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Prenatal Diethylstilbestrol (DES) Exposure and Mammographic Density

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Abstract

In a prospective cohort study of the health effects associated with prenatal Diethylstilbestrol (DES) exposure, DES was associated with an increased breast cancer risk after 40 years of age. It is unknown whether it is associated with greater mammographic density, which strongly predicts breast cancer risk. A cohort of DES-exposed and unexposed women was assembled at the Mayo Clinic in 1975, and followed through 2012 as part of the National Cancer Institute's DES Follow-up Study. Mammographic density from 3,637 mammograms for 332 (222 DES-exposed, 110 unexposed) women in this cohort screened at the Mayo Clinic, Rochester between 1996 and 2015 were determined clinically using the Breast Imaging Reporting and Data System (BI-RADS). Any effect of prenatal DES exposure on mammographic density was estimated using repeated measures logistic regression. There was no association between prenatal DES exposure and high mammographic density for either premenopausal (Odds ratios (OR) = 0.92 (95% Confidence Interval (CI): 0.50, 1.7) or postmenopausal women (OR = 0.90; 95% CI: 0.54, 1.5). Among premenopausal women, associations differed by body mass index (BMI), with ORs of 1.47 (0.70, 3.l) for women with BMI above the median, and 0.53 (0.23, 1.3) for those with BMI below the median ($p_{interaction}$ = .05). Overall, however, prenatal DES exposure was not associated with high mammographic density in this sample of DES Study participants. Consequently, this study does not provide evidence that high mammographic density is involved with the influence of DES on breast cancer risk.

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Keywords

Diethylstilbestrol; prenatal exposure; breast density prospective study

Introduction

A cohort of prenatally DES-exposed women over the age of 40 followed prospectively were observed to have an elevated breast cancer risk [1] compared with the general population, and relative to women who were not exposed. The explanation for the risk increase is unknown but could involve structural changes to the developing breast *in utero*, or alterations in reproductive hormones later in life. Dense breast tissue is one of the strongest risk factors for breast cancer. Breast cancer risk among women with ≥75% breast tissue density has been shown to be more than four times greater than that for women with <5% density [2]. Other measures of mammographic density's effect on breast cancer, however, indicate a less extreme influence on breast cancer burden[3]. The mechanism underlying this association has not been elucidated. Extensive mammographic density, however, may reflect cumulative estrogen exposure [4]. Dense breast tissue levels were elevated in Rhesus monkeys prenatally exposed to Bisphenol A (BPA), a compound with weaker estrogen activity than DES, compared to those untreated with BPA[5]. *In utero* effects of DES could affect subsequent mammographic density in the pre- and postmenopausal periods that would subsequently increase breast cancer risk among DES-exposed women. The increase in postmenopausal breast cancer observed among obese women is suspected to be due to increases in estradiol (E_2) production [6, 7]. This raises the possibility that BMI could potentiate any effect of prenatal DES exposure on mammographic density.

Linkage of records of women from the Mayo Clinic who were recruited into the DES Follow-up Study with their mammographic density data provided a unique opportunity to explore whether prenatal DES exposure influences mammographic density, which, in turn, could affect breast cancer risk.

Materials and Methods

The DES Combined Cohort Follow-up Study is a prospective cohort study of women who were confirmed to be either prenatally DES-exposed or unexposed via review of medical records or other physician-related verification, and has been described previously[8]. Briefly, the medical records of women who received prenatal care at the Mayo Clinic from 1943 through 1959 were reviewed and mothers of 818 women were identified who had been prescribed DES while pregnant with them[9]. Of these women, 633 were able to be traced and consented to be followed in the DES Follow-up Study. An additional 203 women whose medical records indicated that their mothers did not receive DES while pregnant with them were sampled and also consented to participate in the study. These women were followed by questionnaire for medical and reproductive outcomes, lifestyle and other exposures from 1975 through 1989 [8] as part of the original cohort study, and beginning in 1994 and approximately every 5 years subsequently (1997, 2001, 2006, 2011) as part of the National Cancer Institute (NCI) DES Combined Cohort Follow-up Study[10].

