# CDC'S DES UPDATE – CANCER RISKS FOR DES DAUGHTERS
**May 14, 2003**
**7:30 p.m. CDT**

***This transcript has been edited for clarity.**

**Moderator** Ladies and gentlemen, thank you for standing by. Welcome to the CDC's DES Update, "Cancer Risks for DES Daughters." At this time, all lines are in a muted position. Later during the conference, we will have time for questions and answers. As a reminder, this conference is being recorded. I would now like to turn the conference over to your host, Ms. Amy Harcar. Please go ahead.

**A. Harcar** Thank you. Good evening, everyone, and welcome. My name is Amy Harcar. I'm a member of the staff in the office of communication at the National Center for Environmental Health at the CDC in Atlanta and I'll be your moderator for tonight's call. I'd like to thank everyone for joining us in the third in a series of CDC's DES Update conferences.

Tonight's presentation and question and answer period will highlight cancer risks for DES daughters, but 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 and fact sheets, resources and materials for healthcare providers. The information is available through the CDC Web site, where you can download and print all materials directly from the site. CDC has also 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 the Web site address is www.cdc.gov/des.

At the conclusion of this teleconference I will repeat the number and the Web site address, so make sure you have a pen or pencil available. Also the teleconference transcript of this call will be posted on CDC's Web site. I'd like to remind everyone that we'll have a question and answer period after the presentation, so please feel free to jot down questions while you're listening.

Before we begin, I'd like to introduce our speakers tonight. Dr. Elizabeth Hatch received her Ph.D. in chronic disease epidemiology from Yale University in 1990 and her Master of Science degree in health policy and management from the Harvard School of Public Health in 1981. Dr. Hatch is an assistant professor at the Department of Epidemiology at the

Boston University School of Public Health. She conducted cancer research for nine years at the National Cancer Institute, where she was the co-principal investigator of the follow-up study of DES-exposed cohorts. She has published numerous articles and presented on the topic of DES for many years and has been a member of the CDC's DES National Education Campaign Steering Committee for three years. In addition to the health effects of DES exposure, her research interests include breast cancer, brain cancer and childhood cancers and she has published over 30 articles in these areas. Tonight, Elizabeth will present her latest research concerning cancer risks for DES daughters.

Also on the call with us tonight is Ms. Candy Tedeschi. Ms. Tedeschi will talk about the kinds of screenings recommended for DES daughters and answer any clinical questions from our audience following Dr. Hatch's presentation. Ms. Tedeschi has spent most of her career in nursing caring for women exposed in utero to DES. She was the coordinator of the DES Screening Center for three Long Island counties for 20 years. The center was sponsored by a New York State grant from the Department of Health. As coordinator, Candy provided total gynecologic care for DES daughters, including colposcopy, education for the entire DES family and outreach to the general population and to the nursing and medical communities.

Candy has lectured on a national scale, speaking at the National Institutes of Health sponsored conference in 1993 that resulted in a DES education grant studying the most effective ways of educating the medical and general population about DES-related concerns. She has also written many articles and a book chapter about DES problems. She has been involved, for several years, in the development of CDC's DES Update, as a member of the working group. Candy was on the board of directors for DES Action USA and continues to serve on their medical advisory committee. She is also active with the Society of Colposcopy and Cervical Pathology, sitting on several committees and is currently developing new DES educational materials for their Web site and journal.

Now I'll turn it over to Dr. Hatch.

**E. Hatch**

Thank you. It's a pleasure to talk with you tonight. I will be discussing some of the recent findings on the relationship between in utero exposure to DES and cancer risk in DES daughters, but first, I'd like to review some background on DES, including the methods of the ongoing research study that has been overseen by the National Cancer Institute for the last ten years. Then I'll discuss some of our findings on overall cancer risk, including the risk of clear cell adenocarcinoma of the vagina and cervix. Finally, I'll give a brief overview of cervical cancer risks and the possible

relationship between cervical dysplasia, which sometimes can progress to cervical cancer, and DES exposure.

