American Journal of Epidemiology
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Vol. 179, No. 2
DOI: 10.1093/aje/kwt250
Advance Access publication:
November 18, 2013

Original Contribution

Prenatal Diethylstilbestrol Exposure and Risk of Uterine Leiomyomata in the Nurses' Health Study II

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Initially submitted May 23, 2013; accepted for publication September 23, 2013.

Previous studies evaluating the association of prenatal exposure to diethylstilbestrol (DES), a potent endocrine disruptor, with incidence of uterine leiomyomata (UL) have had conflicting results. We evaluated the association between prenatal DES exposure and incident UL in women in the Nurses' Health Study II from 1989 to 2009. Women were aged 25–42 years at enrollment and had a prenatal exposure window corresponding to DES use. The analytical sample was larger than previous studies and included 102,164 premenopausal women with intact uteri, no prior history of UL or cancer, and prenatal DES exposure. Multivariable-adjusted Cox proportional hazard models were used to estimate the relationship between DES exposure and UL risk. During 1,273,342 person-years of follow-up, there were 11,831 incident cases of UL. Women with prenatal exposure to DES had a higher incidence of UL compared with unexposed women, with an adjusted hazard ratio of 1.12 (95% confidence interval: 0.98, 1.27). Risk was strongest for women exposed to DES in the first trimester, when exposure corresponds to early stages of fetal Müllerian development (adjusted hazard ratio = 1.21, 95% confidence interval: 1.02, 1.43). These results suggest that first-trimester DES exposure may be associated with an increased risk of UL, but they must be interpreted with concern for detection and recall biases.

diethylstilbestrol; prospective cohort; uterine fibroid

Abbreviations: BMI, body mass index; CI, confidence interval; DES, diethylstilbestrol; HR, hazard ratio; UL, uterine leiomyomata.

Diethylstilbestrol (DES), now considered a potent endocrine disruptor, is a synthetic estrogen that was once used to support pregnancy prior to being removed from the market (1–3). Prenatal DES exposure was subsequently linked with anatomical anomalies of the reproductive tract, including T-shaped uterus, coxcomb deformity of the cervix, infertility, and vaginal tract cancers (4). As a result of initial studies showing an association between DES and reproductive tract diseases, the US Food and Drug Administration in 1971 advised physicians to stop prescribing DES to pregnant women (5). Prenatal exposure to DES has been previously evaluated in relationship to uterine leiomyomata (UL) with inconsistent results (2, 6–8). UL are clinically recognized in approximately 25%–30% of women, but their lifetime prevalence is closer to 70%–80% based on ultrasonography evidence (9). With symptoms including heavy menstruation, anemia, abdominal pain, urinary frequency, and bloating (10), UL remain the primary indication for hysterectomy in the United States (11).

The DES Collaborative Follow-up Study, a prospective cohort study, found no association between prenatal medically documented DES exposure and risk of UL as pathologically reported on hysterectomy specimens (2). Two cross-sectional studies found a positive association between self-reported prenatal DES exposure and prevalence of UL (6,7). A previous study combining 3 cohorts of DES-exposed women with long-term follow-up demonstrated that prenatal exposure to DES conferred a broad range of adverse health outcomes, including several reproductive outcomes, such as infertility and spontaneous abortion (12). However, UL were not evaluated

(12). The objective of the present study was to evaluate the association between prenatal DES exposure and development of UL in the Nurses' Health Study II cohort.

MATERIALS AND METHODS

Study population

The Nurses' Health Study II is a prospective cohort study of US nurses initiated in September 1989 when 116,686 female registered nurses, 25–42 years of age, completed a mailed questionnaire and provided implied informed consent. At baseline, the nurses resided in 14 states (California, Connecticut, Indiana, Iowa, Kentucky, Massachusetts, Michigan, Missouri, New York, North Carolina, Ohio, Pennsylvania, South Carolina, and Texas); however, there is now at least 1 cohort member in all 50 states. Follow-up questionnaires, with response rates above 90%, are mailed every 2 years to update information on risk factors and the occurrence of major illnesses. For this analysis, we excluded women who were unsure of their DES exposure ($n = 356$) and those with a diagnosis of UL ($n = 5,265$), cancer (other than nonmelanoma skin cancer) ($n = 1,002$), or hysterectomy ($n = 2,880$) prior to study initiation in 1989, leaving 102,164 premenopausal women available for analysis.

