CDC's DES Update Presents
DES & Breast Cancer: A Research Update for DES Daughters and Women Prescribed DES While Pregnant
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***This transcript has been edited for clarity**

INTRODUCTION

Dr. Forsythe

Thank you. Good evening, everyone, and welcome. My name is Dr. Ann Forsythe and I'm a health communication specialist at the CDC in Atlanta. I'll be your moderator for tonight's call.

I'd like to thank everyone for joining us in this first in a series of CDC's DES Update teleconferences. Tonight's presentations and question and answer period will highlight current breast cancer research information for DES daughters and women prescribed DES while pregnant.

Before we begin, there's some information I'd like to share with everyone. CDC has additional DES materials for the public, such as current DES research information, the history of DES, DES health effects, fact sheets, resources, and materials for healthcare providers. The information will be available through the CDC Web site where you can download and print all materials directly from the site.

CDC also has established a toll-free number where you can call to ask questions, locate DES organizations, and order materials for yourself or to share with others. The number for CDC's DES update is 1-888-232-6789 and our Web site address is www.cdc.gov/des. At the conclusion of this teleconference I'll repeat the number and Web site address so make sure you have a pen or pencil available.

If you are a member of DES Action USA, the DES Cancer Network, or the Registry for Research on Hormonal Transcendental Carcinogenesis, you'll be receiving the DES information I just spoke of in the mail so there's no need to order the materials off the Web site or by calling CDC's toll-free number.

Before we begin, I'd like to introduce our presenters tonight. We're very pleased to have with us two DES researchers, Dr. Julie Palmer and Dr. Linda Titus-Ernstoff.

PRESENTER BIOGRAPHIES

Dr. Julie Palmer

Dr. Palmer received her Master of Public Health degree from Boston University in 1985 and her Doctorate of Science from Harvard University in 1988. She is an associate professor of epidemiology at Boston University. Dr. Palmer is also an associate editor for the *American Journal of Epidemiology* and has served on numerous review panels for the National Institutes of Health. Her research is focused on the area of women's health, and she has published over 70 articles in this field, including articles on breast cancer, ovarian cancer, reproductive disorders, and heart disease.

She is a co-investigator of the Black Women's Health Study, an ongoing follow-up study of the health of 65,000 African-American women. Dr. Palmer has carried out research on the health effects of DES exposure since 1992, and she is the principal investigator of the Boston Center for the collaborative follow up study of long-term health effects of DES exposure. Tonight Julie will be addressing breast cancer research information for DES daughters.

Dr. Linda Titus-Ernstoff

Our next presenter is ***Dr. Linda Titus-Ernstoff.*** Linda received her Ph.D. in epidemiology from Yale University in 1989. She is an associate professor of community and family medicine at the Dartmouth Medical School. Doctor Titus-Ernstoff served on several breast cancer scientific review panels and served for four years on the Epidemiology Scientific Review Committee of the National Institutes of Health. Her research interests include women's cancer, melanoma, and the health effects of DES exposure, and she has published over 60 articles in these areas.

Currently, she oversees Dartmouth's study of ovarian cancer risk, and co-leads two large studies of breast cancer based on the New Hampshire Mammography network. Since 1992, Dr. Titus-Ernstoff has led Dartmouth's participation in the National Cancer Institute's collaborative study of DES. Linda's presentation tonight will focus on breast cancer research information for women prescribed DES while pregnant.

CONFERENCE CALL PRESENTATIONS

Dr. Palmer Thank you. It's a pleasure to be with you tonight. I'd like to share some recent findings on the relation of breast cancer risks to prenatal exposure to DES, but I'll start with a little background. As most of you probably know, DES or diethylstilbestrol is a synthetic non-steroidal estrogen that was first synthesized in 1938, and was widely prescribed to pregnant women in the United States and other countries in the 1950s and '60s.

