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Identification of Risk Factors for Diethylstilbestrol-associated Clear Cell Adenocarcinoma of the Vagina: Similarities to Endometrial Cancer

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This epidemiologic case-control study describes risk factors for clear cell adenocarcinoma of the vagina among 106 cases and 447 controls with in utero exposure to diethylstilbestrol (DES). Controlling for age, socioeconomic status, and time during gestation of initial DES exposure, the authors found a significantly increased risk of this cancer in women who were taller or more obese then their contemporaries at age 14–15 years. The relative risk of this cancer for women in the highest tertile for height compared with those in the lowest tertile was 2.5 (95% confidence interval 1.23–4.90). The relative risk from a similar comparison of body mass was 2.8 (95% confidence interval 1.20–6.53). Trend tests indicated that both factors had significant dose-response relations with risk of vaginal clear cell adenocarcinoma. These findings are particularly interesting since height and body mass are risk factors for endometrial cancer. DES-positive cases interviewed more than 10 years after diagnosis were also significantly thinner than cases interviewed less than 7 years after diagnosis ($p = 0.01$), providing the first evidence that adolescent adiposity level is associated with survival times for women with this disease. *Am J Epidemiol* 1991;134:1316–24.

body height; body mass index; diethylstilbestrol; vaginal neoplasms

Women who take diethylstilbestrol (DES) during pregnancy significantly increase their daughters' risks for clear cell adenocarcinoma of the vagina and cervix (1–3). Additional risk factors for this disease among daughters exposed in utero to DES include early exposure, maternal history of spontaneous abortion prior to the index pregnancy, birth weight of 5.5 or fewer pounds, and birth during the autumn (4). Early in utero exposure to DES has also been associated with the development of both vaginal adenosis and cervical ectropion (5, 6). The distribution of induction periods for both cancers suggests that in utero DES exposure causes both adenosis and an increased susceptibility to a second agent acting at the time of puberty (7–9). Studies of DES-exposed rodents also suggest the presence of a puberty-linked hormonal component in the etiology of this adenocarcinoma (10–12).

Similarities between the tuboendometrial cells associated with vaginal adenosis and cells normally found in the endometrium (13) have been reported, as well as similarities between genital tract clear cell adenocarcinomas and endometrial adenocarcino-

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Abbreviations. CI, confidence interval; DES, diethylstilbestrol, DESAD, Diethylstilbestrol Adenosis Study, RR, relative risk.

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mas (14). Our study is the first to investigate whether some of the major risk factors for endometrial cancer are risk factors for vaginal clear cell adenocarcinoma among DES-positive women.

MATERIALS AND METHODS

Selection of cases

Cases were drawn from 366 predominantly US-born women who developed vaginal or indeterminate vaginal-exocervical clear cell adenocarcinoma and who were accessioned by the DES Registry at the University of Chicago 1971–1983 (table 1). The DES Registry has attempted to accession all cases of this disease occurring in women born after 1940 regardless of maternal DES exposure (15, 16). After pathology reports and slides were reviewed, cases were classified as vaginal or cervical based on site of tumor origin (16). If the tumor included both sites, or if for some other reason the site of origin was not clear, a case was classified as indeterminate vaginal-exocervical (16). We sent questionnaires to 193 women classified as either vaginal or indeterminate vaginal-exocervical cases, excluding cervical cases from the study because of differences in the etiologies of vaginal and cervical clear cell adenocarcinoma (16, 17). A total of 152 subjects (79 percent) participated (table 1). Because the number of nonwhite respondents was small, these were excluded (table 1).

TABLE 1. Vaginal/vaginal-exocervical cases and controls, United States, 1971–1983

Characteristic	Registry cases	Controls	
		Dieckmann cohort	DESAD* cohort
Number in group	366	408	353
Dead, lost to follow-up, or unavailable	173	105	53
Contacted	193	303	300
Participating			
Number (%)	152 (79)	222 (73)	234 (78)
White race, DES*-positive	106	213	234
White race, DES-negative or DES-unknown	44†	0	0
Nonwhite‡	2	9	0

* DESAD, Diethylstilbestrol Adenosis Study; DES, diethylstilbestrol.

† Of these, five were DES-negative; the rest had an unknown DES exposure history.

‡ Because of small numbers, nonwhite respondents were excluded from all analysis.

