

Breast cancer following diethylstilbestrol exposure in utero: insights from a tragedy

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European Journal of Epidemiology
Affiliated to the European Epidemiology
Federation

ISSN 0393-2990

Eur J Epidemiol
DOI 10.1007/s10654-012-9655-0

Editor-in-Chief: **Albert Hofman**

European Journal of
EPIDEMIOLOGY

ISSN 0393-2990 • CODEN: EJEPEB • Volume 21 • No. 4 • 2006

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Breast cancer following diethylstilbestrol exposure in utero: insights from a tragedy

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Received: 30 December 2011 / Accepted: 16 January 2012
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Abstract Diethylstilbestrol (DES), a powerful synthetic estrogen introduced in 1938, was prescribed to prevent pregnancy complications, but was later shown to have a series of adverse side-effects in the offspring, including cancer of the vagina. Recent evidence indicates that in utero exposure to DES is also linked to breast cancer in women over the age of 40 years. This evidence provides support to the hypothesis that in utero exposures may affect breast cancer risk in adult life.

Keywords Diethylstilbestrol · DES · Estrogens · In utero · Breast cancer

August 2006 was a worrisome month for women exposed to diethylstilbestrol (DES) in utero. Evidence from an NCI study, which had just been published, raised serious concerns about a link between this exposure and breast cancer risk in the offspring [1]. DES, a powerful synthetic estrogen introduced in 1938, was prescribed to prevent pregnancy complications. When adequate scientific assessment finally became available in the early 1950s, the treatment was shown to lack efficacy altogether and was taken off the

market in 1971 [2]. In the US alone probably several million pregnant women and their offspring had been dragged into what ended up to resemble a tragic human experiment. Follow-up of the exposed mothers and daughters revealed an excess risk of breast cancer in the mothers [3] whilst the daughters often suffered from genital malformations, infertility, pregnancy complications [2] and a more than 100-fold increased risk of vaginal adenocarcinoma at a young age [4]. This latter unexpected effect of DES, now a classic epidemiologic observation of transplacental carcinogenicity in humans, was accepted as causal based on only one study with striking results [4].

It was not until recently, however, that DES exposed women, born in the 1940s, 1950s and 1960s, reached the age when their risk of breast cancer in adulthood could be reliably assessed. A few early studies, including those conducted in the context of the large prospective study of DES exposure, coordinated by the National Cancer Institute in the US, were hampered by low statistical power and short follow-up and could not document an increased breast cancer risk in the DES-exposed offspring [5, 6]. Later analyses of the NCI DES cohort, however, provided worrisome evidence of a 2.5-fold excess breast cancer risk among women 40 years or older already in 2002 [7]. On August 2006, with a larger number of cases and follow-up covering older ages, the evidence from the NCI study became compelling. Merging four different cohorts in the US, the NCI study included over 4,000 women with confirmed DES exposure in utero and a non-exposed cohort of about 2,000 women. In 2006, the salient findings, based on 102 incident invasive breast cancers, were an excess risk of breast cancer among DES exposed women that became discernible after the age of 40 and then increased with age as supported by a significant interaction term ($p = 0.03$). The multivariable relative risk of breast cancer was 2.1

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among women aged 40–49 and 3.85 among those 50 years or older. The DES dose was known for only 38% of the women, but regional prescription practices allowed estimation of the dose for most of the remaining women. Only two dose categories could be established and the misclassification might be substantial, but a significant dose–response was nevertheless documented (p for trend 0.01) [1].

Recently, an update of the NCI cohort study was published, now with the broader scope of summarizing 12 different adverse outcomes in women exposed in utero to DES [2]. This publication adds limited evidence with regard to the risk of breast cancer overall because compared with the previous report in 2006 the total number of incident breast cancers among women 40 years or older, both exposed and unexposed to DES in utero, had only increased from 77 to 82. However, the updated report allowed the women with documented DES exposure to be stratified into those with and without vaginal epithelial changes, an established marker of high dose. As for most of the 12 studied outcomes, the risk of breast cancer was also significantly higher among women with [relative risk (RR) = 2.21; 95% confidence interval (CI) 1.11–4.38] than without (RR = 1.30; 95% CI 0.64–2.67) vaginal epithelial changes.

