Factors Associated with a Lack of Pap Smear Utilization in Women Exposed *In Utero* to Diethylstilbestrol

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Abstract

Background: Women in the 1940s–1960s were prescribed diethylstilbestrol (DES), a nonsteroidal estrogen, to prevent miscarriages, but the practice was terminated after it was discovered that the daughters so exposed *in utero* were at increased risk for developing clear cell adenocarcinoma (CCA) of the vagina or cervix at early ages. Pap smear screening is one of the principal methods used to identify tumor development and is necessary in this group of women to maintain their health. Currently, little is known about the factors associated with nonutilization of this screening tool in this high-risk population of women.

Methods: National cohort data from the National Cancer Institute (NCI) DES Combined Cohort Follow-up Study during 1994, 1997, 2001, and 2006 were used to determine which factors were associated with Pap smear screening nonutilization in 2006 among DES-exposed and unexposed women. Self-reported questionnaire data from 2,861 DES-exposed and 1,027 unexposed women were analyzed using binary logistic regression models.

Results: DES exposure, not having a previous gynecologic dysplasia diagnosis, lack of insurance, originating cohort, increasing age, and previous screening behavior were all factors associated with not reporting a Pap smear examination in the 2006 questionnaire, although college education reduced nonutilization.

Conclusions: Understanding which factors are associated with not acquiring a screening exam can help clinicians better identify which DES-exposed women are at risk for nonutilization and possibly tailor their standard of care to aid in the early detection of cervical and vaginal adenocarcinomas in this high-risk group.

Introduction

DIETHYLSTILBESTROL (DES), a synthetic estrogen, was developed in 1938 and prescribed thereafter predominantly to women in the United States in the belief that it would help prevent miscarriages.^{1–3} In 1971, the exposure of the drug *in utero* was first associated with the subsequent rare development in their daughters of clear cell adenocarcinoma (CCA) occurring in the vagina or cervix, after which the US Food and Drug Administration promptly proscribed its use during pregnancy.^{4–6} During the early 1990s, the National Cancer Institute (NCI) combined all DES cohorts under its purview into the single DES Combined Cohorts Follow-up Study. Since then, several studies published through the national diethylstilbestrol adenosis (DESAD) cohort and the

DES Combined Cohorts Follow-up Study have suggested that women exposed *in utero* are also at a slightly increased risk for dysplasia, although to date, no increased rates for the development of invasive squamous cell cancer of the cervix have been detected in this study cohort.^{7–10} However, cancer registry data from the Netherlands and the United States have shown a bimodal occurrence of vaginal or cervical CCA: one caused by *in utero* DES exposure during adolescence and again after menopause, when the general population is also at risk.^{11,12} It has been suggested that there may be a future risk for developing adenocarcinomas in DES-exposed women as they age.^{11,12} Owing to the current and potential future risks of tumorigenesis, the cancer screening practices of DES-exposed women are highly relevant in maintaining their health.

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Even though much has been written about DES-exposed women's gynecologic pathologies, little is documented about the prevention behaviors this high-risk group of women have practiced.^{1,4,5,7-10,13-16} Cancer screening in this group has been inconsistently reported; currently, there is a more than 20-year gap in data reporting since this behavior was last described using baseline results.^{10,13}

Results from the initial DES Combined Cohort Follow-up Study in 1994 showed that women exposed *in utero* are over twice as likely to report at least five more examinations in the past 5 years than unexposed women.¹³ When stratified by a self-reported history of gynecologic dysplasia, DES-exposed women without cervical dysplasia were 88% more likely to exceed screening recommendations than unexposed women, suggesting that exposed women are knowledgeable of their increased risk of gynecologic dysplasia and cancer, which may well influence their screening behavior. A small percentage of DES-exposed and unexposed women did not report any exams during the baseline mailout (0.07% and 0.27%, respectively), with a majority reporting four or more exams in the past 5 years (67.4% and 62.9%, respectively).¹³

Given that DES-exposed women are at a higher risk for vaginal and cervical cancers, their utilization of Pap smear exams is necessary, as preventive care plays an important role in healthy living. In this study, we aimed to determine what demographic and clinical factors (including previous cervical cancer screenings) were associated with a lack of Pap smear utilization in both DES-exposed and unexposed women during the 2006 cohort follow-up. The objective was to provide clinicians who treat women exposed *in utero* to DES with additional insights why many have insufficient cervical cancer screening. This, in turn, could allow the patients' physicians to better identify and possibly tailor their standard of care to aid in the early detection of cancer in this high-risk group of women.