The third edition of the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) was used to visually categorize mammographic density into one of four categories (1=almost entirely fat, 2=scattered fibroglandular densities, 3=heterogeneously dense, or 4=extremely dense) based on visual evaluation[11]. Since 1996, the BI-RADS scores of mammographic density results from mammograms of women screened at the Mayo Clinic, Rochester have been routinely determined as part of clinical practice. Between July of 1996 and August of 2015, there were 332 women (222 DES-exposed and 110 unexposed) in the DES Follow-up Study identified who had at least one mammographic screening at the Mayo Clinic, with a total of 3,637 mammograms. Follow-up on these women began at their first mammogram in July of 1996 or later. Their follow-up continued until their last mammogram before the close of the follow-up in August of 2015 or the close of follow-up, which ever occurred first. These 332 women signed a research authorization consent form allowing for the use of medical record and imaging data for research. The study was approved by the Mayo Clinic's Institutional Review Board.

Information on prenatal DES exposure was obtained from DES Follow-up Study records. Also date of birth, age at menopause, hormone therapy (HT) use, family breast cancer history and time-specific BMI from the NCI DES Follow-up questionnaires were considered as potential confounders. Use of HT use was adjusted considering it a time-dependent covariate. If the examination date, included in the Mayo Clinic's electronic records, fell within the period during which the participant reported HT use on her follow-up questionnaire, then she was considered to have used HT use at the time of her mammography. The BMI, weight (kg) divided by height squared (m^2), was derived from height and weight information from the participant's medical record closest to the day of the mammogram. The time between BMI determination and mammogram ranged from 0 days to 17 years. The mean time between BMI measurement and the index mammogram was 193 days but the median time was 10 days. The BMI was determined within two days for 25% of the mammograms and within six months for 75%.

The association between prenatal DES exposure and mammographic density was analyzed with the mammogram as the analytic unit. The effect of DES on high mammographic density was estimated without regard to menopausal status. Analyses were also conducted separately on mammograms done when the participant was premenopausal or post-menopausal. Women could contribute to both the premenopausal and postmenopausal analyses if their screenings spanned both their premenopausal and postmenopausal years. Analyses were also stratified by BMI (above or below menopause-specific median) at the time of mammography. To control for age and to address the possibility of residual confounding by BMI[12] within BMI strata, age and BMI were also added to the model. The analyses without considering BMI as a modifier was conducted by modelling the risk of a BI-RADS density of 3 or 4 by including terms for prenatal DES exposure, age and BMI. A multiplicative term for prenatal DES exposure and BMI (above or below the menopause status-specific median) was added to test the hypothesis that the BMI-specific effect estimates of DES on mammographic density did not differ. In separate models, we further adjusted for parity and HT use.

High mammographic density on each mammogram was modelled using multivariate logistic regression. There were multiple mammographic measurements over time for each participant. To account for these multiple measurements and their correlation within each participant, we fit generalized estimating equations within the logistic regression framework. An independent correlation matrix structure was assumed[13]. The analysis was conducted using SAS version 9.4 (Cary, NC).

Results

Overall, there were 3,637 (2,331 DES-exposed, 1,306 unexposed) mammograms taken on the 332 (222 DES-exposed, 110 unexposed) DES Study participants who had a least one screening visit at the Mayo Clinic. There were 706 mammograms (463 DES-exposed, 243 unexposed) taken on 162 (105 DES-exposed, 57 unexposed) women who were premenopausal when these mammograms were taken. There were also 2,562 (1,679 DES-exposed, 883 unexposed) mammograms taken on 280 (190 DES-exposed, 90 unexposed) post-menopausal women. Overall, the median number of mammograms for each participant over the course of the follow-up was 11 (range: 1 – 23, interquartile range: 6 - 16). On average, there were 4.4 mammograms taken for each participant who was screened before they reached menopause (4.4 DES-exposed, 4.3 unexposed). The mean age at mammography during these years was 48.6. Among the women screened during their postmenopausal years, there were on average, 9.2 mammograms available on each participant (8.8 DES-exposed, 9.8 unexposed). The mean age at mammography during these years was 57.8.

Prenatally DES exposed women were less likely to have had a live birth, and appeared more likely to have a higher current BMI as reported on the 2011 questionnaire compared to unexposed women. The mean ages of the exposed and unexposed women in 2011 were 59.7 and 60.6, respectively. The mean age of menopause for the exposed was 47.3 and for the unexposed was 48.6 (Table 1).

