN and 34% reported no history of CIN. These percentages are of concern because DES-exposed women are recommended to have annual Papanicolaou smear examinations [8–10]. Future efforts should be focused on prevention by encouraging this exposed

population to comply with their recommended annual cervical and vaginal screenings. Furthermore, periodic reminders from the offices of their attending gynecologists may also increase the number of their annual visits.

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