

DES RESEARCH UPDATE



Fall 2010

Report of the DES Follow-up Study from the National Cancer Institute

Findings from the Third Generation

We are now studying health effects in granddaughters of women who were given DES during pregnancy. Dr. Linda Titus-Ernstoff at the Dartmouth Medical School leads the study. All five DES study centers are contributing. In 2001, nearly 800 adult granddaughters enrolled in the first phase of the "Third Generation Study." These women will complete questionnaires and share medical records to verify certain health conditions. Additional information on the granddaughters and grandsons was collected on questionnaires sent to the second generation participants.

DES researchers have already published three papers about the third generation.

Periods and Fertility

The first paper, based on the Third generation Study, shows that granddaughters of women who were exposed to DES started their periods at a later age than their peers whose grandmothers were not exposed to DES. This group was more likely to

Thank you for Helping Our Research

Thank you for taking part in the National Cancer Institute (NCI) Diethylstilbestrol (DES) Follow-up Study. Because of your help, we are able to better understand how DES exposure affects the health of millions of women and men. By taking part over the years, we have been able to review the effects of DES across the life-span. Our goal is to find any new health concerns and to make recommendations for medical care.

We would like to share our latest research results in this newsletter. Our findings relate to daughters and sons exposed to DES, and also to grandchildren and possible health effects of exposure. Please contact your study center if you have any questions about this research, or the recommendations resulting from our study (see contact information on the back page).

Once again we are truly grateful for your support.



have irregular cycles. There was also a suggestion that older granddaughters were more likely to have fertility problems. But this was an early finding and must be confirmed.

Cancer Diagnoses

The other two papers looked at cancer diagnoses and birth defects, as reported by the granddaughters. We also asked their mothers to tell us about cancers and birth defects for all of their children. This gave us information about the third generation of men and women, not just the mothers who take part in our study.

We found little evidence of an overall increase of cancer in either the grandsons or granddaughters of DES-exposed women. But we did see more ovarian cancer cases (3 in total) than we expected in the granddaughters of DES-exposed women. While this finding is worrisome, it was based on very small numbers and further research is needed.

Birth Defects

The third report looked at birth defects in the grandsons and granddaughters. There was some increase in overall birth defects

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Future Plans for Our Study

Our study began sixteen years ago in 1994. Since then the research team has been tracking the health of people in the study. We are now looking at health effects of three generations. Even in a time of tight budgets, we are pleased to be able to continue this research.

You will be receiving a new questionnaire in 2011. A questionnaire will also be sent to granddaughters in 2014.

The DES Steering Committee (right) includes physicians, epidemiologists, researchers, and advocates, who are responsible for the study and dedicated to increasing our knowledge and understanding about DES exposure.



No Difference in Autoimmune Disease for DES Exposed and Unexposed Women

By Dr. William Strohsnitter

When the body is not able to fight off infection, it is called an autoimmune disease. This happens when the body does not recognize its own tissue and directs an attack on this tissue. We studied four types of autoimmune disease to find out whether prenatal exposure to DES may increase a person's risk of these diseases.

We looked at the following diseases:

- **Lupus** – Lupus is caused by an antibody attack on tissues and organs resulting in skin rashes, chronic joint swelling, kidney failure, or nervous system disorders. It is also called SLE, or Systemic Lupus Erythematosus.
- **Rheumatoid arthritis (RA)** – This disease causes joint swelling and stiffness and is due to an immune

response to a person's own connective tissue.

- **Optic neuritis (ON)** – This is a swelling of the optic nerve (the nerve that carries messages from the eye to the brain) due to immune response. It can cause vision loss in one eye, painful eye movement, and loss of color vision.
- **ITP** – This disease causes an unexplained drop in the amount of platelets, the blood cells that help your blood to clot. Its full name is Idiopathic Thrombocytopenia Purpura (ITP).

What did we find?

We found that there was *no difference* in the rates of having these four diseases between DES-exposed and unexposed women. There was *no difference* in the rates of lupus and ON in these two groups. There was *no*

overall difference in RA between the two groups. But there did appear to be a higher rate of RA among exposed women under the age of 45 compared to unexposed women of the same age. There is some uncertainty in applying this to all women, as the difference was based on a small number of cases (17 DES-exposed and 2 unexposed).