Materials and Methods

This study is a secondary analysis using data collected through the NCI DES Combined Cohort Follow-up Study. This ongoing study is a collective cohort of DES-exposed women across the United States who were identified through previous research projects. Cohort enrollment has been discussed previously.^{7-8,10,14-18}

The largest group of participants came from the original DESAD cohort, assembled in the early 1970s from Boston, Houston, Olmsted County (Mayo Clinic) in MN, and Los Angeles.^{10,14} DES-exposed women were recruited into the study through three primary methods: medical record review, physician referral with written documentation, or volunteer without documentation but physical manifestation of *in utero* exposure.¹⁹ Unexposed women were also recruited through record review at the same sites and were matched by the DES-exposed women's age (± 6 months) and their mothers' age (± 5 years).¹⁹ An absence of *in utero* DES exposure in their medical record was required to be considered an eligible control.¹⁹ Over 4,000 prenatally DES-exposed and unexposed women were enrolled and followed closely for approximately 2 decades (1975-1990), with yearly gynecologic examinations provided during the first 9 years.¹⁰

The Women's Health Cohort Study (WHS), the second cohort, consisted of daughters exposed *in utero* and whose

mothers were from Boston, Lebanon (NH), Olmsted County (Mayo Clinic) in MN, and Portland (ME).²⁰ Eligibility for enrollment required documentation that the daughter was so exposed *in utero*. These daughters were later invited to participate in the DES Follow-up Study.¹⁰

The third group of women had been exposed to DES *in utero* through a pharmaceutical double-blind study. The Dieckmann project was a clinical trial conducted from 1950 to 1952 in Chicago to test the efficacy of preventive DES therapy.²¹ As with the WHS, both DES-exposed and unexposed female offspring during the study period were invited to participate in the combined cohort.

The fourth and final study group came from the Horne cohort. DES-exposed and unexposed daughters of mothers who were treated at an infertility clinic in Boston beginning in 1952 were followed using questionnaire data during the 1980s.¹⁰ Specific details of this study, although not published alone in the literature, have been included in combined data reported through the DES Follow-up Study.

Beginning in 1994, and approximately every 4-5 years since (1997, 2001, 2006) questionnaires were mailed to daughters enrolled in the NCI DES Combined Cohort Follow-up Study.¹⁷ Informed consent was obtained through an assent process by returning the completed questionnaire. All participating sites received approval from their respective internal review boards before initial and current research began. Data collected from the surveys included medical diagnoses, gynecologic history, contraception usage, infertility and pregnancy outcomes, screening practices, and familial cancer diagnoses. Questionnaire data collected at baseline (1994), when women were routinely screened for gynecologic cancers through their study cohorts, and in 2006, when routine examinations were not provided, were utilized to assess the effects of previous routine screening on future screening behaviors. All data were managed through an off-site coordinating center (Westat, Inc., Rockville, MD), which was responsible for all mailed materials, data coding, resolution, entering, and data processing, including data collected through pathology slides and death certificates.

DES-exposed and unexposed women were surveyed on their frequency of Pap smear examinations they had acquired within the past 5 years during the 1994 and 2006 follow-up. Other variables considered in this analysis were the originating study (DESAD, WHS, Horne, and Dieckmann); a self-reported abnormal Pap smear result (1994 only); current reported cervical, vaginal, or vulva dysplasia (2006 only); current reported cancer and familial diagnoses (2006 only); study site; age; race (1994 only); marital (1994 only) and education status (1994 only); and insurance status (2006 only). Variables were also created to analyze any gynecologic precancers, cancers, and familial cancer diagnoses self-reported during the 1994, 1997, and/or 2001 questionnaire timeframes to better assess screening predictability. Participants were eligible in this study if they responded to both the 1994 (baseline) and 2006 Pap smear frequency question.

