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Early-life factors and endometriosis risk

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Abstract

Objective—To study early-life factors in relation to endometriosis risk in adulthood.

Design—Population-based case-control study.

Setting—Women's Risk of Endometriosis (WREN) study was conducted among female enrollees ages 18-49 years of a large, integrated healthcare system in western Washington State.

Patients—Cases (n=310) were women diagnosed for the first time with endometriosis between years 1996-2001 and controls (n=727) were women without a diagnosis of endometriosis randomly selected from the healthcare system population.

Interventions—None.

Main outcome measures—Adjusted odds ratios (aOR) and 95% confidence intervals (CI) for the associations between intrauterine diethylstilbestrol (DES) exposure, maternal smoking, mother's age at delivery, firstborn status, birth weight, fetal number, prematurity, and regular soy formula feeding during infancy and endometriosis were estimated using unconditional logistic regression, adjusting for frequency matching and confounding variables. Information on early-life factors was ascertained retrospectively by in-person interview, with information on maternal DES

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use and regular soy formula feeding directly gathered from the participant's mother or other family member.

Results—We observed that women who were regularly fed soy formula as infants had over twice the risk of endometriosis compared to unexposed women (aOR 2.4, 95% CI: 1.2-4.9). Our data also suggested increased endometriosis risk with prematurity (aOR 1.7, 95% CI: 0.9-3.1) and maternal use of DES (OR 2.0, 95% CI: 0.8-4.9, adjusting only for frequency matching variables), although these confidence intervals included the null.

Conclusion—Our results support the hypothesis that disruption of development during fetal and infant periods may increase the risk of endometriosis in adulthood.

Keywords

population-based case-control study; endometriosis; early-life; soy formula

Introduction

Endometriosis is characterized by the presence of endometrial glands and stroma outside of the uterus, usually within the peritoneal cavity. Women with endometriosis frequently report pain symptoms, including chronic pelvic pain, painful menstrual periods, and pain with intercourse (1, 2). For many women with this condition, these pain symptoms can be chronic and debilitating, negatively affecting health-related quality of life, personal relationships, and work productivity (3-5). The impact of this condition on reproductive-age women is concerning given that endometriosis is estimated to affect 6-11% of reproductive-age women in the United States (6-9) and that the etiology of endometriosis is not well understood.

The most widely accepted theory of disease pathogenesis postulates that endometriosis develops from the reflux of shed endometrial tissue during menses (10). The establishment and persistence of the refluxed endometrial tissue in the peritoneal cavity is promoted by additional immunologic, inflammatory, angiogenic, and anti-apoptotic cellular and molecular mechanisms (as reviewed in Bulun (11), Guidice (12), and Ulukus *et al.* (13)). These mechanisms appear to be regulated to some extent by hormonal signaling from ovarian steroids (14-18). This is in alignment with epidemiologic studies that have contributed strong circumstantial evidence that endometriosis is an estrogen-driven condition (8, 19). Thus, changes in ovarian steroid production regulated by the hypothalamus-pituitary-ovarian (HPO) axis as well as alterations in uterine tissue may increase the risk of developing endometriosis.

The uterus and HPO-axis rapidly develop during the fetal and infants periods. By the 10th week of gestation, fused Mullerian ducts differentiate into the uterus (20). The estrogen-receptor rich uterine tissue (21) continues to proliferate and differentiate throughout gestation and postnatally (22); uterine endometrial glands, in particular, primarily proliferate after birth, including during the infant period (21, 23). The development of the HPO-axis begins early in gestation as well, with the pituitary gonadotropins follicle stimulating hormone (FSH) and luteinizing hormone (LH) detectable in fetal serum by 12 weeks (24).

The HPO-axis is active during the fetal and infant periods, with activity peaking mid-gestation and the first few months after birth (25).