Assessment of outcome

The initial assessment of UL was performed in 1993. Participants were asked if they had ever had UL diagnosed by a physician. If a participant answered "yes," she was asked for the date of diagnosis and the method of confirmation (pelvic examination, ultrasonography, or hysterectomy). For all subsequent questionnaires, women were asked if they had been diagnosed with UL before, during, or after the current 2-year study period.

During these follow-up intervals, a woman was considered a case only if she reported ultrasonography- or hysterectomy-confirmed UL during that time period. Women who reported new diagnoses of UL that had not been confirmed by ultrasonography or hysterectomy (i.e., pelvic examination only) did not contribute case person-time but were allowed to reenter the analysis in the future if the UL were confirmed by either ultrasonography or hysterectomy. The midpoint between the time of receipt of the questionnaire before diagnosis and the time of receipt of the questionnaire after diagnosis was assigned as the date of diagnosis. We used date of diagnosis to mark incidence as opposed to the initiation of UL development. Marshall et al. (13) performed a validation study of 243 Nurses' Health Study II participants who self-reported a new diagnosis of UL confirmed by ultrasonography or hysterectomy compared with medical record review with an average confirmation rate of 93%.

Assessment of exposure

All participants were born when DES was available to pregnant women (1946–1965). The 1993 questionnaire included questions on their mothers' use of DES or "other hormones" during pregnancies with the participants. A supplementary questionnaire was mailed to all women who reported prenatal exposure to DES. The supplementary follow-up questionnaire had questions to obtain additional details on the DES exposure, including trimester of initiation, duration of use, and their certainty of exposure. Women who indicated on the 1993 questionnaire that they were exposed but indicated on the supplementary questionnaire that they were not exposed were excluded from analyses ($n = 356$), as noted above. We considered women to be exposed if they confirmed they were "certain/somewhat certain" that they were exposed prenatally to DES. In 2001, participants' mothers completed a questionnaire pertaining to their pregnancies with the participants and the early life exposures of the participants. The agreement between DES exposure as reported by daughters in the supplementary questionnaire and DES exposure as reported by mothers was high, with a $\kappa = 0.74$ (14). Therefore, this method of assessing DES exposure is likely valid. Of the 29,699 participants' mothers who returned questionnaires, 98.8% (29,332) of participants had perfect agreement with their mothers on DES exposure.

Additional covariates

Information on potential confounders is available every 2 years. Therefore, when appropriate, each woman was assigned updated covariate values for each questionnaire cycle. We examined possible confounding by numerous risk factors for UL, including the following time-varying variables updated at each survey: age (in months), smoking status (current/former/never), body mass index (BMI) (weight (kg)/height $(m)^2$), parity, infertility, oral contraceptive use, age at first birth, age at last birth, time since last birth, total months of exclusive breastfeeding, antihypertensive medication use, blood pressure, and whether the participant had a physical examination or pelvic examination in the past 2 years. Non–time-varying variables entered at baseline included race and age at menarche.

Statistical analysis

Prospective time-varying Cox proportional hazard models were used to assess the relationship between UL and prenatal DES exposure. Person-months of follow-up time were calculated from July 1, 1989, until censoring, UL diagnosis, date of death, or the end of follow-up on June 30, 2009. Women were censored if they reported menopause, cancer (other than nonmelanoma skin cancer), or hysterectomy, whichever occurred first. All models were based on a biennial time scale, stratified on current age in months and time period, and used to estimate hazard ratios and 95% confidence intervals. To determine potential confounding, we added each variable (or set of indicator variables) separately to a model including age and race. Variables that changed the effect estimates by 10% or more in univariate models were considered to confound the association of DES and UL. To determine whether there was effect modification of the association of DES and UL by age ($\leq$35 or >35 years), smoking status (ever/never), and BMI (<25 or $\geq$25), we performed stratified analyses within each group and determined whether the effect estimates were significantly different by creating multiplicative interaction terms.