Since Pap smear recommendations are based on clinical histories, the participants' hysterectomy status was considered when defining nonutilization for this study. Guidelines for cytology screening after a hysterectomy are varied, dependent on the surgery type (partial or whole). Unexposed women with subtotal (or partial) hysterectomies were recommended to follow the same guidelines as the general

population, whereas women with a total hysterectomy can cease their cervical cancer screening after their surgery.^{22–24} It's uncertain whether the unexposed women had a total or partial hysterectomy, since that information was not included in the questionnaire; therefore, any unexposed women with an affirmative response to the hysterectomy question was excluded from the analysis. However, as screening is recommended for DES-exposed women regardless of surgery status, we included all exposed women in the study.²²

During the study period (1994–2006), several changes were made to the American Cancer Society (ACS) guidelines for cervical screening in the general population.^{22–24} Although the DES-exposed women's annual recommendations have not changed, annual Pap smear exams for the general population were revised in 2002 and replaced with staggered recommendations based on previous exam results.²⁵ Given the complexity of the recommendations and the uncertainty of the recommendations discussed between a woman and her physician, compliance would be difficult to ascertain. Therefore, for both DES-exposed and unexposed women, nonutilization was defined as not acquiring a Pap smear exam in the past 5 years.

For the descriptive analysis, the Pearson chi-square test for categorical variables and the Student *t*-test for age (continuous variable) were utilized to identify significant differences between the exposure groups. Factors were considered potential confounders if their *p*-values were less than 0.20.²⁶ Binary logistic regression was chosen to statistically answer the research question of the factors associated with not obtaining a reported Pap smear examination during the 2006 mailout among DES-exposed and unexposed women. A backward-step modeling approach was taken to determine which factors (including previous Pap smear usage in 1994) were independently associated with not receiving a Pap smear examination during the 2006 mailout, with significance defined as a *p*-value less than 0.05 in the final model.²⁷ Subsequent models were further stratified on exposure status

to assess which factors were relevant to each group. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20 software (IBM Corp., Armonk, NY).

Results

Response rates from all four questionnaires were over 85%. The 1994 questionnaire had a response rate of 87.1%; the rate was 91.0% in 1997, 92.9% in 2001, and 88.7% in 2006. Demographically, originating study (*p*-value < 0.001), education (1994) (*p*-value = 0.002), and marital status (1994) (*p*-value = 0.001) were significantly different between DES-exposed and unexposed women (Table 1). The mean age difference was only 0.8 years: DES-exposed 52.1 years (standard deviation [SD] ± 5.3) and unexposed 52.9 years (SD ± 6.4), with median values (interquartile range [IQR]) differing by 1 year (median = 53.0 [49.0, 56.0] and median = 54.0 [50.0, 57.0], respectively). This resulted in significant differences in both parametric and nonparametric testing (*p*-value < 0.001) (results not shown).

The clinical histories of the two cohorts also differed in part. More DES-exposed women reported an abnormal Pap smear exam result at baseline (1994) (*p*-value < 0.001), previously reported dysplasia (*p*-value < 0.001), currently reported dysplasia (2006) (*p*-value = 0.05), previously reported cancer (*p*-value = 0.01), and lack of insurance prevented care (*p*-value = 0.18) when compared to unexposed women (Table 2). Factors that were not statistically different between exposure groups included race (*p*-value = 0.93), current diagnosis of cancer reported (2006 questionnaire) (*p*-value = 0.50), a history of family cancer (*p*-value = 0.89), and current familial cancer diagnosis (2006 questionnaire) (*p*-value = 0.82) (Tables 1 and 2).

The frequency of Pap smear examinations reported in the 1994 baseline questionnaire was similar to the frequency later reported in 2006 (Table 3). Both timeframes revealed

TABLE 1. DESCRIPTIVE COMPARISON OF DEMOGRAPHIC FACTORS (N=3,888)

	Unexposed women: n = 1,027 (26.4%) n (%)	DES-exposed women: n = 2,861 (73.6%) n (%)	Chi-square p-value
Originating study			
DESAD cohort	488 (47.5)	2,315 (80.9)	
WHS	319 (31.1)	208 (7.3)	
Horne study	107 (10.4)	166 (5.8)	
Dieckmann cohort	113 (11.0)	172 (6.0)	<0.001
Education (baseline)			
High school degree or less	170 (16.6)	341 (11.9)	
Post-high school/junior college	231 (22.5)	636 (22.3)	
Undergraduate degree	347 (33.9)	1,044 (36.6)	
Graduate degree or higher	277 (27.0)	834 (29.2)	0.002
Marital status (baseline)			
Not married ^a	324 (32.0)	747 (26.5)	
Married	690 (68.0)	2,074 (73.5)	0.001
Race			
Caucasian	1,006 (98.2)	2,810 (98.3)	
All other races	18 (1.8)	49 (1.7)	0.93

^aThis group includes women who reported being single, widowed, divorced, or separated.