A case was classified DES-positive if the mother's written obstetric, hospital, or pharmacy records noted that she took DES (or the similar compounds dienestrol or hexestrol) during her daughter's gestation, if she remembered taking DES, or if her obstetrician remembered prescribing DES during the index pregnancy. Our decision to include women who were DES-positive by recall alone was supported by a high rate of agreement between the memories of mothers who said they took DES and their written obstetric records (18). Analysis was confined to the 106 cases identified as DES-positive by these criteria (table 1).

Selection of controls

Because we sought to identify promotional factors for this vaginal cancer, our study was limited to DES-positive cases and controls. Ideally, we would have selected controls by matching them by birth site of cases, establishing their DES exposure status exactly as for cases, and then excluding DES-negative subjects. However, the rarity of in utero DES exposure made this impractical. Instead, controls were drawn from two cohorts of women who had been classified as DES-positive in earlier studies.

One control group was derived from the Dieckmann cohort, which consisted of daughters of pregnant women who took DES during a clinical trial conducted at the University of Chicago 1950–1952 (19). We sent questionnaires to 303 of the initial cohort of 408 DES-positive daughters for whom maternal DES therapy records were available; the remainder were deceased, lost to follow-up, or unavailable for contact. In all, 222 subjects participated (73 percent), and 213 white respondents were included in this study (table 1).

A second control group was derived from the Diethylstilbestrol Adenosis Study

(DESAD) cohort, which consisted of Houston-born DES-positive participants in the multicenter DESAD begun in the mid-1970s (20). DESAD investigators in Houston surveyed 118,185 maternity records from volunteer physicians who remembered prescribing DES. We sent questionnaires to 300 of the original 353 DES-positive participants. The others were deceased, lost to follow-up, or unavailable for contact; 234 white DESAD subjects (78 percent) participated (table 1).

Questionnaire design and data analysis

Up to three copies of a self-administered, 20-minute-long questionnaire were mailed to subjects. Each subject was asked if she was "underweight," of "average weight," or "overweight" at the time of her first period, and her weight and height at the beginning of high school, when she would have been 14–15 years old. Quetelet body mass index (weight in kg)/(height in m^2) was calculated, and both height and body mass scores were trichotomized according to their distributions among controls. Unconditional logistic regression was used to estimate odds ratios adjusted for year of birth, week of initial DES exposure during gestation, and mother's length of formal education as a measure of social class (21). Week of initial DES exposure during gestation was entered in logistic models as weeks 1 through 12, with later dates of DES initiation comprising a single category. Maternal education was entered as categories <12 years, 12 years, or ≥13 years. Coding education as a continuous variable, and also including paternal education in the model, did not affect results. To increase the likelihood that information concerning cases pertained to the time preceding cancer diagnosis, cases diagnosed before age 16 years were excluded from most analyses. Since relative risk estimates were similar for both sets of controls, we combined them into a single control group. The overall effects of height and body mass were evaluated using the Mantel extension test for linear trend, calculating two-tailed p values (22).

To examine interaction between height and body mass and vaginal cancer, height and body mass scores were also dichotomized according to their distributions in the control group. We confined analysis to white, DES-positive subjects and cases diagnosed at age 16 years or later and interviewed within 10 years of diagnosis, and compared shorter and thinner subjects to subjects who were either taller or more obese, or both. Relative risks and 95 percent confidence intervals were calculated controlling for year of birth, week of first in utero DES exposure, and maternal education.

Because this study relied on prevalent cases, it disproportionately favored cancer survivors. To assess whether factors associated with case status were risk factors for disease rather than prognostic factors for survival, risk factors were compared according to follow-up times. DES-positive cases were divided into three approximately equal groups based on the length of time from diagnosis to interview. We compared adolescent body mass and height for cases diagnosed the longest and shortest times before interview.

RESULTS

Relation of adiposity to survival

Cases interviewed 11 or more years after diagnosis were found to be significantly thinner, not more obese, than those interviewed less than 7 years after diagnosis (mean scores: 19.4 kg/m^2 and 21.0 kg/m^2, respectively; $p = 0.01$) (table 2). Mean weight at the start of high school was also significantly lower for cases surviving at least 11 years (11 or more years: 52.2 kg; less than 7 years: 57.0 kg; $p = 0.03$) (table 2). Adolescent height was not significantly associated with length of follow-up ($p = 0.49$) (table 2). No significant correlations were found between age at diagnosis and either adolescent height

TABLE 2. Follow-up times from diagnosis to interview for DES*-positive cases: relation to body mass, weight, and height, United States, 1971–1983