Also there was *no increase* in RA among DES-exposed women 45 years and older compared with unexposed women of the same age. There were too few ITP cases to conclude whether or not there was a difference in the rate of this disease in the two groups.



William Strohsnitter, D.Sc.
Principal Investigator
Tufts University

Study Finds Slight Increase in Depression among DES-exposed Daughters

Nurses' Study Findings

The Nurses' Health Study reports a slightly higher risk of depression in women whose mothers took DES during their pregnancies compared with those who did not. This large follow-up study of women began in 1989.

The risk of depression, defined by women reporting their symptoms and taking medicine for depression, was 40% greater in prenatally DES-exposed women. When other factors related to depression, such as smoking and alcohol use were taken into consideration, the risk was smaller (30%).

DES Follow-Up Study Findings

We assessed this association in the DES Follow-up Study earlier and found no greater risk of depression in prenatally

exposed compared with unexposed women and men (www.jstor.org/pss/3703450).

The number of women reporting depression was similar in the two studies, based on diagnosis and treatment.

There are differences in how the two studies are set up. In our study, we relied on information in the medical records. In the Nurses' Health Study, women had to report on their own whether they were exposed to DES. It is important that both men and women who are taking part in our DES Follow-up Study accurately report their history of and treatment for depression so that we can estimate the true risk of depression among DES-exposed women and men. As the DES Follow-up Study progresses we will be looking for opportunities to re-evaluate this association.

The Nurses' findings included symptoms of depression. In the Nurses' Health

Study, exposure to DES was self-reported by the women, whereas the DES Follow-up Study used information from medical records. These differences may be real. Or it might be that the different approaches of the two studies explains the slightly greater risk of depression in prenatally DES exposed women in the Nurses' study. Women who were exposed to DES might also be more likely to report their depression than women who were not exposed. Another possible explanation for the Nurses' Study findings is that there were differences between DES exposed and unexposed women in factors that are related to depression that were not taken into consideration in the study. That could result in a false increase in risk of depression among prenatally DES exposed women. However, this seems unlikely as they considered many factors and the increased risk of depression in the DES-exposed remained.

Study Findings Confirm Minor Genital Abnormalities in DES-Exposed Men

By Dr. Julie Palmer

Families often ask us whether their sons might have health problems if they were exposed to DES. To find answers to this question, over 1,000 sons exposed to DES and over 1,000 other men of the same ages who were never exposed to DES are part of our study.

These men have been completing questionnaires on the same schedule as women in the study, in 1994, 1997, 2001, and 2006. While many of the questions are the same, some are different. The men were asked whether they had ever been diagnosed with any genital problems.

This same issue was studied more than 20 years ago in a University of Chicago DES clinical trial and in a group of sons born to mothers at the Mayo Clinic. The two studies reported different findings:

- The University of Chicago found a higher chance of problems in the DES-exposed sons, compared to the unexposed group.
- The Mayo Clinic found no difference between sons who were exposed to DES and sons who were not.

We thought we might be able to find more answers by looking at data from the centers with sons – including sons from Mayo and Chicago, and from women who gave birth in Massachusetts.

Our Findings

We found that urinary and genital problems were fairly rare among DES-exposed sons. This is also true for the general U.S. population.

Sons exposed to DES did have a higher chance of having both a testis that does not move into the scrotum (called an undescended testicle) and a cyst in the coiled tube that lies above and behind each testicle (called an epididymal cyst).

Sons exposed to DES were two times more likely to have had one of these conditions compared to men who were not exposed. For both of these conditions, the number of cases was highest if the son was exposed during the first 10 weeks of gestation.

In sons of women in the Mayo study group, while DES exposure was not a major factor with these conditions overall, there was a significant association with undescended testicle and epididymal cyst for sons exposed early in the pregnancy.

In the University of Chicago clinical trial, DES was given as soon as a pregnancy was identified and was continued until the last weeks of pregnancy. This same practice was typical in Boston and in some other regions of the U.S. At the Mayo Clinic women usually began DES later in pregnancy and took it for only a few months. Differences in patterns of use may explain the conflicting findings noted in the earlier studies.