Given the rapid tissue differentiation and complex hormonal, cellular, and molecular mechanisms that occur during the fetal and infant periods, these developmental periods are susceptible to hormonal disruption. Studies of animal models have demonstrated the ability of early-life hormonal disruption to permanently alter the uterus and HPO-axis during development, resulting in changes that persist in adulthood (26-29). Results from these animal models corroborate clinical observations (30, 31) as well as associations reported in epidemiologic studies of early-life exposures and adverse reproductive outcomes in adulthood (32-40).

Early-life hormonal factors, such as prenatal exposure to diethylstilbestrol (DES) and cigarette smoking, as well as perinatal characteristics indicative of altered hormonal milieu, have been investigated in relation to endometriosis risk in prior epidemiologic studies (38, 41-43). Results of those studies have been inconsistent, and some of the studies were limited by relatively small sample size or small numbers of exposed cases and controls (41-43). The purpose of this study was to further investigate the relationship between early-life factors and endometriosis using data from a large, population-based case-control study of endometriosis.

Materials and methods

Study Population

For the present analyses, we used data from the Women's Risk of Endometriosis (WREN) study, a five-year population-based case-control study of endometriosis for which the study population and methods have been previously described (44). Briefly, WREN was conducted among 18-49 year old female enrollees of Group Health Cooperative (GH), a large integrated healthcare system in western Washington State. Cases (n=340) were women diagnosed for the first time with endometriosis (International Classification of Disease 9th Revision diagnostic codes 617.0-617.5, 617.8-617.9) between April 1, 1996 and March 31, 2001. The diagnoses were confirmed by medical record documentation of direct surgical visualization of endometriotic lesions, with histological confirmation when available. Population-based controls (n=741) were female GH enrollees without a diagnosis of endometriosis who were randomly selected from computerized GH enrollment databases and frequency matched to cases in five-year age groups. Cases and controls were interviewed in person by trained female interviewers and information was collected pertaining to the period prior to the reference date assigned to cases and controls. For cases, the reference date was the date of the first visit for symptoms leading to endometriosis diagnosis listed in the GH medical records. Controls were assigned reference dates using the distribution of reference dates among cases. The interview covered a range of topics including demographic characteristics and lifestyle behaviors as well as early-life factors.

Eligibility criteria for both cases and controls in the WREN study included enrollment in GH for at least six months prior to the reference date, an intact uterus, and at least one ovary. Women diagnosed with surgically-confirmed endometriosis before April 1, 1996 were not

eligible, nor were postmenopausal women. Based on information ascertained during the interview, we excluded 12 cases and 14 controls who reported a diagnosis of surgically confirmed endometriosis prior to the reference date. We also excluded three cases whose endometriosis diagnosis was not surgically confirmed based on review of the medical records. We additionally excluded 15 cases not meeting the definition of definite or possible endometriotic disease (45). This disease definition focuses on endometriosis with evidence of tissue invasiveness or interference with normal physiologic processes. The study sample for the present analyses was comprised of 310 cases and 727 controls. Institutional review board approval was received from the Fred Hutchinson Cancer Research Center Institutional Review Board and each participant provided informed consent prior to participation in the study.

Early-life factors

Data on early-life factors were ascertained by participant self-report during the WREN structured interview. We used these data to create variables for the exposures of interest with categories similar to those of prior studies (38, 41-43). The exposures of interest in the present analyses were the use of diethylstilbestrol (DES) (yes, no) or smoking (yes, no) by the participant's mother while pregnant with the participant, mother's age at delivery (15-24, 25-34, 35-49 years), perinatal characteristics of the participant including first born status (yes, no), fetal number (singleton, multiple), birth weight (<5.5, 5.5 to <9.0, 9.0 lbs), prematurity (born two or more weeks early) (yes, no), and regular soy formula feeding during infancy (yes, no).