Physical parameter at start of high school	Follow-up time (years)			p value†	Pearson r	No.
	1–6	7–10	≥11			
Mean body mass (kg/m^2)	21.0	21.8	19.4	0.01	−0.17	98
Mean weight (kg)	57.0	58.7	52.2	0.03	−0.15	98
Mean height (cm)	164.7	163.4	163.5	0.49	−0.08	103

* DES, diethylstilbestrol.
† Two-tailed *t* tests comparing cases with shortest and longest follow-up times.

or adiposity level ($r = 0.05$ and 0.10, respectively). The apparently reduced survival times for subjects who were heavier during adolescence decreased adiposity-related relative risks of vaginal cancer. To reduce the effects of this bias and obtain more accurate relative risk estimates, cases diagnosed more than 10 years before interview were excluded from obesity-related analyses.

Body mass and height as risk factors

Cases diagnosed at age 16 years or later tended to be more obese than controls at both menarche and start of high school (table 3). At both times, DES-positive subjects who recalled being of average weight or who had a midrange adiposity score tended to be at increased risk for the vaginal tumor compared with the thinnest women (adjusted relative risk (RR) = 1.5, 95 percent confidence interval (CI) 0.50–4.60; and adjusted RR = 1.8, 95 percent CI 0.75–4.55, respectively) (table 3). This risk increased when women who classified themselves as overweight or had body mass indexes in excess of 20.4 kg/m^2 were compared with the thinnest women (adjusted RR = 1.8, 95 percent CI 0.78–7.98; and adjusted RR = 2.8, 95 percent CI 1.20–6.53, respectively) (table 3). Two-sided trend test *p* values from the Mantel extension tests were 0.10 for weight classification at menarche and 0.01 for adiposity level at start of high school (table 3).

Among DES-positive women, those of medium height at the beginning of high school were at increased risk of the vaginal cancer compared with the shortest women (adjusted RR = 2.1, 95 percent CI 0.98–4.63), and this risk increased when the women in the tallest group were compared with those in the shortest group (adjusted RR = 2.5, 95 percent CI 1.23–4.90) (χ^2, trend test = 5.81 , $p = 0.02$) (table 3).

Body mass and height at the beginning of high school were each significantly associated with the vaginal tumor when both risk factors were included in the same logistic model with confounders (table 4). Excluding cases diagnosed before age 16 years or interviewed more than 10 years after diagnosis, the multiplicative constant derived from the logistic model per 1 kg/m^2 increase in adiposity level was 1.14 (95 percent CI 1.04–1.25) (table 4). Thus, the risk of the vaginal cancer among women at the 75 percent level of the distribution of adiposity scores for white controls (21.3 kg/m^2) compared with women at the 25 percent level (18.3 kg/m^2) was $1.14^{(21.3-18.3)} = 1.14^3 = 1.5$. The multiplicative constant per 1 cm increase in height was 1.06 (95 percent CI 1.02–1.12) (table 4). The heights and Quetelet indexes of our subjects were not significantly correlated ($r = 0.02$, $p = 0.73$). Comparing the recalled heights of our subjects at the beginning of high school with the heights of a randomly selected group of 16-year-old, white, US females who were measured between 1966 and 1970, we found that our controls had the same mean height (162 cm) as the national sample (23). The recalled mean height of cases interviewed less than 7 years after diagnosis was 164.7 cm (table 2).

Comparing the more obese and taller subjects with the thinner and shorter subjects, we found little or no interaction on either the multiplicative or additive scales between

TABLE 3. Numbers of DES*-positive cases and controls, according to body mass index and height, United States, 1971–1983†

Characteristic	Cases‡	Dieckmann controls	DESAD* controls	Crude relative risk	Adjusted relative risk§	95% confidence interval	χ^2, Mantel extension (p value)‖
Weight at menarche							
Underweight¶	5	29	26	1.0	1.0		2.70
Average weight	50	140	164	1.8	1.5	0.50–4.60	(0.10)
Overweight	19	44	44	2.4	1.8	0.78–7.98	
Body mass at start of high school							
<18.6 kg/m^2¶	13	68	70	1.0	1.0		6.20
18.6–20.4 kg/m^2	24	62	78	1.8	1.8	0.75–4.55	(0.01)
>20.4 kg/m^2	32	71	72	2.4	2.8	1.20–6.53	
Height at start of high school							
<158 cm (62.2 inches)¶	19	68	77	1.0	1.0		5.81
158–164 cm (62.2–64.6 inches)	29	54	69	1.8	2.1	0.98–4.63	(0.02)
≥165 cm (65.0 inches)	45	86	80	2.1	2.5	1.23–4.90	