It was believed that DES, by raising estrogen levels, could help to prevent miscarriage, although later it was shown that it had absolutely no beneficial effects. It's estimated that at least a million U.S. women took DES while pregnant.

In 1971 a link between a mother's DES use and a rare cancer of the vagina in the daughters led to the banning of DES during pregnancy, and prompted research on whether there were other adverse affects of DES use. One of the questions that mothers, daughters, and DES researchers have all had is whether the daughters will have a higher risk of breast cancer due to their prenatal DES exposure.

We know that breast cancer is a hormone-related disease, although no one has been able to pin down exactly how estrogens and other female hormones are involved. Women who go through puberty at a relatively young age have a higher risk of breast cancer, presumably because they have a longer period of estrogen production from their ovaries.

For the same reason, women who go through menopause at an early age, and thus have decreased estrogen levels early on, have a lower risk of breast cancer. We also know that taking estrogen pills, often called hormone replacement therapy, slightly increases a woman's risk of breast cancer.

We know little about the effects of prenatal hormone exposure. We do know that normal estrogen levels are higher during pregnancy, and that there can be great variation from one pregnant woman to another. For example, a woman who is pregnant with twins will have much higher levels of estrogens than a woman pregnant with only one baby. The woman who has pre-eclamptic pregnancy seems to have much lower estrogen levels.

Researchers have examined these types of pregnancies as an indirect way of getting at the question of whether prenatal estrogen exposure influences later breast cancer risks. The findings are inconclusive, but some studies have in fact found that women who are twins and thus received the higher exposure to prenatal estrogens have a higher risk of breast cancer. Also that women born of pre-eclamptic pregnancies who were exposed to less estrogen have a lower risk. These findings have added to the impetus to study the relation of in utero DES exposure to breast cancer risks.

In 1992 the National Cancer Institute called together investigators who had studied any of the early cohorts of DES-exposed persons with the aim of combining the cohorts to have enough statistical power to evaluate cancer outcomes. I'm using the term cohort here to refer to a group of persons who are followed over time in a study.

In cancer, even breast cancer, it's a rare disease, and the study of cancer requires large numbers of participants. It was agreed that combining existing cohorts might represent the only valid way to study long-term DES effects. Because not all women who took DES are aware of having done so, it's important for exposure data to be validated through prenatal records. These records would be from the 1950s and '60s, and most are no longer accessible today. Thus it's necessary to find and use cohorts of women who are identified through medical records in the 1970s; that is in the early period of DES research.

We were able to find four such cohorts of daughters and combine these for the new period of follow up. By far the largest of the cohorts is the group of exposed and unexposed daughters who participated for many years in what was called the DESAD Project, and that began in the 1970s. Probably many of you have heard of the DESAD Project, perhaps even participated in it. The DESAD Project has provided much of the information on the relation of DES exposure to reproductive disorders in the daughters.

The key feature of the four cohorts that were combined for the current study is that exposure or non-exposure to DES was confirmed by review of prenatal records. Unfortunately, in many cases the prenatal record did not provide a detailed record of the dose and timing, thus women who are counted as exposed actually have a wide range of exposures. Some mothers may have taken DES for only a week, whereas others started in the eighth week and continued up to the end of the pregnancy. Thus the exposed daughters received varying amounts of exposure, and the exact dose received is not available for most women in the study.

Altogether over 6,000 exposed and unexposed daughters were located and included in the current study, and there were about twice as many exposed as unexposed women in this study. They completed mail questionnaires in 1994 and again in 1997. The questionnaires included questions on whether they had been diagnosed with breast cancer or any other cancer, as well as details of their reproductive history.

If a woman reported breast cancer, we obtained the appropriate part of her medical record to confirm the diagnosis and obtain details of stage, type, and other characteristics. Over the entire period of follow up, so that's up through 1997, 58 participants were diagnosed with invasive breast cancer. Forty-three of the breast cancers occurred among the women who were exposed to DES and 15 were in women who were not exposed.