DES, diethylstilbestrol; DESAD, diethylstilbestrol adenosis; WHS, Women's Health Cohort Study.

TABLE 2. DESCRIPTIVE COMPARISON OF CLINICAL HISTORIES IN DIETHYLSTILBESTROL-EXPOSED AND UNEXPOSED WOMEN (N=3,888)

	Unexposed women: n = 1,027 (26.4%) n (%)	DES-exposed women: n = 2,861 (73.6%) n (%)	Chi-square p-value
Ever had a reported abnormal Pap smear (baseline)			
No	710 (70.3)	1,586 (56.7)	
Yes	300 (29.7)	1,213 (43.3)	<0.001
Previously reported diagnosis of cervical, vaginal, or vulva CIS/dysplasia ^a			
No	892 (88.1)	1,943 (70.3)	
Yes	120 (11.9)	819 (29.7)	<0.001
Current reported diagnosis of cervical, vaginal, or vulva CIS/dysplasia (2006)			
No	986 (96.0)	2,702 (94.4)	
Yes	41 (4.0)	159 (5.6)	0.05
Previously reported diagnosis of cancer ^a			
No	978 (95.5)	2,649 (93.2)	
Yes	46 (4.5)	193 (6.8)	0.01
Current reported diagnosis of cancer (2006)			
No	992 (96.6)	2,750 (96.1)	
Yes	35 (3.4)	111 (3.9)	0.50
Previously reported familial cancer diagnosis ^a			
No	402 (41.2)	1,117 (41.5)	
Yes	573 (58.8)	1,575 (58.5)	0.89
Current reported diagnosis of familial cancer (2006)			
No	1,000 (98.7)	2,740 (98.8)	
Yes	13 (1.3)	33 (1.2)	0.82
Lack of insurance prevented care (2006)			
No	927 (91.9)	2,536 (90.4)	
Yes	82 (8.1)	268 (9.6)	0.18

^aReported in the 1994, 1997, and/or 2001 questionnaires.
CIS, carcinoma in situ.

that the vast majority (over 95%) of DES-exposed and unexposed women reported one or more Pap smear examinations within the past 5 years (Table 3). Within both timeframes, there was a significant difference between exposure groups and frequency of reported Pap smear exams in the past 5 years (p -value=0.01). Interestingly, the unadjusted effect estimates reversed over the two time periods. In 1994, DES-exposed women were 43% less likely to report no Pap smear exam in

the past 5 years; in 2006, DES-exposed women were 78% more likely to not report obtaining a screening exam in the past 5 years when compared to unexposed women.

Overall, several demographic factors were significantly associated with nonutilization of cervical cancer screening. Women exposed *in utero* to DES were approximately three times more likely to report nonutilization when compared to unexposed women (odds ratio [OR]=2.72, 95% confidence interval [CI] 1.62–4.57; p -value<0.001) (Table 4). Education is an important factor, with an undergraduate (OR=0.43, 95% CI 0.25–0.75; p -value=0.003) or a graduate (OR=0.51, 95% CI 0.30–0.89; p -value=0.02) degree reducing the likelihood of reporting no Pap smear utilization by 57% and 49%, respectively, when compared to participants with a high school diploma. In addition, increasing age had a positive association with nonutilization (OR=1.08, 95% CI 1.04–1.13; p -value <0.001). Lastly, study origin was associated with a lack in reporting screening exams, with women from the Dieckmann study being 89% more likely to not report usage compared to women enrolled in the initial DESAD cohort study (OR=1.89, 95% CI 1.05–3.39; p -value=0.03).