There was no association between prenatal DES exposure and having a BI-RADS score of 3 or 4 when menopause status was not considered. Adjusting for age and BMI the associated Odds Ratio (OR) was 0.91 (95% confidence interval CI): 0.58, 1.43). Among the 706 mammograms taken on premenopausal women there were 440 (62.3%) with BI-RADS scores of 3 or 4 (280 or 61% DES-exposed, 160 or 66% unexposed). Of the 2,562 mammograms taken on post-menopausal women, there were 965 (37.7%) mammograms with a BI-RADS score of 3 or 4 (625 or 37% DES-exposed, 340 or 39% unexposed). With adjustment for age and BMI, there was no association between prenatal DES exposure and risk of BI-RADS score of 3 or 4 (OR = 0.93; 95% CI: 0.50, 1.7) and OR = 0.90 95% CI: (0.54, 1.5) among pre-menopausal or post-menopausal women, respectively (Table 2). Results were similar with further adjustment for parity (Table 2).

For premenopausal women, results appeared to differ by level of BMI. The age - and BMI-adjusted ORs for premenopausal women above and below the median BMI were 1.47 (95% CI: 0.70, 3.1) and 0.53 (95% CI: 0.23, 1.3) respectively. There was, however, no apparent BMI-specific association between DES exposure and mammographic density for post-

menopausal women: OR = 1.05 95% CI: (0.47, 2.4) and OR = 0.83 95% CI: (0.45, 1.5) for women above and below the median BMI respectively (Table 2). The p-values for the statistical test for interaction to determine if the BMI specific estimates for DES and mammographic density differed were 0.05 and 0.62 for pre-menopausal and post-menopausal women respectively (Table 2). Again, results were similar with additional control for parity (Table 2). Controlling for HT use at the time of the mammography did not appreciably change the results (data not shown).

Discussion

The results of the current investigation indicate that overall there was no association between prenatal DES exposure and dense breast tissue in either pre-menopausal or post-menopausal women. There is no previous information regarding the effects of prenatal estrogen exposure on human mammographic density. Investigations, however, into postmenopausal endogenous estradiol (E_2) levels and mammographic density have been inconsistent[14, 15] and post-menopausal hormone therapy has consistently been positively associated with mammographic density[16, 17]. One previous study of DES exposure during adolescence and mammographic density reported no differences in percent mammographic density for women who had received high-dose estrogen treatment (54% of whom were treated with diethylstilbestrol) for tall stature compared to women who did not receive treatment[18]. Mammary tissue excised from four Rhesus monkeys prenatally exposed to BPA, an endocrine disruptor similar to DES, had a larger number of mammary ducts compared to that from five control animals[5]. To our knowledge, the current analysis represents the first investigation of prenatal DES exposure in relation to mammographic density in humans[19].

In the current analyses, there were suggestive differences in associations of prenatal DES exposure and mammographic density by BMI. These differences were observed among women above and below the menopause status-specific median BMI for pre-menopausal women only. There was a positive association between DES exposure and dense breast tissue among heavier women and an inverse association among lean women. The BMI-specific estimates were, however, imprecise. Consequently, random variation could also explain the differences and there may actually be no effect of DES on mammography density.

Obesity is a suspected breast cancer risk factor for older women[7]. Increases in estrogen production associated with obesity in post-menopausal women[6] might also influence mammographic density and potentiate any possible positive effect of prenatal DES exposure on it. Consequently, there may be some biological plausibility to the observed positive association between prenatal DES exposure and increased mammographic density in heavier women. The inverse association between prenatal DES exposure and breast tissue density among leaner women, however, was unexpected. The positive and inverse associations between prenatal DES exposure and mammographic density for women within the differing BMI categories could be attributable to misclassification of BI-RADS assessment on mammography evaluation. There has been only moderate agreement between observers when grading breast density by BI-RADS[20]. It is, however, unknown whether reliability of mammographic density measurement via BI-RADS scoring is influenced by BMI.

Furthermore, there is no reason to suspect that any possible inaccuracy of BI-RADS measurement imparted by BMI would be differentially affected by prenatal DES exposure. Consequently, the actual BMI-specific effects of DES on mammographic density may be more pronounced than the study results indicate. Alternatively, these could all be chance findings.

Overall, no association between DES and mammographic density was observed in the current study. The association of prenatal DES exposure with increased breast cancer risk was observed predominantly among women who were exposed to higher DES doses in the DES Follow-up study[21]. The women recruited into the study from the Mayo Clinic were exposed to lower doses[1]. Therefore, we cannot rule out the possibility that an association between prenatal DES exposure and mammographic density exists among women with higher levels of exposure. Currently mammographic density data is not readily available for other participants in the DES Follow-up Study. If the BMI-specific association between prenatal DES exposure and mammographic density were less tenuous, possibly weight control could be further explored as a means to offset any adverse effect of DES as it relates to breast cancer. Given the equivocal nature of the BMI-specific results, however, a factor, such as BMI, that could ameliorate the effects of DES on breast cancer remains elusive.