Table 1. Selected Age-standardized Characteristics During the Full Period of Follow-up by DES Exposure in the US Nurses' Health Study II Cohort, 1989–2009

Characteristic	DES Exposure	
	Yes, %[a] (*n* = 1,691)	No, %[a] (*n* = 100,473)
Age, years	40.8 (5.7)[b,c]	40.3 (6.1)[b,c]
Body mass index[d]	25.2 (5.5)[b]	25.5 (5.8)[b]
Caucasian	96	94
Smoking status		
Never	64	67
Current	10	10
Former	25	23
Age at menarche, years		
<12	23	23
12	29	30
>12	48	46
Physical examination in past 2 years		
Yes	85	77
No	7	11
Parity		
Nulliparous	28	22
Parous	72	78
Infertility		
Yes	11	6
No	87	90
Age at first birth, years		
<26	27	33
26–30	30	32
>30	14	13
Age at last birth, years		
<26	7	8
26–30	27	28
31–35	26	28
>35	10	10
Oral contraceptive use		
Never	15	14
Past	74	73
Current	11	11
Missing	1	2
Diastolic blood pressure, mmHg		
No use of antihypertensive drugs		
<65	23	23
65–74	47	48
75–84	23	22
85–89	3	3
≥90	1	2
Use of antihypertensive drugs		
<65	0	0
65–74	0	1
75–84	1	1
85–89	0	0
≥90	0	1
Missing drug use	1	1

Abbreviation: DES, diethylstilbestrol.

[a] Values are standardized to the age distribution of the study population.

[b] Values are expressed as mean (standard deviation) and are standardized to the age distribution of the study population.

[c] Value is not age adjusted.

[d] Weight (kg)/height $(m)^2$.

To determine whether detection bias was present, we also performed models stratified by report on each survey of a physical or pelvic examination in the past 2 years. In sensitivity analyses to examine more severe cases of UL, we ran models restricted to those cases of UL confirmed by hysterectomy. A sensitivity analysis was also run in the group with perfect agreement on exposure status between mothers and daughters. Statistical analyses were performed in SAS, version 9.2, software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Characteristics of the cohort throughout follow-up are presented in Table 1 by DES exposure group. Overall, the average age was 40 years, and the average BMI was 25. Approximately 95% of the cohort was of Caucasian race/ethnicity. There were no differences in the exposed and unexposed groups in age, BMI, age at menarche, age at last birth, oral contraceptive use, antihypertensive medication use, and blood pressure. Women who were prenatally exposed to DES were more likely to have had a physical examination in the last 2 years, to be nulliparous, to be older at their first births, and to have experienced infertility.

There were a total of 11,831 cases of UL during 1,273,342 person-years of follow-up. As shown in Table 2, in basic models adjusted only for age and time period, prenatal DES exposure was associated with an 18% (95% confidence interval (CI): 4%, 34%) increased risk of incident UL relative to no exposure. This risk was similar after adjustment for all potential confounders (hazard ratio (HR) = 1.12, 95% CI: 0.98, 1.27), although only parity, infertility, and whether the participant had a physical examination in the past 2 years met our criteria for confounding.

Table 2. Hazard Ratios of the Association of Prenatal DES Exposure and Risk of Uterine Leiomyomata Overall and by Age Among 102,164 Members of the US Nurses' Health Study II, 1989–2009

DES Exposure by Cohort	No. of Cases	Person-years	Basic HR[a]	95% CI	Fully Adjusted HR[b]	95% CI
Whole cohort						
Yes	238	20,954	1.18	1.04, 1.34	1.12	0.98, 1.27
No	11,593	1,252,388	1.00	Referent	1.00	Referent
≤35 Years of age						
Yes	20	3,363	1.12	0.72, 1.75	1.00	0.64, 1.55
No	1,339	264,742	1.00	Referent	1.00	Referent
>35 Years of age						
Yes	218	17,591	1.18	1.03, 1.35	1.13	0.98, 1.29
No	10,254	987,647	1.00	Referent	1.00	Referent

Abbreviations: CI, confidence interval; DES, diethylstilbestrol; HR, hazard ratio.
[a] Adjusted for age and calendar time.
[b] Additionally adjusted for race, current body mass index (weight (kg)/height $(m)^2$), smoking status, physical examination in the past 2 years (yes/no), parity, oral contraceptive use, age at menarche, age at first and last births, time since last birth, total months of exclusive breastfeeding, infertility, antihypertensive medication use, and blood pressure.