We compared the incidence or the rate of occurrence of breast cancer in the exposed and unexposed groups, taking into account each person's year of birth and own pregnancy history. Overall there was not a statistically significant increase in breast cancer risk associated with DES exposure.

Exposed women had a slightly higher incidence of breast cancer. Their incidence rate was 1.4 four times the rate of breast cancer in the unexposed, but this increase was not specifically significant, meaning that the association may well be due to chance rather than being a sign of a cause/effect relationship.

Since all of the DES-exposed participants received their exposure at about the same age, that is just before birth, their current age will be a marker for the latency period or how long it had been since they were exposed. With most cancers, there's a latency period after a key exposure before cases of cancer begin to develop or become present.

We carried out two separate analyses based on age. The first examined all participants' experience up to age 40, and this analysis included the 24 cases of breast cancer that developed before age 40. We found no association between DES exposure and risk of breast cancer before age 40. In fact, DES-exposed women had a slightly lower incidence of breast cancer, although the decrease was not statistically significant.

The second analysis looked at experience at ages 40 and older, and in this analysis we did observe a positive association. DES-exposed women were estimated to have 2.5 times the risk of breast cancer as compared with non-exposed women of the same ages. This increase was statistically significant. Most of the women had not reached age 50 yet so this 2.5 times higher risk primarily refers to women aged 40 to 49.

We classify cancers according to tumor size, and did not see a difference in risk for smaller and larger tumors. We also looked at risk of breast cancer according to the time of first exposure to DES; that is we compared daughters who were exposed in the first trimester of the mother's pregnancy with those whose first exposure was during the second trimester or later, and we did not see a difference in risk according to timing of exposure.

The chief limitation of our study is the small number of cases. As I pointed out before, there were only 58 total cases. Overall there was not a statistically significant increase in breast cancer incidence associated with prenatal DES exposure.

The 2.5 times increased risk observed among women aged 40 and older does raise concern. However, that finding is based on very small numbers and could represent a statistical fluke.

Because the numbers are so small we still do not know whether or not prenatal DES exposure influences the risk of breast cancer in the daughters, and this is probably frustrating news for women who have been exposed. Obviously, it would be more helpful to have a clear answer.

Fortunately we have been able to continue follow up in the study, and we're now receiving back the latest questionnaires. These questionnaires cover four or five years since the last analysis, and most of the women in the study are now in their 40s or 50s, which is the age at which breast cancer becomes more common.

We expect there to be an appreciable number of new breast cancer cases reported since the last questionnaire. Enough cases so that a future analysis is likely to provide more definitive results, and in the future we may also be able to look within specific sub-groups of women. For example, examine what is the relation between DES exposure and risk of breast cancer among women who have a family history of breast cancer or among women who have never given birth or among women who have used hormone replacement therapy. These are obviously all questions of interest. Thus we hope to have more informed results for you in the next year or two.

At this point I'd like to turn this forum over Dr. Titus-Ernstoff, who will discuss research on the mothers. Thanks.

Dr. Titus-Ernstoff Thank you, Dr. Palmer. By the mid 1970s there were serious concerns about possible health consequences for the women who were given DES while pregnant. In particular, there were worries about possible increases of breast cancer and other cancers that are influenced by hormones.

The causes of breast cancer aren't well understood, but the natural ovarian hormones, in particular estrogen, have long been suspects. It has been known for decades that breast cancer risk is lower in women who have children early, those who have several children, and in those who reach menopause at a young age.

Evidence for the role of natural hormones suggested that pharmaceutical hormones, such as DES, might also influence breast cancer risk. Several studies attempted to determine whether DES might increase breast cancer risk in women who were given this drug while pregnant.