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Abbreviations

DES	Diethylstilbestrol
BI-RADS	Breast Imaging Reporting and Data System
OR	Odds ratios
CI	Confidence Interval
BMI	Body Mass Index
BPA	Bisphenol A
E2	Estradiol
NCI	National Cancer Institute

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Novelty and Impact Statement

Currently it is unknown if prenatal Diethylstilbestrol exposure influences mammographic density, a major breast cancer risk factor. This prospective study explores this association to determine if the breast cancer risk imparted by prenatal DES exposure does so via influence on mammographic density. No association between prenatal DES exposure and mammographic density was observed in the current study. Consequently, we found no evidence that the influence of prenatal DES exposure on breast cancer risk involves mammographic density.

Table 1

Distribution of Factors Related to Breast Density by DES Exposure Status

Factor		
	DES-exposed N = 222	**DES – unexposed N =110**
Age ≥60 in 2011 N (%)	127 (57.2)	71 (64.6)
Mean age in 2011 (std. dev)	59.7 (4.4)	60.6 (4.6)
Mean age at pre-menopausal mammogram (std. dev.)	48.5 (4.2)	48.8 (4.3)
Mean age at post-menopausal mammogram (std. dev.)	57.5 (5.6)	58.4 (5.5)
Ever use hormone therapy N (%)	139 (62.6)	70 (63.6)
Ever have a live birth N (%)	164 (76.6)	93 (87.7)
Mother or sister diagnosed with breast cancer N (%)	46 (21.3)	24 (22.6)
Mean age at menopause (std. dev.)	47.3 (6.4))	48.6 (6.3)
Mean (std. dev) BMI at age of 20	21.4 (3.4)	21.1 (2.8)
Mean (std. dev) BMI in 1994	25.5 (5.5)	25.6 (5.4)
Mean (std. dev) BMI in 2011	27.7 (6.4)	27.4 (6.5)
Mean BMI Pre-menopausal mammograms (std. dev.)	27.9 (6.9)	26.4 (5.5)
Mean BMI Post-menopausal mammograms (std. dev)	29.1 (7.1)	28.8 (6.8)

Table 2

Odds Ratios (OR) and 95% Confidence Intervals (CI) between DES Exposure and Breast Tissue Density using all Mammograms among Premenopausal and Post-Menopausal Women.

	Premenopausal				Postmenopausal			
DES Status	**BIRADS≥3**				**BIRADS ≥3**			
	N (%)	**OR_{crude} (95% CI)**	**OR*95% CI**	**OR+95% CI**	**N (%)**	**OR_{crude} (95% CI)**	**OR*95% CI**	**OR+95% CI**
Total								
Unexposed	160 (66)	1.0	1.0	1.0	340 (39)	1.0	1.0	1.0
Exposed	280 (61)	0.79 (0.41, 1.5)	0.93 (.50, 1.7)	0.88 (0.48, 1.6)	625 (37)	0.95 (0.59, 1.5)	0.90 (0.54, 1.5)	0.82 (0.50, 1.4)
High BMI								
Unexposed	45 (43)	1.0	1.0	1.0	79 (19)	1.0	1.0	1.0
Exposed	122 (49)	1.28 (0.62, 2.7)	**1.47 (0.7, 3.1)	1.50 (0.73, 3.1)	179 (22)	1.18 (0.54, 2.6)	**1.05 (0.47, 2.4)	1.0 (0.44, 2.3)
Low BMI								
Unexposed	115 (83)	1.0	1.0	1.0	261 (56)	1.0	1.0	1.0
Exposed	158 (74)	0.56 (0.24, 1.3)	**0.53 (0.23, 1.3)	++0.46 (0.19, 1.10)	440 (53)	.88 (0.49, 1.6)	**0.83 (0.45, 1.5)	++0.73, (0.40, 1.3)

From repeated measures analysis.

*Odds Ratio (OR) adjusted for age and BMI

+Odds Ratio (OR) adjusted for age, BMI, and parity** p for DES*BMI interaction = .05 among pre-menopausal women and p for DES*BMI interaction = .62 among post-menopausal women.

++p for DES*BMI interaction = .02 among pre-menopausal women and p for DES*BMI interaction = .51 among post-menopausal women.