Among the women who reported the trimester of DES initiation (Table 3), the association of DES and UL risk was observed among only those women initially exposed to DES in the first trimester of gestation. In fully adjusted models, these women had a 21% (95% CI: 2%, 43%) increased risk of UL compared with women with no DES exposure. There was no clear trend of an increasing risk of UL with increasing weeks of DES exposure (data not shown).

There were a total of 3,161 cases of UL confirmed by hysterectomy. In fully adjusted models, the hazard ratio for the association of DES exposure and hysterectomy-confirmed UL was 1.09 (95% CI: 0.85, 1.41) compared with women with no exposure. In this group, there was still a suggestion of an increased risk with DES initiation in the first trimester (HR = 1.15, 95% CI: 0.81, 1.63).

In analyses restricted to women with perfect agreement with their mothers regarding prenatal DES exposure (4,041 cases, 70 exposed cases), the fully adjusted risk of UL was 0.98 (95% CI: 0.77, 1.25) comparing exposed with unexposed. In this group, the risk from exposure in the first trimester was 1.24 (95% CI: 0.94, 1.64). There was no evidence of effect modification by whether the participant had a physical examination in the past 2 years, smoking status, or BMI, (all P for interaction > 0.20, data not shown). Models stratified by age are presented in Table 2. In models restricted to subjects 35 years or younger (with only 20 exposed cases), we noted no significant association between DES exposure and UL risk (fully adjusted HR = 1.00, 95% CI: 0.64, 1.55). In women over 35 years of age, the fully adjusted hazard ratio was 1.13 (95% CI: 0.98, 1.29).

Table 3. Hazard Ratios of the Association of Trimester of Initiation of Prenatal DES Exposure and Risk of Uterine Leiomyomata Among 102,164 Members of the US Nurses' Health Study II, 1989–2007

DES Exposure	No. of Cases	Person-years	Basic HR[a]	95% CI	Fully Adjusted HR[b]	95% CI
No	11,593	1,252,388	1.00	Referent	1.00	Referent
Yes						
Trimester unknown	81	7,360	1.14	0.92, 1.42	1.05	0.84, 1.31
First trimester	134	11,186	1.24	1.05, 1.47	1.21	1.02, 1.43
Second trimester	17	1,741	1.02	0.64, 1.65	0.95	0.59, 1.43
Third trimester	6	668	0.90	0.41, 2.02	0.84	0.38, 1.88

Abbreviations: CI, confidence interval; DES, diethylstilbestrol; HR, hazard ratio.
[a] Adjusted for age and calendar time.
[b] Additionally adjusted for race, current body mass index (weight (kg)/height $(m)^2$), smoking status, physical examination in the past 2 years (yes/no), parity, oral contraceptive use, age at menarche, age at first and last births, time since last birth, total months of exclusive breastfeeding, infertility, antihypertensive medication use, and blood pressure.

DISCUSSION

The current study represents the largest prospective cohort study to date investigating the association between prenatal DES exposure and incidence of UL over 20 years of follow-up. After adjustment for potential confounders, we found a small positive association between DES exposure and UL incidence (HR = 1.12, 95% CI: 0.98, 1.27). Furthermore, the adverse association of DES and UL was stronger for women exposed in the first trimester (HR = 1.21, 95% CI: 1.02, 1.43) in fully adjusted models. A preliminary evaluation of DES exposure and UL incidence from 1989 to 1999 was previously performed in the Nurses' Health Study II cohort and found no statistically significant association (15). The original results (not reported herein) for the years 1989–1999, with 5,500 cases of UL, showed an adjusted hazard ratio of 1.10 (95% CI: 0.89, 1.36) (15). These initial results are comparable to our current study, which included 11,831 cases and, because of the increased sample size, are of borderline statistical significance with an adjusted hazard ratio of 1.12 (95% CI: 0.98, 1.27).

Four previous analyses have been conducted on the association of DES and UL, with mixed results (2, 6–8). In the only other prospective cohort study, the DES Collaborative Follow-up Study, there was no association between DES exposure (determined from medical record review) and UL confirmed by operative or pathology report (2). The lack of an association may be due to the restrictive definition of UL used in that study. Correspondingly, in the current study, when we restricted the analysis to surgically diagnosed cases, no significant association between DES exposure and UL was noted. In the National Institute of Environmental Health Science Uterine Fibroid Study (6), UL was assessed by ultrasonography. A positive association was found between DES exposure and risk of UL, whereby risk increased with increasing size of the tumor. However, a minor limitation of the study by Baird et al. (6) was patients' self-reporting of DES exposure, which may have involved recall bias.