The NCI investigators argued already in 2006 that their findings have clinical implications for women whose mothers received DES during pregnancy [1], and in 2011 that their results provide “additional support for a causal relationship” [2]. Several widely accepted guidelines for causal inference are met by the NCI study: the exposure is well documented and adequately characterized on the basis of the structure of DES; bias or confounding, but even chance, are all unlikely explanations to the findings; the association is strong with a significant dose–response trend (using two different metrics, namely estimated dose and vaginal epithelial changes as a biomarker of high exposure); rates of follow-up were high; in adulthood, the effect appears specific for breast cancer; the temporal relationship between exposure and outcome is obvious; and a carcinogenic effect is biologically plausible, indeed hypothesized more than 20 years ago [8].

But the existing evidence for DES exposure in utero and breast cancer risk falls short of meeting one fundamental criterion for causality emphasized by Hill, and others, including ourselves [9], namely consistency through replication of findings in several studies. This is particularly important in observational studies, because bias and confounding can never be completely ruled out. In the context of in utero exposure to DES and breast cancer risk, it is of limited concern that some early studies were null because they had inadequate statistical power and no informative follow-up into ages above 40. A more important concern is

that a prospective Dutch study with adequate power also among women above age 40 showed no association between in utero exposure to DES and breast cancer risk [10]. In the Dutch study, expected numbers were based on external rates from the general population, an approach which precludes proper adjustment for confounders. In the NCI study, such adjustment did indeed strengthen the association between DES and breast cancer [1]. A more fundamental limitation of the Dutch study is, however, that DES exposure could be confirmed in only 8% of those included in the “exposed” cohort and existence of vaginal epithelial changes was not assessed.

Hence, the issue of DES exposure in utero and breast cancer risk offers an interesting challenge in terms of causal inference, relevant for millions of women. In humans, we are stuck with two prospective studies. One of high quality convincingly showing a dose-dependent substantial excess risk after the age of 40. And another with methodologic limitations, notably uncertainty about actual DES exposure, which provides no evidence of an excess risk. Additional informative studies seem unfeasible because DES is of no commercial interest and its use ended four decades ago and is hard to document retrospectively. We consider in utero DES exposure and breast cancer risk as one of the rare instances when causality can be inferred with a high degree of confidence based on only one observational study supported by substantial mechanistic data. Of note, the causal link between in utero DES exposure and vaginal adenocarcinoma also relied on a single study [4], though, admittedly, the relevant RR estimates were of a different order of magnitude. On the other hand, this latter, generally accepted, causal link triggers another criterion of causality with respect to breast cancer, by invoking evidence through analogy [11].

Whilst the scientific data concerning the consequences of in utero exposure to DES on breast cancer risk [1, 2] further increased the burden on women exposed to DES, the relevant studies also became landmarks for research on breast cancer etiology. Since a defined hypothesis that breast cancer may originate already in utero was formulated in 1990 [8], a wealth of evidence has accumulated and become integrated into a proposed causal model for breast cancer [12]. The hypothesis is, however, uniquely difficult to directly investigate in humans. The relevant intra-uterine processes cannot be immediately observed because such research would be unethical and it takes several decades for the outcome (breast cancer) to become manifest. Hence, research, which has generally been supportive of the hypothesis, has focused on surrogate markers of exposure such as birth weight, preeclampsia and twin pregnancy, factors likely to influence or reflect features of the intra-uterine milieu that might also program risk of breast cancer in adulthood [12].

In that context, the sad DES “experiment” is exceptional. Women were exposed during a well-defined and vulnerable intra-uterine period to a potent synthetic estrogen, which crosses the placenta and was often given in high doses escalating from the 7th to the 35th week of pregnancy [13] according to a fixed regimen. A wealth of experimental data illustrates numerous conceivable mechanisms whereby DES could interfere with cellular processes and disrupt normal breast development. Hence, the landmark NCI study [1, 2] provides the first direct evidence that breast cancer risk in adulthood is indeed influenced by an exposure entirely confined to the intra-uterine period.

Acknowledgments This work was supported by Karolinska Institutet, Distinguished Professor Award (grant number Dnr: 2368/10-221).

Conflict of interest Dr. Adami has been retained as a consultant in litigation on behalf of DES daughters claiming breast cancer injury due to DES exposure.

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