Many of you may have been on the CDC teleconference call on breast cancer that was held in January, so I will only briefly touch on breast cancer risk during this call, but you may access the transcript of the breast cancer teleconference on the CDC Web site for more information.

As most of you probably already know, DES, or diethylstilbestrol, was first synthesized in 1938 and was used extensively from the 1940's through the 1960's to prevent miscarriages. The total number of people exposed to DES in the U.S. is not precisely known, but is thought to have been on the order of several million pregnancies. As it turned out, clinical trials conducted during the 1950's showed that DES was completely ineffective in preventing miscarriage and actually caused a higher rate of low birth rate and other pregnancy problems. Even so, DES continued to be used in this country up until 1971, when Dr. Arthur Herbst published the first study to link it with clear cell cancer of the vagina and cervix, otherwise known as CCA, in young women who were exposed in utero.

Beginning in the mid-1970's, several large research efforts were started to find daughters who we exposed to DES in utero so that they could be monitored for CCA and other health risks. The largest of these was the DESAD study that many of you may have heard about before. That study identified several thousand DES-exposed daughters, mostly through a review of medical records as well as a smaller comparison group of women who were not exposed to DES. Around the same time, researchers at the University of Chicago began to try to locate both the daughters and the sons who were born to mothers who had participated in one of the first clinical trials of DES called the Dieckmann Study so that they could be followed for health risks. As you can imagine, it was difficult for these researchers to find and contact people over 20 years later due to changes of names and addressees. However, they had pretty good success and were able to contact over 80% of the original study members. A third study consisted of offspring of mothers who had been infertile and were routinely given DES by an infertility doctor in the Boston area if they became pregnant, and also, their unexposed siblings.

Then, in 1992, the National Cancer Institute convened a meeting of investigators who had followed cohorts or groups of DES-exposed individuals in the past. The goal was to try to combine all of the past studies of individuals who had documented exposure to DES, to increase our ability to ascertain any health risks due to DES exposure. About 4,500

DES-exposed daughters and 1,500 unexposed women who had been previously studied were found and their current addresses were traced.

Since that time, three separate health questionnaires have been mailed to members of the study, one in 1994, one in 1997 and one in 2001. About 90% of those contacted have answered the questionnaires in each cycle. We ask questions about any and all types of cancer and benign tumors including benign breast disease, cervical and other gynecological tumors, autoimmune diseases, pregnancy and fertility problems, the occurrence of menopause and use of oral contraceptives and hormonal replacement therapy. If a woman reported cancer, we asked for permission to collect a copy of her medical record so that we could look at details of the diagnosis, such as the size and specific cell type of the tumor. I don't know if any of you participating tonight are part of this continuing study, but if you are, we owe you our deepest appreciation because without your participation, it would be virtually impossible to uncover potential human health risks related to DES.

We often get inquiries from people who would like to join the study. While we really appreciate the willingness to help with the research, at this point, we cannot add any more people to the study. The study subjects that have been participating have been followed on average now since they were in their late teens and early 20's and a wealth of information has been collected on them over the years. Also, all of them have records to document their exposure to DES, or in the case of the unexposed women, records that document that they were not exposed. That's one of the key features of this study that makes it unique. However, we do try to incorporate ongoing concerns of the DES-exposed population into our ongoing research.

Now I'm going to talk about some of the results that we've found from the study. During the first analysis of data from the study, we compared the cancer rates that were observed in the DES-exposed, with those expected based on rates from the general population in the United States. There were a total of 127 cancers reported. We found that overall, the rate of all types of cancers combined was approximately the same as that expected in the general population. We also compared the cancer rates between the exposed and the unexposed women and found the same pattern. The only cancer, which was significantly elevated in risk at the end of that first follow-up, was CCA, which was already known to be strongly linked to DES. There were three cases among the exposed and none in the unexposed, which corresponded to a 40-fold relative risk of CCA among the DES-exposed.