*DES, diethylstilbestrol; DESAD, Diethylstilbestrol Adenosis Study.
† Because relative risks were similar when calculated separately using each control group, control groups were combined for this analysis.
‡ To help insure that precancer weights and heights were studied, analysis was restricted to 95 cases diagnosed at age 16 years or later. In addition, because of a strong relation between obesity and case survival, the analysis relating to menarche weight and high school body mass was further restricted to 74 cases interviewed within 10 years of diagnosis.
§ Adjusted for year of birth, socioeconomic status (maternal education: <12, 12, or ≥13 years), and week of initial maternal DES exposure (1 through 12 or ≥13).
‖ Two-tailed test
¶ Reference category.

TABLE 4. Relative risks, confidence intervals, and p values for body mass and height risk factors obtained from the multiple logistic model, DES*-positive subjects, United States, 1971–1983†

Characteristic	Level	Relative risk per one unit change‡	95% confidence interval	p value
Body mass (kg/m^2)	Range: 13.7–33.0	1.14	1.04–1.25	0.007
Height (cm)	Range: 134–180	1.06	1.02–1.12	0.009
Week of initial DES exposure during pregnancy	1 to 12, ≥13	0.78	0.68–0.89	0.0002
Year of birth	In years	1.10	1.02–1.19	0.01
Maternal education (years)	<12, 12, ≥13	0.52	0.34–0.80	0.003

* DES, diethylstilbestrol.
† Analysis was restricted to 74 cases diagnosed at age 16 years or later and interviewed within 10 years of diagnosis.
‡ For example, the relative risk of vaginal/vaginal-exocervical clear cell adenocarcinoma for women at the limits (75%, 25%) of the interquartile range of heights for white controls is $1.06^{(166\,cm-156\,cm)} = 1.06^{10} = 1.8$

adolescent body mass and height in their relation with the vaginal tumor (table 5).

Education

Mothers of cases had a mean 12.6 years of education, which was less than either the mean 13.1 years ($p = 0.06$) for mothers of Houston-born controls and the mean 13.1 years ($p = 0.08$) for mothers of Chicago-born controls. Fathers of cases had a mean 13.2 years of education, significantly less than either fathers of the Houston-born con-

TABLE 5. Numbers of DES*-positive cases and controls, according to dichotomized adolescent body mass indexes and heights, United States, 1971–1983†

Characteristic	Cases	Controls	Crude relative risk	95% confidence interval	Adjusted relative risk‡	95% confidence interval
Shorter/thinner§	3	101	1.0		1.0	
Taller/thinner	17	105	5.4	1.74–17.09	3.5	0.90–13.72
Shorter/more obese	17	103	5.6	1.78–17.39	2.9	0.76–11.19
Taller/more obese	31	112	9.3	3.31–26.25	7.4	2.13–25.54

* DES, diethylstilbestrol

† Body mass indexes were 13.7–19.2 kg/m^2 for "thinner" subjects and 19.3–33.0 kg/m^2 for "more obese" subjects. Heights of "shorter" subjects were 134–161 cm and heights of "taller" subjects were 162–180 cm. Analysis was restricted to 74 cases diagnosed at age 16 years or later and interviewed within 10 years of diagnosis.

‡ Adjusted for year of birth, socioeconomic status (maternal education: <12, 12, or ≥13 years), and week of initial maternal DES exposure (1 through 12 or ≥13).

§ Reference category.

trols (14.0 years; $p = 0.003$) or fathers of the Chicago-born controls (14.3 years; $p = 0.03$).

DISCUSSION

Several new and potentially important findings come from this study. Increased adiposity and height during adolescence appear to be strong, independent, but not interactive risk factors for vaginal clear cell carcinoma among women with in utero exposure to DES. Both factors have a significant dose-response relation to this cancer, with moderately obese and tall women being at greater risk than thinner and shorter women.