Additionally, a supplemental questionnaire, the Mother's Information Form, was administered to clarify or confirm the participant's response to four WREN interview questions with the participant's mother (or another knowledgeable family member if the mother was not available or deceased). This questionnaire included two questions relevant to this study: use of DES while the mother was pregnant with the participant, and soy formula feeding during the participant's infancy. Study interviewers requested contact information to directly telephone or to have the participant telephone the participant's mother or other family member after the interview. If telephone contact at the time of study interview was not possible, the Mother's Information Form was given to participants and returned by postal mail. The forms were completed for 233 cases (75%) and 535 controls (74%); the participant's mother confirmed or clarified the responses on 95% of the completed forms and the frequency of mother's participation was similar between cases and controls. Given the low concordance as estimated by Cohen's kappa (κ) (Supplemental Material, Calculation) between the participant's response and those of her mother or proxy for maternal DES use (cases $\kappa=0.42$, controls $\kappa=0.22$) and infant soy formula feeding (cases $\kappa=0.18$, controls $\kappa=0.16$), we used only the data from the Mother's Information Form available for 75% of participants for these exposures in the present analyses.

Statistical analyses

We used unconditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals for the association between individual early-life exposures and endometriosis risk. All analyses were adjusted for the frequency matching variables of participant age at the

reference date (19, 20-24, 25-29, 30-34, 40-44, 45-49 years) and the reference date year (1995, 1996, 1997, 1998, 1999, 2000, 2001). We repeated the analyses additionally adjusting for *in utero* exposures and perinatal characteristics associated with endometriosis in prior studies (38, 41): maternal smoking (yes, no), birth weight (<5.5, 5.5 to <9.9, 9.9), fetal number (singleton, multiple), and prematurity (yes, no). We report the results for both sets of analyses.

We conducted several sensitivity analyses. First, when investigating the association between maternal smoking and endometriosis risk, we restricted the analyses to cases and controls who reported never smoking themselves to examine the independent effect of maternal smoking on endometriosis risk (166 cases, 406 controls). Second, when examining the association between soy formula feeding and endometriosis risk, we excluded cases and controls who reported eating any of the following soy foods at least once a month over the year prior to study interview: tofu, tempeh, soy cheese, soy yogurt, soy ice cream, and soy milk as well as vegetarian burgers and hot dogs that were sometimes, often, or almost always made with soy products (restricted study sample: 160 cases, 364 controls). Third, since it was not feasible to surgically-confirm the absence of endometriotic disease among population-based controls, we repeated the analyses excluding controls (n=157) who reported infertility (12 months of unprotected heterosexual intercourse without contraception that was not attributable to a cause), moderate or severe pelvic pain when not menstruating, and/or moderate or severe pain with intercourse, using definitions for these symptoms similar to those used in the definition of possible endometriotic disease (45).

We additionally performed an exploratory analysis of the association between regular soy formula feeding during infancy and endometriosis risk stratified on birth year, before 1965 (161 cases, 394 controls) and in or after 1965 (68 cases, 132 controls), the approximate time when the soy component of formulas changed from soy flour to isolated soy protein (46). The statistical analyses were performed using STATA 14.0 (StataCorp, College Station, TX) and we considered $\alpha=0.05$ as the significance level in all analyses.

Results

Cases and controls were generally similar with regard to demographic and lifestyle factors, with the exception that a greater percentage of cases than controls graduated from college, were current consumers of alcohol, and were nulliparous, and a greater percentage of controls than cases reported total annual household incomes $\geq \$70,000$ (Table 1). Prior to the reference date, cases were enrolled in GH for a shorter median time than controls (cases, median 8 years, interquartile range (IQR): 4-14 years; controls, median 10 years, IQR: 4-17 years).

In the multivariable-adjusted analyses, we observed an association between exposure to regular soy formula feeding during infancy and increased risk of endometriosis (OR 2.4, 95% CI: 1.2-4.9). Our data also suggested increased endometriosis risk with premature birth (OR 1.7, 95% CI: 0.9-3.1) (Table 2). The multivariable-adjusted estimates for DES use and multiple fetal number were statistically unstable due to the small number of exposed cases

and controls. We did not observe meaningful associations with the other early life exposures in the multivariable analyses.