Even with this much higher risk in the exposed, CCA is a very rare disease. It is estimated that between 1 in 1,000 and 1 in 10,000 exposed women will get it. All of these cases from the first follow-up questionnaire occurred in women when they were in their teens and twenties. During the 1997 questionnaire follow-up, there was one additional confirmed case of CCA that was diagnosed in a woman in her 30's. There is an ongoing concern that there may be additional cases of CCA found in women as they enter their menopausal years, since this is the age range when CCA occurs normally in women who are not exposed to DES. There have been several cases of CCA in exposed women in their 40's and early 50's that have been reported to the registry of CCA cases that is kept at the University of Chicago.

Therefore, if you are exposed to DES, it is important to continue to be screened by a gynecologist on a yearly basis because there is no known upper age limit beyond which the disease will definitely not occur. However, it's also important to keep in mind that this is an extremely rare type of cancer, so that even though there's a much higher risk among the DES exposed, based on current estimates, at least 999 out of every 1,000 exposed to DES will not get CCA.

The only cancer type that occurred in more than a handful of women in the first study was breast cancer, and even breast cancer was quite rare in our study. This is because in general, cancer is rare among younger people, and women who are exposed to DES are just beginning now to enter the age groups when breast and other cancers become more common. We've analyzed breast cancer incidence up through 1997. There were a total of 58 breast cancers that occurred. We found that there was no statistically significant increase in breast cancer risk overall among the DES-exposed women. Two separate analyses were then carried out based upon a woman's age. There was no increase in breast cancer occurring very early, that is, before age 40, among the exposed. If anything, there was as slight decrease in risk, but this wasn't statistically significant. However, among women who were over age 40, primarily those in the 40- to 49-year-old age range, there was a two and a half fold increase in the risk of breast cancer. There were no differences based on the size of the tumors or on when the women were exposed to DES during fetal life.

This finding does raise some concern. However, it is based on very small numbers of cases and could be a statistical fluke. We are just beginning to analyze the data on breast cancer from the most recent questionnaire data based on cancers which have occurred through 2001. Within the next year or so, we should have a more definitive answer to the question of whether DES is related to breast cancer in exposed daughters.

In addition to concerns about CCA and breast cancer, there has been an ongoing concern about whether the more common type of cervical cancer, squamous cell cancer, as opposed to clear cell adenocarcinoma, may be increased among the DES exposed. This type of cervical cancer has actually been steadily declining in incidence since the introduction of the Pap smear, which can detect early cellular changes in the cervix. These early changes are commonly referred to as cervical dysplasia and they may eventually progress to cancer if not treated. The problem with studying cervical dysplasia, also known as CIN, is that it is very difficult to know which cellular changes will progress to cancer and which will eventually revert to normal looking cells.

We now know that the primary cause of cervical dysplasia in cervical cancer is infection with human papilloma virus, or HPV. HPV is a very common sexually transmitted infection, which, in some women, can persist and cause cancerous changes. Other risk factors, such as smoking, dietary factors, oral contraceptive use and perhaps DES exposure may predispose women with HPV to be more susceptible to carcinogenic changes.

There have been two major studies of the association between DES and cervical dysplasia. During the DESAD project, which began in the mid-1970's, exposed and unexposed study participants had a yearly clinical exam conducted by gynecologists. This exam consisted of a Pap smear, colposcopy, which is a special exam that uses a magnifying device to find cellular changes in the cervix and upper vagina, and then cervical biopsies were done of any suspicious areas that were found. The exam procedures were identical for the exposed and unexposed women. During each examination, abnormal findings were recorded and the study pathologist reviewed the results of the Pap smears and biopsies without knowing which women were DES-exposed. This is called blinding and is scientifically more sound.

This first study, which examined cases occurring from the mid-1970's up through the early 1980's, found that DES-exposed women had a two-fold excess risk of new cases of dysplasia. In the more recent study, we examined the risk of new cases of dysplasia from the early 1980's up through the mid-1990's in the same group of women from the DESAD study as well as in women from the Dieckmann cohort and the infertility cohort that I talked about earlier.

