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Women exposed to DES in the womb face increased cancer risk; NIH study followed daughters of women given diethylstilbestrol during pregnancy and found increased fertility problems and cancer risks

A large study of the daughters of women who had been given DES, the first synthetic form of estrogen, during pregnancy has found that exposure to the drug while in the womb (*in utero*) is associated with many reproductive problems and an increased risk of certain cancers and pre-cancerous conditions. The results of this analysis, conducted by researchers at the National Cancer Institute (NCI), part of the National Institutes of Health, and collaborators across the country, were published Oct. 6, 2011, in the *New England Journal of Medicine*.

Beginning in 1940, diethylstilbestrol, known as DES, was used clinically to prevent certain complications of pregnancy. In the 1950s, clinical studies showed DES was ineffective for this purpose. In the late 1960s, an unusual occurrence of a rare cancer of the vagina among young women, called clear cell adenocarcinoma (CCA), was observed and subsequently linked to their exposure to DES while in the womb.

In 1971, the U.S. Food and Drug Administration notified physicians that DES should not be prescribed to pregnant women. However, between 5 million and 10 million pregnant women and babies had been exposed to the drug. It was manufactured under many different product names, and came in various forms, including pills, creams and vaginal suppositories.

“Our study carefully documents elevated risk for DES-exposed daughters for a host of medical problems—many of them also quite common in the general population,” said study author Robert N. Hoover, M.D., director of the Epidemiology and Biostatistics Program in NCI’s Division of Cancer Epidemiology and Genetics. “Without the sentinel finding of a very rare cancer in young women, and without the sustained follow-up of those who were exposed, we would not know the full extent of harm caused by DES exposure in the womb.”

In this study, which included over 6,500 women (4,600 exposed and 1,900 unexposed), the researchers found that the daughters with exposure to DES while in the womb had an increased risk of 12 medical conditions, including a twofold higher risk of infertility and a fivefold increased risk of having a preterm delivery. (See table below for complete list of increased risks.)

This study is also the first to estimate the cumulative proportion of all DES-exposed women who developed these conditions because of their exposure. Of all DES-exposed women, 1 in 5 will experience some level of infertility because of their exposure. And of all those exposed women who are successful in having at least one birth, 1 in 3 will have a preterm delivery due to DES.

Although DES-exposed daughters have about 40 times the risk of developing CCA than unexposed women, CCA is still a rare disease, occurring in 1 in 1,000 DES-exposed daughters.

While the first women diagnosed with this condition in the late 1960s were adolescents and young adults at the time of their diagnosis, the research now shows that the risk for DES-exposed daughters continues through at least age 40. In addition, these women are more than twice as likely to develop pre-cancerous cells in the cervix or vagina (called cervical intraepithelial neoplasia) and have an 80 percent higher chance of developing breast cancer after age 40. According to the results of this study, by age 55, 1 in 25 DES-exposed daughters will develop abnormal cellular changes in the cervix or vagina, and 1 in 50 will develop breast cancer due to their DES exposure.

Risks for DES-Exposed Daughters Compared to Non-Exposed	
Outcome	Increased Risk
Clear-cell adenocarcinoma	40 times higher
Neonatal death	8 times higher
Pre-term delivery	4.7 times higher
Loss of 2nd-trimester pregnancy	3.8 times higher
Ectopic pregnancy	3.7 times higher
Stillbirth	2.4 times higher
Infertility	2.4 times higher
Early menopause	2.4 times higher
Cervical intraepithelial neoplasia	2.3 times higher
Breast cancer	1.8 times higher
First trimester miscarriage	1.6 times higher
Preeclampsia	1.4 times higher

This study was the first to assess risk based on the presence of vaginal epithelial changes as a biomarker of timing and dose of DES exposure. Exposed daughters with higher total dose of DES and younger age of the embryo at first exposure had evidence of these changes in the lining of the vagina. Women with these changes were at even greater risk for 9 of the 12 conditions compared to exposed women who did not have the biomarker.

This study did not evaluate sons with DES exposure in the womb, but previous reports have indicated an increased risk for certain testicular abnormalities, including undescended testicles or the development of cysts in the epididymis ~~the~~ tightly coiled tubes connected to the testicles. As DES-exposed sons grow older, more data will be available to assess their cancer risk. So far, research has shown no decreased fertility for these men, even with testicular abnormalities.

The women in this study were followed as part of the NCI's DES Follow-up Study, which began in 1992. NCI researchers will continue to study DES-exposed daughters as they move into menopausal years. The cancer risks for exposed daughters, as well as sons, are continually being studied to determine if they differ from an unexposed population. In addition, researchers are studying possible health effects on the grandchildren of mothers who took DES during pregnancy, because some of the genetic changes caused by DES exposure in the womb may be inherited.

The other research centers involved in this work are Boston University Slone Epidemiology Center, Boston; Cedars-Sinai Medical Center DES Project, Los Angeles; University of Chicago Department of Obstetrics and Gynecology; Dartmouth-Hitchcock Medical Center, Lebanon, N.H.; The Mayo Clinic DES Project, Rochester, Minn.; The Methodist Hospital-Research Institute Department of Obstetrics and Gynecology, Houston; and Tufts Medical Center, Boston.

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For more information about DES exposure and cancer risk, please go to <http://www.cancer.gov/cancertopics/factsheet/Risk/DES>.

For more information about NCI's Division of Cancer Epidemiology and Genetics, please visit <http://dceg.cancer.gov>.

NCI leads the National Cancer Program and the NIH effort to dramatically reduce the burden of cancer and improve the lives of cancer patients and their families, through research into prevention and cancer biology, the development of new interventions, and the training and mentoring of new researchers. For more information about cancer, please visit the NCI Web site at www.cancer.gov or call NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237).

About the National Institutes of Health (NIH): NIH, the nation's medical research agency, includes 27 Institutes and Centers and is a component of the U.S. Department of Health and Human Services. NIH is the primary federal agency conducting and supporting basic, clinical, and translational medical research, and is investigating the causes, treatments, and cures for both common and rare diseases. For more information about NIH and its programs, visit www.nih.gov.

Reference: Hoover RN, Hyer M, Pfeiffer RM, Adam E, Bond B, Cheville AL, Colton T, Hartge P, Hatch EE, Herbst AL, Karlan BY, Kaufman R, Noller KL, Palmer JR, Robboy SJ, Saal RC, Strohsnitter W, Titus-Ernstoff L, Troisi R. Adverse Health Outcomes in Women Exposed *In Utero* to Diethylstilbestrol. *NEJM*. Oct. 6, 2011.