Data from our analyses adjusting only for frequency matching variables suggested an increased risk of endometriosis with maternal use of DES and multiple fetal number. Given the statistically unstable multivariable-adjusted estimates for these exposures, we conducted post hoc analyses using restriction to control for confounding. When evaluating DES exposure and endometriosis, we restricted the study population to women who were singleton infants, not born prematurely, and not fed soy formula as infants (180 cases, 466 controls); for multiple fetal number, we restricted the study population to women who were not born prematurely, not exposed to DES, and not fed soy formula as infants (178 cases, 466 controls). In these post hoc analyses, we observed that the magnitude of the association was stronger for DES use (OR 2.3, 95% CI: 0.7-7.9) and weaker for multiple fetal number (OR 1.3, 95% CI: 0.3-5.3), although the OR estimates were accompanied by wide confidence intervals.

As for our sensitivity analysis restricting the study population to women who reported never smoking themselves, we observed a null association between maternal smoking and endometriosis (OR 1.0, 95% CI: 0.6-1.5). After excluding cases and controls who consumed soy foods in the year prior to study interview, the association between soy formula feeding and endometriosis risk was stronger in magnitude than in our main analysis, but accompanied by a wider confidence interval (OR 2.9, 95% CI: 1.2-6.9). With regard to the sensitivity analysis excluding controls who reported a history of infertility, moderate/severe pelvic pain or pain with intercourse, we observed stronger magnitudes of associations for maternal use of DES (OR 2.9, 95% CI: 1.0-8.5, $P=0.047$, adjusting only for matching variables) and birth weight ≥ 9.0 lbs. (vs. <9.0 lbs.) (OR 1.5, 95% CI: 0.8-2.6) in relation to endometriosis risk. The remaining ORs and 95% CIs were similar to those reported in Table 2, including the association between soy formula feeding and endometriosis (OR 2.5, 95% CI: 1.2-5.3).

In our exploratory analysis of soy formula feeding and endometriosis risk stratified by birth year, we observed a stronger association between infant soy formula feeding and endometriosis among women born in 1965 or later (OR 4.4, 95% CI: 1.3-14.6) than among those born before 1965 (OR 1.7, 95% CI: 0.7-4.2). However, the estimates were less precise than in the main analyses.

Discussion

In the present analyses, the early-life factor associated most strongly with endometriosis was regular feeding of soy formula during infancy. It is biologically plausible that a hormonal exposure during infancy, such as soy formula, may increase endometriosis risk in adulthood. Infant soy formula contains phytoestrogens, predominantly the isoflavones genistein and daidzein, that can be absorbed and digested by infants (47). Infants can be substantially exposed to these isoflavones, particularly when they are primarily fed soy formula (48). These isoflavones are structurally similar to estradiol (49) and can bind to estrogen receptors (as reviewed in Shanle *et al.*(50)). Animal models have demonstrated that early-life

administration of genistein results in changes to the uterus and HPO-axis in adulthood that may be relevant to endometriosis. These changes include the hypertrophy of uterine epithelial cells (28) and dose-dependent changes in the HPO-axis (26, 27); at higher doses of genistein, anovulation (27), decreased pituitary response to GnRH and lower LH secretion (26) were observed in adulthood. However, the opposite effects have been observed at lower doses of genistein, including a greater number of corpora lutea in the ovary (27), increased pituitary response to GnRH and higher LH secretion (26).

To our knowledge, no prior human studies have evaluated the association between infant soy formula feeding and endometriosis. The increased endometriosis risk that we observed in relation to this exposure is supported by results from other human studies reporting an association between soy formula feeding and reproductive outcomes that are risk factors and symptoms of endometriosis, including early menarche (32, 35), slightly longer menses duration, and greater menstrual discomfort (39). Soy formula feeding has also been associated with another hormonally-mediated uterine condition, uterine leiomyomas (33, 34, 51).