Our conclusion is that sons exposed to DES have a higher risk of certain urinary and genital problems, particularly

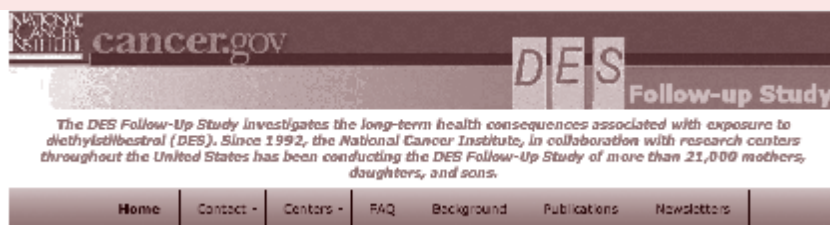
if they were exposed in the early months of fetal development. We and others have already shown that prenatal DES exposure does not affect fertility in men, even in men with these abnormalities.

We also asked the sons if they had ever been diagnosed with infection or inflammation of the genital organs. Prenatal DES exposure was not linked with infection or inflammation of the prostate, urethra, or epididymus, or with an enlarged prostate (benign prostatic hypertrophy or BPH). But DES-exposed sons were about two and a half times more likely to have had an infection or inflammation of the testes. We do not yet know the reasons for such an increase. It is possible that small defects, such as minor blockages, could explain the increase in infection and inflammation.

We will continue to research these conditions, especially BPH, as men in the study grow older.



Julie Palmer, Sc.D.
Principal Investigator
Boston University



Have You Visited the DES Follow-up Study Web Site?

Our study website (www.DESfollowupstudy.org) was introduced in the summer of 2005 to keep study participants and their families informed of the most current information on DES research. In addition to providing the latest study results, the site offers links to other DES resources, gives answers to some frequently asked questions about DES, and provides contact information so you can reach the staff at your study center.

We hope the site continues to be helpful to you. We would appreciate your input. If you have any comments about the web site or would like information on a specific issue, please contact your study center by accessing the Centers tab on the web site. The center's contact information is also listed on the back page.

Findings from the Third Generation

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in the children of women who were exposed to DES during pregnancy. But this finding may be biased since mothers who were exposed to DES during pregnancy were more likely to remember birth defects in their children than women who were not exposed to DES.

While some types of birth defects were more common in the DES granddaughters, it is not yet clear that these defects can be linked to DES. For example, complete or partial dislocation of the hip (called hip dysplasia) may be due to pregnancy and birth problems by the mothers, rather than effects of DES in the grandchildren. Heart problems were also more common in third generation women, but this seems to reflect an underreporting of similar problems by the unexposed women.

Most of the granddaughters are still young and most have not yet started families. We found no evidence that DES granddaughters were more likely

to have reproductive tract conditions. Also, there was no evidence that DES grandsons were at higher risk of genital-urinary conditions, such as sperm-filled cysts that may form in the scrotum (called epididymal cysts). These cysts have been reported in men whose mothers were exposed to DES during pregnancy.

A new phase of the Third Generation Study is underway. We have sent follow-up questionnaires to those granddaughters who were already enrolled. We are also asking a new group of granddaughters to join the study. The questionnaires can be completed on our secure web site (<https://des.dartmouth.edu>).

We appreciate everyone's help with this study. Our thanks go out to the centers who are working hard to enroll participants.



*Linda Titus-Ernstoff, Ph.D.
Dartmouth Medical School*

Complete the 2011 Questionnaire Online

The next follow-up is scheduled to begin in the spring of 2011. You may also complete the questionnaire online through a secure web site at desfollowupstudy.org. If you would like to complete the web-based questionnaire, please contact your study center (see center information on the right) and give us your email address. When the 2011 follow-up begins, your center's coordinator will email you a code that will allow you to access the online questionnaire on a secure page of our web site.



The web survey is safe, easy to use, saves paper, postage and allows us to process your information more quickly. If you prefer a paper questionnaire, you will continue to have that option. Also, if you have moved since we last contacted you or plan to move in the near future, please contact your study center and let us know your new mailing address.

Study Investigators

The DES Follow-up Study is carried out at five research centers in the United States. The NCI coordinates and funds the study. The investigators responsible for the study have been leaders in DES research and education for more than 25 years. The team includes physicians, epidemiologists, researchers and DES advocates. The team's goal is to obtain scientific and medical knowledge about DES exposure so that the study participants, their families, health care professionals and the public are informed about the health effects of DES.

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