Clinical factors were also associated with not reporting a Pap smear exam in the past 5 years during the 2006 follow-up. Women who reported no history of dysplasia were 76% more likely to not report Pap smear utilization in the past 5 years compared to women who did report a history of dysplasia (OR=1.76, 95% CI 1.09–2.85; p -value=0.02). Additionally, women who reported that a lack of insurance prevented care were 3 times as likely to not utilize cervical screening exams compared to women who did not report insurance being an issue in obtaining care (OR=3.06, 95% CI 1.97–4.74; p -value<0.001). Lastly, women who did not report any Pap smear exams in the past 5 years at baseline were over 12 times as likely to not report any Pap smear exams in the past 5 years during the 2006 follow-up (OR=12.42, 95% CI 7.31–21.11; p -value <0.001).

After stratification, unexposed women had fewer factors associated with Pap smear nonutilization than DES-exposed women. Unexposed women were 7 times more likely to not acquire a Pap smear exam if they reported a lack of insurance prevented care than unexposed women who did not (OR=7.36, 95% CI 2.97–18.23; p -value <0.001) (Table 5). The other factor associated with nonutilization in the unexposed group was not reporting a Pap smear exam at baseline (OR=13.28, 95% CI 4.84–36.49; p -value <0.001) when compared to unexposed women who did report use. Among the DES-exposed group, other factors were significantly

TABLE 3. UNADJUSTED EFFECT ESTIMATES FOR PAP SMEAR NONUTILIZATION AND DIETHYLSTILBESTROL EXPOSURE IN 1994 AND 2006 (N=3,888)

Number of Pap smear examinations in the past 5 years	Unexposed women: n = 1,027 (26.4%) n (%)	DES-exposed women: n = 2,861 (73.6%) n (%)	OR	95% CI	p-value
1994					
One or more	990 (96.4)	2,801 (97.9)			
None	37 (3.6)	60 (2.1)	0.57	0.38–0.87	0.01
2006					
One or more	1,003 (97.7)	2,744 (95.9)			
None	24 (2.3)	117 (4.1)	1.78	1.14–2.78	0.01

CI, confidence interval; OR, odds ratio.

TABLE 4. BINARY LOGISTIC REGRESSION MODEL OF SIGNIFICANT FACTORS RELATED TO NOT REPORTING PAP SMEAR USAGE OVER THE PAST 5 YEARS IN 2006 (N=3,693)

<i>Factor</i>	<i>Number frequency</i>	<i>OR</i>	<i>95% CI</i>	<i>p-value</i>
DES exposed	2,700	2.72	1.62–4.57	<0.001
Education				
High school or less	490	Ref	Ref	Ref
Post-high school or junior college	824	0.88	0.54–1.45	0.62
Undergraduate school	1,329	0.43	0.25–0.75	0.003
Graduate school	1,050	0.51	0.30–0.89	0.02
Age (2006)	3,693	1.08	1.04–1.13	<0.001
DESAD cohort	2,648	Ref	Ref	Ref
WHS cohort	518	0.99	0.57–1.72	0.97
Horne study cohort	265	0.93	0.26–3.39	0.91
Dieckmann study cohort	262	1.89	1.05–3.39	0.03
No reported prior dysplasia diagnosis ^a	2,765	1.76	1.09–2.85	0.02
Lack of insurance prevented care (2006)	341	3.06	1.97–4.74	<0.001
No Pap smear examinations (baseline)	92	12.42	7.31–21.11	<0.001

^aReported in the 1994, 1997, and/or 2001 questionnaires.
Ref, reference.

associated with nonutilization. Undergraduate (OR=0.44, 95% CI 0.24–0.81; *p*-value=0.01) and graduate education (OR=0.52, 95% CI 0.28–0.95; *p*-value=0.04) reduced the likelihood of reporting no Pap smear utilization when compared to women with a high school diploma (Table 5). Exposed women who reported that a lack of insurance prevented care were over twice as likely to not report an exam during the 2006 follow-up compared to women who did not report such an issue (OR=2.40, 95% CI 1.46–3.95; *p*-value=0.001). Similarly, women who did not report a Pap smear exam at baseline were over 14 times as likely to not report an exam during the 2006 follow-up (OR=14.59, 95% CI 8.03–26.51; *p*-value<0.001) when compared to exposed women who did report an exam. Increasing age also had a positive association with nonutilization (OR=1.10, 95% CI 1.05–1.15; *p*-value<0.001).