In our exploratory analyses, we observed that the magnitude of the association between infant soy formula feeding and endometriosis risk was stronger among women born after the mid-1960s than those born in earlier years. The stronger association may be related to the change in the soy component of commercially-available soy formulas; in the mid-1960s, the soy component changed from soy flour to the highly digestible isolated soy protein (46, 52). In support of this hypothesis, in one study of early-life factors and age at menarche, the association between soy formula feeding and very early menarche was only observed among those born in 1960 or later (35).

Our study had a small number of DES-exposed cases and controls. Despite this, our data suggested an increased risk of endometriosis with mother's use of DES while pregnant with the participant. DES is a potent estrogen that was prescribed to pregnant women in the United States for the prevention of miscarriage and other pregnancy complications until 1971, when it was found to increase the risk of a rare vaginal cancer in prenatally-exposed daughters (36). Structural abnormalities of the reproductive tract have also been observed among women prenatally-exposed to DES (30, 31) as well as increased risk of reproductive dysfunction, including infertility and pregnancy complications (37). Laboratory animal studies have demonstrated the persistent effects of early-life DES exposure on the reproductive tract in adulthood (as reviewed in Newbold *et al.* (29)) and epigenetic studies have proposed mechanisms by which DES may induce developmental reprogramming of reproductive tract tissue (53-56).

Our study result is similar to that reported in another epidemiologic study that also used a population-based sampling frame. That study was conducted among participants of the Nurses' Health Study II (38) and observed an incident rate ratio of 1.8 (95% CI: 1.2-2.8) for the association between prenatal DES exposure and self-report of laparoscopically-confirmed endometriosis (38). Other studies investigating prenatal-DES exposure in relation to endometriosis were not able to report an effect size due to the extremely few women reporting DES exposure, most likely due to a greater proportion of participants having been

born after the discontinuation of its use in the early 1970s (43) or a relatively small sample size (41).

Our data also suggested an increased risk of endometriosis in relation to participants having been born two or more weeks early. Infants born prematurely are not exposed to the surge of placental estrogens (57) that occurs towards the end of full-term gestation (58) and that stimulates fetal target organs including the uterus and the brain (57). This placental estrogen surge may be involved in the maturation of organs (57) and appears to suppress fetal HPO-axis activity, resulting in low fetal gonadotropins levels at birth (25, 59). Compared to full-term infants, premature infants instead demonstrate higher gonadotropin levels at birth and prolonged HPO-axis activity after birth (57, 59-61). Hence, it is possible that the lack of fetal estrogen stimulation towards the end of gestation and the prolonged HPO-axis activity after birth in premature infants may alter reproductive-axis development (25) and contribute to increased endometriosis risk in adulthood.

Prior epidemiologic studies have reported no association between prematurity and endometriosis (38, 42, 43). However, one of the studies was underpowered to detect an association (42) and the remaining two studies reported associations in opposite directions in sensitivity analyses (38, 43). One study that considered endometriosis confirmed by both visual inspection and histopathology among a cohort of women undergoing surgery reported an inverse association in relation to prematurity (43). Results derived from the study of only women undergoing surgery are susceptible to selection bias as the exposure may also be associated with the medical indication for surgery, resulting in a selection of atypical controls. The other study used a population-based sampling framework similar to our study (38). That study reported a modest positive association between prematurity and symptomatic laparoscopically-confirmed endometriosis (38).

The present analyses may have been limited by several aspects related to the ascertainment of the early-life factors. First, we relied on participant self-report, similar to most prior studies of these factors and endometriosis (38, 41, 43). However, for the early-life exposures of DES and regular soy formula feeding, we were able to use information that was directly gathered from the participant's mother or other family member. This was important given the low concordance we observed between the participant's report and that of her mother (or proxy) for these exposures.