There were a total of about 3,900 exposed women and 1,400 unexposed women included in this analysis. The major difference between our recent

study and the first study is that we had to rely on questionnaire reports of cervical dysplasia and cancer and on medical records. In other words, during this study, we were not actually systematically examining the women. Because of this, we restricted our analysis to women who were confirmed to have a high-grade cervical dysplasia. This type is easier to diagnose correctly and is also more likely to progress to invasive cervical cancer than some of the earlier-stage cellular changes.

We found a total of 124 cases of high-grade cervical dysplasia in our study cohort, which were confirmed by pathology reports. We were also able to review pathology slides that had been stored for 95 of these cases so that we could determine whether the diagnosis had been accurate since there's a lot of disagreement over these diagnoses in the medical community. Overall, we found good agreement between what was reported on the pathology report and the diagnosis given by our expert study pathologist.

Consistent with the earlier study, we also found a two-fold higher risk of high-grade cervical dysplasia among the DES-exposed. We also analyzed the results according to when during gestation the women had been exposed to DES. In this analysis, we found that the earlier a woman was exposed during gestation, the higher the risk of cervical dysplasia. Women exposed very early, at seven weeks post-conception or before, had 2.8 times the risk compared to unexposed women, whereas those exposed at 15 weeks or later only had a 1.4-fold increase risk, which was not statistically significant.

The main limitation of our study is that it was not based on systematic clinical exams as the first study was. DES-exposed women tend to be more aware of potential health problems and their doctors are much more likely to examine them more closely with biopsies and colposcopy when there's a suspicion of cancerous changes of the cervix. We tried to take these factors into account in our analysis, but it's difficult to completely account for them.

Therefore, we're left with a non-definitive study which suggests a higher risk, but we can't rule out the fact that it may be due simply to greater rates of medical care and cervical cancer screening among the DES-exposed. The fact that we found higher risks in women who were exposed to DES earlier in gestation suggests that this might be a true increased risk, however.

If this is a true causal association, there are a couple of theories about why DES-exposed women might be at higher risk. The first is that DES causes structural changes in the cervix, which may make it more susceptible to

infection with HPV. The second theory is that perhaps DES-exposed women might have some immune system changes that result in their being less able to fight off HPV infection. There's some evidence to suggest that there may be immune system changes in animals, but this has not been well studied in humans. In any case, most cases of cervical dysplasia do not go on to progress to invasive cancer, and regular screening examinations and appropriate treatment can usually prevent this progression.

Now I'd like to turn it over to Candy Tedeschi, who will discuss what the latest screening recommendations are for DES daughters.

**C. Tedeschi**

Thank you, Dr. Hatch, for that clear, concise review of the current status of cancer. I think from here, it's logical for DES daughters to ask how should they be screened so that they can decrease their risk for cancer. What are the components of a good DES exam? I'm sure many of you have gone to your healthcare provider and have told them that you're DES-exposed and you have assumed that you are receiving the appropriate exam. Don't make that assumption. Ask your healthcare provider what kind of exam you will be receiving.

Of course, before you ask, you should already know the correct answer. Don't hesitate to ask for what you want and need. A GYN exam for a non-DES-exposed woman should include a breast exam; a visual examination of the cervix, the vagina and the vulva; a Pap smear; a pelvic exam or palpation of the uterus and ovaries and a rectal exam where it's age-appropriate. DES daughters need those same yearly examinations, but with some modifications and additions. I'd like to talk about those differences.

Most women know that the Pap smear is a screening examination for cervical cancer and its precursors. The Pap smear will detect squamous cell cancers and dysplasias, but has not proven very sensitive for clear cell adenocarcinoma, which is a glandular cell type of cancer. We do not have an easy way of screening for clear cell adenocarcinoma. Please be sure to let your healthcare provider know if you have any abnormal bleeding or a persistent abnormal vaginal discharge. While these are usually not serious problems, they can be an early sign of clear cell. These symptoms should be evaluated carefully.