Discussion

Cervical cancer should rarely occur in women who undergo regular Pap smear screening.²⁴ Typically, most vaginal and cervical CCAs occur later in life, except in DES-exposed women where these glandular are commonly diagnosed

within the first few years of adolescence. It's uncertain whether this group of DES-exposed women will experience a second peak in cancer incidence rates as they age and enter the same risk period as the general population.^{11,12} Owing to this increased risk, yearly cervical cancer screening guidelines have been implemented for these exposed women, which is prudent for monitoring and maintaining their health. The factors associated with nonutilization of Pap smear screening exams in both DES-exposed and unexposed women were exposure status, education level, increasing age, study origin, past self-reported history of dysplasia, insurance status, and previous Pap smear nonutilization at baseline.

Earlier studies have also identified relationships between a lack of education, insurance status, age, and the inability to obtain a cancer screening examination.^{28–36} Our study found similar results, with a college education reducing the nonutilization of screening practice. A lack of insurance was also related to nonutilization as other studies have identified, although in this study population, insurability was high (over 90%).^{29,32–36} Another factor is age. In this analysis, as age increases, Pap smear usage decreases. Others report similar findings that as women age, cancer screenings decline.^{28,31–36} The DES-exposed women were on average age 52 at the time

TABLE 5. BINARY LOGISTIC REGRESSION MODELS FOR SIGNIFICANT FACTORS RELATED TO NOT REPORTING PAP SMEAR USAGE IN 2006 AMONG BOTH DIETHYLSTILBESTROL-EXPOSED AND UNEXPOSED WOMEN (N=3,807)

<i>Factor</i>	<i>Unexposed women: n=1,009</i>				<i>DES-exposed women: n=2,798</i>			
	<i>Number frequency</i>	<i>OR</i>	<i>95% CI</i>	<i>p-value</i>	<i>Number frequency</i>	<i>OR</i>	<i>95% CI</i>	<i>p-value</i>
Education								
High school or less	—	—	—	—	336	Ref	Ref	Ref
Post-high school or junior college	—	—	—	—	620	1.02	0.58–1.80	0.93
Undergraduate school	—	—	—	—	1,024	0.44	0.24–0.81	0.01
Graduate school	—	—	—	—	818	0.52	0.28–0.95	0.04
Lack of insurance prevented care (2006)	82	7.36	2.97–18.23	<0.001	268	2.40	1.46–3.95	0.001
No Pap smear examinations (baseline)	36	13.28	4.84–36.49	<0.001	59	14.59	8.03–26.51	<0.001
Age (2006)	—	—	—	—	2,798	1.10	1.05–1.15	<0.001

Items marked — were not included in the final model.

of the 2006 follow-up. In the US general population, vaginal and cervical clear cell cancer is typically diagnosed in women over 50 years of age; it is uncertain today whether the DES-exposed population of women will experience a new spike in cancer development (bimodal incidence rate) as they age.^{3,37} In addition, given that invasive squamous cell cancers typically develop in older women, annual Pap smear screening is still highly recommended among DES-exposed women, notwithstanding that screening standards may shift now that the Food and Drug Administration is permitting primary human papillomavirus (HPV) screening.³⁸

The origin of the cohort was also associated with nonutilization. Participants who were enrolled through the Dieckmann randomized trial were more likely to lack cervical cancer screening exams compared to DESAD study participants. Demographics from the original study population in the Dieckmann project were never published.²¹ When reviewing their demographics within our current study, Dieckmann participants reported that a lack of insurance prevented care more often (11.6% vs. <10.0%) and were more racially diverse (7.7% vs. <2.0%), potentially contributing to the screening differences.