The earliest study of DES exposed mothers took place in the middle 1970s and was followed by four other studies in the 1980s and two in the 1990s. Most of these studies showed that breast cancer risk was higher in the women who used DES compared to those who didn't, but some of the studies are small and not all found a statistically significant association. As a result, the link between DES and breast cancer risk in the mothers was suspicious, but it wasn't confirmed.

In the early 1990s the National Cancer Institute (NCI) brought together a group of scientists who had studied DES previously, and invited them to pool together their samples of exposed and unexposed individuals. The result was a large combined study of two generations. The mothers in the new combined study included DES exposed and unexposed women who had participated earlier in the University of Chicago clinical trial or in the Women's Health Study.

For all the mothers in the combined group, which we call a cohort, DES use or lack of use had been verified by medical records. This doesn't mean that we had perfect records. There were probably a few women who were prescribed DES, but never took it or perhaps others had taken DES, but it wasn't noted in their medical record. Nevertheless, medical records provide the best possible documentation of DES exposure so we had some assurances that the results of our study would be valid.

Of course, many of the women in the NCI's new combined study had not been contacted for many years. In the early to mid 1990s we conducted intense searches to try to locate all the mothers who had been previously studied. Ultimately the study centers found 4,400 of the mothers, about half of whom were DES exposed. A questionnaire was sent to them asking them to update their health experiences, and this effort was extremely successful.

We received completed questionnaires from nearly 4,000 women. Of the 4,000 study participants, a breast cancer diagnosis was reported by 290 of the DES exposed mothers and 221 of the unexposed mothers. The information obtained from these women was used in our statistical analysis of breast cancer risk.

These analyses showed that the relative risk of breast cancer was 1.3 for women who were exposed to DES compared to those who were not. In other words, we found that the risk of breast cancer is 1.3 times greater for DES-exposed women compared to unexposed women.

We were curious about whether the effects of DES might differ according to the dose of DES, the timing of use during pregnancy, or the duration of use. Unfortunately, the medical records did not consistently document the dose of DES or other details of its use.

However, our study results were similar to those of other studies in which the dose was known to be either high or low. Also, we know the DES doses were very high in the sub-group of women who had participated in the University of Chicago clinical trial, but the breast cancer risk in those DES-exposed mothers was not higher than in other exposed groups. Thus it appears that higher DES doses do not have a stronger influence on breast cancer risk.

We were also concerned that DES exposure might interact or combine with other characteristics of the women, such as their reproductive history, use of hormone replacement therapy, or a family history of breast cancer, to make risk even higher in the DES exposed. However, we found no evidence that any of the characteristics enhanced the effect of DES exposure on breast cancer risk.

Finally, we checked to see whether the influence of DES increased with the amount of time elapsed since exposure or with the increasing age of the women. Our analysis showed that the association between DES and breast cancer does not get worse over time and does not grow stronger as women get older.

Over the last two decades scientists have shown that post-menopausal hormone replacement therapy, which contains estrogens, is associated with an increased risk of breast cancer. Interestingly, hormone replacement therapy increases breast cancer risk by about 1.3 times, which is the same increase that is seen with DES. While an increase of 1.3 may seem large or alarming, it is actually modest. By comparison, cigarette smoking increases the risk of lung cancer by about ten times.

So although DES does not have a strong impact on breast cancer risk, the evidence is considered quite solid. The association has withstood the test of time and has been seen in numerous studies. We have confidence in our study results. The National Cancer Institute study of DES exposed mothers was much larger than any previous effort so our conclusions should be reliable. Also, the methods used in our study were good, adding to the validity of our finding.

In all likelihood this will prove to be the final and definitive investigation of breast cancer risk in the DES mothers. I think we can conclude this era of research by saying that women who were given DES during pregnancy have a modestly increased risk of breast cancer, and that this increased risk is about 1.3 times greater than that of unexposed women.

I want to thank all of you for your interest in our research. Dr. Ann Forsythe will now take your questions on the DES mothers and daughters studies.

QUESTION & ANSWER SESSION CONCLUDED THE CALL