A third important finding was that DES-positive cases interviewed more than 10 years after diagnosis were significantly thinner at adolescence than those interviewed less than 7 years after diagnosis. Because age at diagnosis was not associated with either adolescent body mass or height, this finding cannot be attributed to those who were heavier during adolescence developing the vaginal tumor earlier than thinner women. Our study was not designed to investigate case survival, and our comparison of these cases is conservative because, while women followed for more than 10 years are long-term survivors, women interviewed less than 7 years after diagnosis are a mixture of potential long-term and short-term survivors. Thus, the significant differences between these groups in adolescent adiposity levels that we report might be greater if true short-term survivors were compared with long-term survivors of clear cell carcinoma of the vagina. The explanation for this finding is unclear. The finding is consistent with the shorter survival times reported for more obese breast cancer patients (24, 25) but not with a previous study of endometrial cancer where increased weight at diagnosis was associated with prolonged survival (26).

Although recall may be inaccurate, there is no reason to expect that the memories of controls were different from those of cases, and response rates were similar. Although controls did not have cancer, many of them had DES-associated vaginal adenosis or cervical ectropion. Most controls had been told several years earlier of their exposure to a drug strongly linked to cancer, and, like the cases, they had been repeatedly examined and questioned in recent years. Thus, all subjects would be expected to provide equally thoughtful answers to the questionnaire, and height and weight reporting errors in our study are likely to have been random, as such errors were in an earlier study of breast cancer (27). Thus, the relative risks of cancer for adiposity and height reported here are likely to be conservatively biased toward a finding of no association. While our reported relative risks of vaginal cancer for obesity and height may or may not be underestimated, they should not be overestimated.

Education is the most frequently used measure of social class in epidemiology (28),

and maternal education, specifically, is considered to have the greatest impact on children's health behavior of all social class measures (29). We found that mothers of cases had significantly less formal education than mothers of controls, a finding we interpret to mean that the social class of cases was lower than that of controls. Because lower social class subjects are more readily lost to follow-up than higher status subjects (30), this difference is probably due to the fact that, in tracing controls from birth and cases from diagnosis, more controls were lost to follow-up than were cases. It is also possible, however, that low social class is a risk factor for this vaginal cancer among DES-positive women. To control for the social class difference, all relative risk estimates were adjusted for maternal education. While we cannot rule out residual confounding as a partial explanation for our results, since maternal education appears to be a good measure of social class and since controlling for paternal education in addition to maternal education did not affect results, residual confounding is unlikely to be important in this study.

To determine if regional variation in height could account for our finding that cases, who were born throughout the United States, were taller during adolescence than the Houston- and Chicago-born controls, we compared subjects in this study with a national sample of white 16-year-old females measured in the late 1960s (23). Because the mean heights of the national sample and our controls were the same, it seems unlikely that the association between height and vaginal clear cell carcinoma is explained by regional differences in height.

Our findings that increased body mass and height during adolescence may increase the risk of this vaginal cancer are interesting since these same risk factors have been reported for endometrial (31, 32) and uterine cancer (33). Our findings are consistent with the strong association between the vaginal tumor and vaginal adenosis (14), similarities between the tuboendometrial cells associated with vaginal adenosis and the cells normally found in the endometrium (13), and similarities in vaginal clear cell adenocarcinomas and endometrial adenocarcinomas (14).

Previous investigators have also reported an association between increased body mass and height and increased risk of breast cancer (24, 34–37). Like vaginal clear cell adenocarcinoma, breast cancer appears to be related to events occurring during puberty and adolescence (38, 39). Additionally, increased body mass has been linked with higher risks of cervical adenocarcinoma and certain ovarian tumors (40, 41).

Girls who are more obese or taller during puberty have been found to have increased plasma levels of estradiol as well as other differences in their hormone profiles (42, 43). Thus, our findings are consistent with animal studies that have shown hormonal factors, in addition to DES exposure, to be related to genital tumors. Leavitt et al. (10) found that 38 percent of adult hamsters neonatally exposed to DES developed endometrial tumors. However, when DES-exposed animals are ovariectomized, the incidence of endometrial cancer is reduced to control adult female levels. When ovariectomized DES-exposed animals are given estradiol, about twice as many develop endometrial cancer as DES-exposed animals with intact ovaries not given estradiol (10).

Studies in animals suggest that DES acts as an initiator during early development, and that other estrogens act as promoters to stimulate tumor growth in the adult uterus (10). Since increased estrogen levels are known to be associated with increased body mass and height, it is reasonable to suggest that DES also acts as an initiator in young women, and that hormonal factors during adolescence, perhaps estrogen levels, act as promoters for this vaginal tumor.

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