Second, we did not have detailed infant feeding data including information on the timing of initiation, duration, and exclusiveness of soy formula feeding as well as information on other sources of infant nutrition such as non-soy formulas and breastfeeding. However, exposure to breastfeeding was not associated with endometriosis in two prior studies (38, 42) and the prevalence of breastfeeding was likely low in WREN; the majority of participants were born in the 1950s and 1960s when breastfeeding was on a downward trend, reaching a nadir in 1971 when <25% of U.S. infants were initially breastfed and ~14% continued to be breastfed at 2-3 months of age (46). Lastly, it is possible that greater medical surveillance among women who were prenatally-exposed to DES than unexposed women may have resulted in the incidental detection of endometriosis, explaining the association we observed in this study. However, this scenario involving incidental disease detection is unlikely given

the endometriosis case definition employed in our study; the case definition of endometriotic disease incorporates both disease invasiveness and the presence of symptoms indicative of interference with normal physiologic processes (45).

Since surgery is required for the definitive diagnosis of endometriosis, it is possible that not all cases of endometriotic disease in the GH population were identified in WREN. Similarly, since it was not feasible to surgically evaluate population-based controls for the absence of disease, some of the WREN controls may have undiagnosed endometriotic disease. However, the prevalence of undiagnosed disease among controls is likely to be low, less than 2% (45). This estimate was determined using data on the prevalence of undiagnosed chronic pelvic pain (9%) from a population-based study (62) and the frequency of Stages III and IV endometriosis among women with chronic pelvic pain (18%) (63). As previously described (64), the use of data on the frequency of any endometriosis (45%) (63), would only result in a 4% prevalence of undiagnosed endometriotic disease. Hence, the likely low prevalence of undiagnosed disease among the controls would only minimally bias our results.

The population-based sampling design instead strengthened our study; in WREN, controls were randomly sampled from the defined source population that gave rise to cases with endometriotic disease. This allowed us to conduct a relatively large case-control study and compare the frequency of early-life factors among women selected from the same underlying population as that of the women diagnosed with endometriosis. Our study was additionally strengthened by the years in which our study participants were born. The WREN participants were born in the decades during which DES was prescribed to pregnant women and the soy component of infant soy formulas changed. This provided us with the unique opportunity to evaluate a well-established transplacental estrogenic carcinogen in relation to endometriosis as well as investigate endometriosis risk before and after the current-day soy formulas containing isolated soy protein became commercially available.

To our knowledge, this is the first study to investigate regular soy formula feeding during infancy in relation to endometriosis. Additional studies are warranted to confirm the association we observed and to evaluate other sources of infant nutrition, including breastfeeding and commercially-prepared non-soy formulas, and aspects of soy formula feeding, such as timing of initiation and duration, which may contribute to greater endometriosis risk.

Conclusions

We observed that the early-life exogenous exposure of infant soy formula feeding was associated with an increased risk of endometriosis. Our data also suggested an increased risk of endometriosis with maternal DES use and prematurity. Our results support the hypothesis that disruption of development during the critical infant period and possibly the fetal period may increase the risk of endometriosis in adulthood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1Sociodemographic characteristics of WREN participants, Group Health, 1996-2001.^a

Characteristic	Cases (n=310) n (%)	Controls (n=727) n (%)
Age at reference date (years)		
17-24	28 (9)	64 (9)
25-34	65 (21)	140 (19)
35-44	149 (48)	358 (49)
44-49	68 (22)	165 (23)
Race		
White	261 (85)	602 (83)
Black	11 (4)	37 (5)
Asian/Pacific Islander	27 (9)	51 (7)
American Indian, Aleut, Eskimo	2 (1)	7 (1)
More than one race	7 (2)	27 (4)
Ethnicity		
Hispanic	22 (7)	22 (3)
Non-Hispanic	286 (93)	701 (97)
Income (US\$)		
<35,000	92 (31)	200 (28)
35,000-69,999	139 (47)	309 (44)
70,000	67 (23)	195 (28)
Education		
<HS	11 (4)	23 (3)
HS graduate	54 (17)	136 (19)
Some college	102 (33)	268 (37)
College graduate	91 (29)	163 (22)
Post graduate	52 (17)	137 (19)
Smoker		
Current	63 (20)	120 (17)
Former	72 (23)	170 (23)
Never	175 (56)	436 (60)
Alcohol use		
Current	162 (52)	322 (44)
Former	56 (18)	147 (20)
Never	91 (29)	258 (35)
Body mass index (kg/m ²)		
<18.5	8 (3)	15 (2)
18.5-<25.0	160 (52)	373 (52)
25.0-<30.0	75 (24)	186 (26)
30.0	65 (21)	146 (20)