One important, relevant factor associated with screening nonutilization was DES-exposure status. In one study, only 56% of the primary care physicians (PCPs) considered DES exposure moderately important when determining screening interval length among low-income women.³⁹ If under half the clinicians do not consider DES exposure an important factor in interval screening, this known high-risk group of women may not know the importance and recommendation of annual Pap smear exams. Results from this study show that DES exposure triples the odds for Pap smear nonutilization, making this group of women more vulnerable to gynecological cancer risk. Perhaps one explanation for our finding is that DES-exposed women may have become exhausted with the yearly screening process. Given the possible lack of recommendation knowledge in the PCP group in regard to DES exposure, DES-exposed women's apparent fatigue with cervical cancer screening and their increasing age, the public health implications of these occurrences could be considerable, given the potential for increased gynecological cancer cases and medical costs.⁴⁰

Past reported screening behavior appears predictive of more current behavior, with women more likely to not utilize screening exams in 2006 if they did not report obtaining a baseline Pap smear examination. These results are not uncommon, as past behavior has been linked to current behavior in psychologic studies, with the frequency of past behavior strengthening accrued habits.⁴¹⁻⁴² Implementing change in old behaviors may be difficult to achieve; possibly new behaviors can be encouraged with short-term rewards.⁴² Additionally, not reporting a prior (1994, 1997, or 2001) dysplasia diagnosis increased the chances for future nonutilization, which may suggest that a lack of dysplasia history may prevent women from obtaining future examinations.

In comparison, several study factors were not associated with reported Pap smear nonutilization during the 2006 follow-up. Although reported marital status is subject to change, baseline relationships did not appear to be associated with screening nonutilization in this study, despite findings in other studies, which have shown a relationship between marriage, health insurance acquisition, and obtaining screening examinations.^{28,43-46} Additionally, not having reported an abnormal

Pap smear examination result at baseline, not reporting a current dysplasia diagnosis (2006 questionnaire), and not reporting a previous cancer diagnosis did not appear to influence later screening behavior in this population of women. This may suggest that the timing of various diagnoses could influence future screening behaviors.

This secondary data analysis has certain limitations. The Pap smear responses were not verified through medical record review. The research question was also framed within a 5-year context and could lend itself to a nondifferential misclassification bias through inaccurate reporting. Details regarding any follow-up Pap smear exams were excluded from the questionnaire, which could distort the actual number of exams listed. Yet, comparing "none" to "any" exams should not differentially affect the behavior of nonutilization and the total of Pap smear exams obtained. The type of hysterectomy (partial or whole) the women received was also not included in the survey. This may mean that unexposed women were unnecessarily excluded from the study, which may potentially move the effect estimate away from the null.

Despite the limitations, there are a number of study strengths. Although this is a secondary data analysis, the parent study is a cohort design, which reduces the recall bias often found in other studies.⁴⁷ As questionnaire data are collected over time, the coordinating center has taken additional steps to ensure accuracy and completeness. Lastly, the study sample is highly representative of the DES population as a whole, since participants were recruited across the United States and were predominantly of one race (Caucasian).³⁶

Although we identified several factors that contributed to not obtaining a Pap smear examination, future studies could benefit from the following recommendations. Within this population of high-risk women, both DES-exposed and unexposed women should be directly asked how they assess their own personal risk for cancer, given their exposure status. Currently, it is only assumed that DES-exposed women are aware of their increased risk of cervical and vaginal cancer, based on their high rate of Pap smear examinations.¹³ This added information can help develop for this study population the theoretical framework that motivates their preventive screening practices.⁴⁸ It could also be beneficial to ask women whether they have access to regular gynecologic care, as this could be an important factor in screening utilization. Lastly, frequency questions regarding screening examinations could be written in an open-ended format. This would allow for more statistical options, thereby improving statistical efficiency.⁴⁹

Conclusions

This research found several factors associated with not acquiring a Pap smear examination among high-risk women enrolled in the NCI DES Combined Cohort Follow-up Study. Overall, not having a previous self-reported gynecologic dysplasia diagnosis, a lack of insurance preventing care, DES exposure, originating cohort (Dieckmann study), increasing age, and previous nonutilization screening behaviors were all factors associated with not reporting a Pap smear examination in the 2006 questionnaire. Conversely, obtaining an undergraduate or graduate degree reduces the likelihood of not acquiring an exam. As this cohort ages, it is uncertain whether another spike in vaginal or cervical clear cell

adenocarcinoma incidence will occur, making screening examinations necessary in maintaining their health. Understanding which factors are associated with not acquiring a screening exam can help clinicians better identify which DES-exposed women are at risk for nonutilization and possibly tailor their standard of care to aid in the early detection of cervical and vaginal adenocarcinomas found in this high-risk group.

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