In 2 cross-sectional analyses of the Sister Study baseline data (within white women and black women separately), a positive association was observed between self-reported prenatal DES exposure and risk of UL (7, 8). Among black women, positive associations were found for both "definite" (risk ratio = 1.87) and "probable" (risk ratio = 2.22) DES exposure, but there were only 13 exposed cases. These analyses were restricted to early-onset UL, defined as self-reported cases diagnosed before age 30 years (8). Among white women, self-reported early-onset UL was defined as cases diagnosed before age 35 years (7). "Probable" (risk ratio = 2.07), but not "definite" (risk ratio = 1.04), exposure to DES was positively associated with risk of UL, suggesting that recall bias could have explained these results. However, we defined DES exposure with only those women who reported they were "certain/somewhat certain" and who had no discrepancy between their supplemental questionnaire and the 1993 main study questionnaire. To minimize the influence of reporting bias, future studies should seek medical documentation of DES exposure and more accurate classification of UL.

In laboratory rodents, exposure to DES in early life is associated with an increased incidence of UL (16–18), and long-term changes in estrogen-related gene expression have been implicated in this increase (18). There is biological plausibility for an association between UL and prenatal exposure to DES, a chemical that binds to the estrogen receptor as Müllerian structures develop embryologically between 6 and 10 weeks of gestation and are uniquely sensitive to estrogen and estrogen-like compounds (19). Consistent with these observations, a stronger association with initiation of DES in the first trimester of pregnancy and UL risk was shown in our study.

The limitations of this study include low ethnic diversity and insufficient numbers to examine effects in different ethnic groups separately. Also, DES exposure was determined through participant and mother-of-participant self-reports as opposed to medical record documentation, which may increase the potential for recall bias. However, participants were surveyed twice, and mothers of participants were asked as well for exposure information, with high agreement between mothers and daughters. At the time of the DES survey, information regarding DES and UL was not well known, however DES exposure and vaginal tract cancers and infertility were already known. As such, truly exposed women are under increased gynecological surveillance for other DES-associated sequelae, and detection bias is a concern. It is possible that recall and detection biases may account for the small positive association shown in this study. To directly address detection bias in our models, we adjusted for self-report of a physical examination in the past 2 years of each survey period. It is still possible that increased surveillance among women with DES exposure may account for our findings. However, women exposed at any time during gestation would be subject to heightened gynecological evaluation, independent of exposure timing. Therefore, our results demonstrating an increased risk of UL mainly in the first trimester, which coincides with fetal gynecological development, more strongly support a biological mechanism than spurious results due to detection bias. Another limitation is that some of our potential confounders could also be viewed as mediators of this association; however, fully adjusted models were very similar to the basic model.

The strengths of this study include prospective cohort design, a large sample size, long follow-up, and biennially updated information on several covariates. UL outcomes were validated with medical record review in a subset of cases showing a high level of accuracy (93%) and are included as cases only if there is either ultrasonography diagnosis, surgical diagnosis, or both. Because we were unable to screen all women in the cohort for UL, we were unable to capture the full range of UL in this group.

In conclusion, we found a small positive association between DES exposure and risk of UL. Among women reporting trimester of DES initiation, the association was strongest when DES was initiated in the first trimester. These results should be interpreted with caution because of the possibility of recall bias in both participants and their mothers, as well as detection bias due to increased gynecological surveillance in exposed women. Because DES-exposed women are aging out of leiomyomata research, the possibility for future study of this association is limited. However, studies of DES exposure and outcomes of concern may provide a

framework for other similarly acting estrogenic endocrine disruptors, such as bisphenol A and dioxin (20–22).

ACKNOWLEDGMENTS

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This work was supported by the National Institute of Child Health and Human Development (grant 5K12HD043444-10), the National Cancer Institute (grant R01CA50385), the National Institute for Environmental Health Sciences (grant 5R01ES017017), and a research grant from the Boston University Department of Obstetrics and Gynecology. The Nurses' Health Study II is additionally supported by infrastructure grant UM1 CA176726.