One part of your examination that is very important is the palpation or feeling of the vaginal walls. Generally speaking, when the healthcare provider puts his or her fingers in your vagina, the other hand is then placed on the lower abdomen and the uterus and ovaries are felt. That's

appropriate, but those fingers in your vagina should also be rotated all around 360 degrees to carefully feel all the walls of the vagina and the cervix. What he or she is feeling for is any lumps or bumps or anything unusual. Anything unusual should be thoroughly evaluated with colposcopy as many of the early clear cells were felt before they were seen.

Your healthcare provider will insert a speculum and take a quick look at the cervix and vagina before doing your Pap smear. They should take a really good look, to make sure there aren't any ulcers, bleeding areas or anything different from your prior exam as well as any DES associated structural changes such as cervical ridges or hoods or coxcombs shape that can be visible with the naked eye. The speculum should then be rotated to visualize all the walls of the vagina. Rotating the speculum is not done routinely in a non-DES-exposed woman, but it is important for the DES-exposed. Abnormalities, including CCA, can be on the vaginal wall.

Many DES daughters have questions as to what kind of Pap smear they should have. I'd like to backtrack first and give you some general information. All women have two types of cells or tissue on their cervix. Inside the cervix, and to some extent around the opening of the cervix, women have glandular type cells. The vagina and the remainder of the cervix have squamous or skin-like cells. The two meet somewhere on the mouth of the cervix. If your mother took DES during the time of her pregnancy that the genital organs were being formed - that's between the sixth and the 18$^{th}$ week - DES can change where the two types of cells meet. In a DES daughter, it is not uncommon for the glandular cells to extend out and cover all of the cervix and even the upper vagina. This is called adenosis. Adenosis is normal tissue; it's just in an abnormal place. In other words, it extends further out than where it belongs.

Every DES daughter is different as to the extent of extra glandular cells or adenosis that she has. Many women have no adenosis. A DES daughter is born with adenosis; it does not develop after birth. Starting at the age you start getting your period, you start producing estrogen and the environment in the vagina changes. A cell change process starts going on where the glandular cells will gradually change into squamous cells. This process will continue for the rest of your life and it is called squamous metaplasia. The HPV virus that Dr. Hatch discussed likes to get into those changing cells and cause dysplasia.

Pap smears are the way that we detect this dysplasia. A Pap smear should be taken from the inside of the cervix with a brush that looks like a little mascara wand, and for around the outside of the cervix, near the opening,

with a little spatula that looks like a popsicle stick. These samples can then be placed on a glass slide or into a liquid medium. DES-exposed women need the same area sample, but in addition, they need that same spatula to be scraped along the outer edge of the cervix and the upper vaginal wall. This is commonly called a 4-quadrant Pap smear. A common misconception is that the 4-quadrant smear should be obtained with a separate spatula and be placed on an extra slide. That was how we did it years ago, but today we don't consider that necessary; it can all be put into one specimen.

If any abnormalities are found on the Pap smear or in any other part of the examination, a colposcopy should be performed. Colposcopy, basically it's a fancy microscope that fits between the healthcare provider and the patient and we look through it. It magnifies the tissue on the cervix and vagina. That will assist us in trying to locate where any abnormalities are so that we can then take biopsies and treat appropriately as needed. Many healthcare providers do not consider colposcopy a routine part of a DES exam, but others do. It is very helpful, particularly the first time a DES daughter is examined, to determine the extent of changes the woman has from her DES exposure.

Another test that can be helpful is the use of iodine staining. Iodine stains squamous cells dark brown, but it will not stain adenosis or glandular cells. Healthcare providers use this test to determine the extent of glandular cells without doing a colposcopy, but it does have some limitation. For instance, if there is an abnormal Pap smear, the iodine staining does not replace colposcopy and colposcopy should be done before iodine staining. Abnormal cells do not stain with iodine, so both normal glandular cells and abnormal cells don't stain, so it's not an overly specific test. Also, be careful if you have an allergy to iodine or shellfish. Make sure you tell your healthcare provider so that you don't have an allergic reaction. I think this covers most of the essential differences in the exam.

**Question and Answer Session Concluded the Call**