Characteristic	Cases (n=310) n (%)	Controls (n=727) n (%)
Parity		
Nulliparous	150 (48)	216 (30)
Parous	160 (52)	510 (70)

Abbreviations: WREN=Women's Risk of Endometriosis; HS=High School.

^aNumbers do not add to column totals due to missing data.

Table 2

Adjusted odds ratios and 95% confidence intervals for the associations between individual intrauterine and infant exposures and endometriosis, Group Health, 1996-2001.

Exposure	Cases (n=310) n (%)	Controls (n=727) n (%)	Matching variable- adjusted aOR ^a (95% CI)	Multivariable- adjusted aOR ^b (95% CI)
Maternal use of DES ^c				
No	214 (96)	517 (98)	1.0 (reference)	1.0 (reference)
Yes	9 (4)	11 (2)	2.0 (0.8-4.9)	1.3 (0.5-3.6)
Maternal smoking				
No	200 (70)	486 (72)	1.0 (reference)	1.0 (reference)
Yes	85 (30)	192 (28)	1.1 (0.8-1.5)	1.1 (0.8-1.5)
Maternal age at delivery (years)				
15-24	116 (38)	299 (42)	0.9 (0.6-1.1)	0.9 (0.7-1.2)
25-34	147 (49)	327 (46)	1.0 (reference)	1.0 (reference)
35-49	40 (13)	85 (12)	1.1 (0.7-1.6)	1.0 (0.7-1.6)
Firstborn				
No	199 (66)	473 (66)	1.0 (reference)	1.0 (reference)
Yes	104 (34)	242 (34)	1.0 (0.8-1.3)	1.0 (0.7-1.3)
Birth weight (lbs)				
<5.5	33 (11)	58 (8)	1.4 (0.9-2.2)	1.0 (0.5-1.8)
5.5 to <9.0	245 (81)	600 (85)	1.0 (reference)	1.0 (reference)
9.0	24 (8)	48 (7)	1.2 (0.7-2.1)	1.3 (0.8-2.2)
Fetal number				
Singleton	302 (98)	715 (98)	1.0 (reference)	1.0 (reference)
Multiple	7 (2)	11 (2)	1.4 (0.6-3.8)	1.3 (0.5-3.6)
Premature (born 2 weeks early)				
No	277 (91)	672 (94)	1.0 (reference)	1.0 (reference)
Yes	28 (9)	43 (6)	1.6 (1.0-2.6)	1.7 (0.9-3.1)
Regular soy formula feeding during infancy ^c				
No	209 (91)	506 (96)	1.0 (reference)	1.0 (reference)
Yes	20 (9)	20 (4)	2.4 (1.3-4.7)	2.4 (1.2-4.9)

Abbreviations: DES=diethylstilbestrol; aOR=adjusted odds ratio; CI=confidence interval.

^a Adjusted for frequency matching variables of reference age and reference date year.

^b Adjusted for frequency matching variables of reference age and reference date year as well as maternal smoking, birth weight, fetal number, and prematurity.

^c Among subset of women with report of exposures based on the input from mothers or others knowledgeable about the mother's use of DES while pregnant with the participant or soy formula feeding of the participant during infancy (233 cases, 535 controls).