We thank Danielle Payne for her contributions to this manuscript.

Conflict of interest: none declared.

REFERENCES

1. Greenwald P, Barlow JJ, Nasca PC, et al. Vaginal cancer after maternal treatment with synthetic estrogens. *N Engl J Med*. 1971;285(7):390–392.
2. Wise LA, Palmer JR, Rowlings K, et al. Risk of benign gynecologic tumors in relation to prenatal diethylstilbestrol exposure. *Obstet Gynecol*. 2005;105(1):167–173.
3. Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocr Rev*. 2009;30(4):293–342.
4. Kaufman RH, Adam E, Hatch EE, et al. Continued follow-up of pregnancy outcomes in diethylstilbestrol-exposed offspring. *Obstet Gynecol*. 2000;96(4):483–489.
5. Centers for Disease Control and Prevention. DES history. Atlanta, GA: Centers for Disease Control and Prevention; 2003. (http://www.cdc.gov/DES/consumers/about/history.html). (Accessed May 10, 2013).
6. Baird DD, Newbold R. Prenatal diethylstilbestrol (DES) exposure is associated with uterine leiomyoma development. *Reprod Toxicol*. 2005;20(1):81–84.
7. D'Aloisio AA, Baird DD, DeRoo LA, et al. Association of intrauterine and early-life exposures with diagnosis of uterine leiomyomata by 35 years of age in the Sister Study. *Environ Health Perspect*. 2010;118(3):375–381.
8. D'Aloisio AA, Baird DD, DeRoo LA, et al. Early-life exposures and early-onset uterine leiomyomata in black women in the Sister Study. *Environ Health Perspect*. 2012; 120(3):406–412.
9. Baird DD, Dunson DB, Hill MC, et al. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. *Am J Obstet Gynecol*. 2003;188(1): 100–107.
10. Stewart EA. Uterine fibroids. *Lancet*. 2001;357(9252): 293–298.
11. Farquhar CM, Steiner CA. Hysterectomy rates in the United States 1990–1997. *Obstet Gynecol*. 2002;99(2):229–234.
12. Hoover RN, Hyer M, Pfeiffer RM, et al. Adverse health outcomes in women exposed in utero to diethylstilbestrol. *N Engl J Med*. 2011;365(14):1304–1314.
13. Marshall LM, Spiegelman D, Barbieri RL, et al. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. *Obstet Gynecol*. 1997;90(6):967–973.
14. O'Reilly EJ, Mirzaei F, Forman MR, et al. Diethylstilbestrol exposure in utero and depression in women. *Am J Epidemiol*. 2010;171(8):876–882.
15. Missmer SA, Hankinson SE, Spiegelman D, et al. In utero exposures and the incidence of endometriosis. *Fertil Steril*. 2004;82(6):1501–1508.
16. Newbold RR. Cellular and molecular effects of developmental exposure to diethylstilbestrol: implications for other environmental estrogens. *Environ Health Perspect*. 1995; 103(suppl 7):83–87.
17. Newbold RR, Moore AB, Dixon D. Characterization of uterine leiomyomas in CD-1 mice following developmental exposure to diethylstilbestrol (DES). *Toxicol Pathol*. 2002;30(5): 611–616.
18. Greathouse KL, Cook JD, Lin K, et al. Identification of uterine leiomyoma genes developmentally reprogrammed by neonatal exposure to diethylstilbestrol. *Reprod Sci*. 2008;15(8):765–778.
19. Newbold RR. Lessons learned from perinatal exposure to diethylstilbestrol. *Toxicol Appl Pharmacol*. 2004;199(2): 142–150.
20. Anderson OS, Nahar MS, Faulk C, et al. Epigenetic responses following maternal dietary exposure to physiologically relevant levels of bisphenol A. *Environ Mol Mutagen*. 2012;53(5): 334–342.
21. Tuomisto J, Tuomisto JT. Is the fear of dioxin cancer more harmful than dioxin? *Toxicol Lett*. 2012;210(3):338–344.
22. Bromer JG, Wu J, Zhou Y, et al. Hypermethylation of homeobox A10 by in utero diethylstilbestrol exposure: an epigenetic mechanism for altered developmental programming. *Endocrinology*. 2009;150(7):3376–3382.