DES Action® VOICE

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A Focus On Diethylstilbestrol

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Lack of Data Leads to Lack of Screening Recommendations for DES Daughters

Editor's Note: *The DES Action website includes a helpful PDF print-out under the Resources menu that includes information your doctor needs to know about caring for women exposed in utero to DES. The print-out lists the screening recommendations developed years ago, but those may not necessarily be appropriate for postmenopausal DES Daughters. So we looked into the evidence again to see if any recommendations had been updated for DES Daughters today.*

Despite the confusion in the DES community about recommendations for annual gynecological cancer screenings, a review of current research does not provide much present-day guidance. Since DES Daughters are the first and only generation exposed to DES, no data exist on their risk of clear cell adenocarcinoma (CCA) or other gynecological cancers at their current ages—scientists are learning from today's DES Daughters themselves.

"If there were data, we would publish guidelines," explained Otis Brawley, MD, chief medical officer for the American Cancer Society. "It's really unfortunate. It ends up becoming a physician's best guess, and when it becomes physician's best guess, you very commonly run into screening overkill."

Excessive screening might sound wise for DES Daughters, but even in a population with a higher risk of cancer, too much screening could identify temporary abnormalities that aren't actually serious problems and could lead to more medical interventions that aren't necessary. "This is one of the problems in medicine when you have zero data to make a clinical decision," Brawley said. "People start guessing and sometimes people get hurt."

Yet not screening enough for cancers in a population already at much higher risk than other populations could also be disastrous. And that's the dilemma frustratingly faced by DES Daughters and their physicians.

The only guidelines in the research currently are those from the early 2000s, which closely resemble those on the DES Action website. A 2003 article in the *Journal of Midwifery & Women's Health*, for example, included recommendations similar to those in a Centers for Disease Control document designed to educate other physicians. They included an annual gynecological exam with a routine breast exam, a routine inspection of the vulva (the outside of the vagina), and a routine manual vaginal and rectal examination.

Then it recommended four additional steps for DES Daughters. The first is examination with a speculum (the metal tool

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New Research on Intersection of DES and Psychosis

Most DES research has focused on the drug's physical effects on those who were exposed, but its potential effects on mental health should not be ignored. A new study highlights the importance of continuing research on ways that prenatal DES exposure may have influenced brain chemistry, possibly increasing the risk of certain mental health conditions.

Researchers were specifically looking for differences in DNA methylation in those exposed prenatally to DES, and then whether those differences, if they existed, influenced the risk of psychosis. Psychosis refers to having delusions and/or losing touch with reality. A person is "psychotic" when they see hallucinations or see or hear things that don't exist.

The researchers did not find

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New Member Benefits!

Part of our upgrade to the DES Action USA website includes a new members-only area. As a member, you'll be able to log in to the Members Area for access to:

- **Searchable Doctor Listings**—If you are looking for a DES-aware doctor in your area, you can go to the members-only searchable Doctors List and search by city, state or ZIP code. You'll find doctors' names, practice names, specialties and contact information. These listings have been created by recommendations from DES Action members.
- **VOICE Newsletter**—current and historical. The VOICE is the most popular member benefit of DES Action. Now access all 36 years of newsletters and search for any topics or articles you need. The VOICE documents the history, the science and the personal stories of DES and all of us who were exposed.
- **Attorney List**—If you're interested in getting involved in possible future DES-related litigation, we offer a list of knowledgeable attorneys DES Action members have shared with us who might be able to help.
- **Exclusive Content**—an expanding collection of articles and videos accessible only to current DES members.

And more! Update your mailing address, pay your membership dues or make a donation online.

DES Action USA on Facebook

Like DES Action USA on Facebook and follow us on Twitter to stay up to date on medical and environmental health news that affects you, your loved ones and the planet. Share your thoughts with an engaged and active community. There's a ton of information swirling online 24/7 that affects the DES population—don't let it pass you by!

Online Support Group for DES Daughters

Here is a safe place for discussing very personal issues that arise for DES Daughters. We live in the farthest reaches of the country but have developed a sense of community together, via our email listserv.

What we talk about is private—just between us—so we can feel free to raise questions on topics we aren't comfortable bringing up with others. What is amazing is the depth of knowledge in the responses.

It's a terrific resource for information and support from DES Daughters who wrestle with the effects of menopause, family relationships and medical diagnosis issues specific to DES exposure. To join the support group, send an email to: DESactionDaughters-subscribe@yahoogroups.com.

New Website Information

We're changing to a new membership program to improve our service. The big thing to know is that we've reset the passwords. The new default password is: **desUSA?&B5V**

You'll find the same great content: a searchable list of doctors, a list of lawyers, and back issues of the VOICE in flipbook and PDF formats.

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MISSION STATEMENT

The mission of DES Action USA is to identify, educate, empower and advocate for DES-exposed individuals.

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Elinor Greenberg: Conversation with a DES Mother

Since the discovery of the devastating effects of prenatal DES exposure, most research has appropriately focused on what those effects are, primarily in DES Daughters but also in DES Sons and Grandchildren. Often lost in the discussion are the experiences of DES Mothers. These women have not experienced the same health impacts from DES exposure as many of their children, but their social, medical, emotional and other personal experiences are a vital part of the DES story.

Here we present a conversation with Elinor Greenberg, an 84-year-old DES Mother and educator living in Centennial, Colorado. She was prescribed DES during her second and third pregnancies, a daughter born in 1958 and a son born in 1960. Her doctor implied the DES would ensure her second and third babies would be larger after her first was born at 5 lbs, 8 oz. But he didn't discuss any risks of DES that she recalls, and she believes she took it throughout most of both pregnancies.


Elinor Greenberg

The DES VOICE also spoke briefly with Elinor's second daughter, Julie, about her experiences related to DES. She feels fortunate to have had two healthy children from two healthy pregnancies, without any fertility issues. "I'm not aware of anything in my life affected by DES," Julie said. Her first reaction to learning about the drug's effects, however, is familiar to many DES Daughters: "I was just shocked and surprised and worried and concerned," she said. She provided it in her family history at medical visits and wrote a paper, "Autobiography of a DES Daughter," in college about it.

Q: When did you become aware of the risks of DES to those exposed prenatally?

A: I can't tell you for sure when I became aware of the dangers of DES, but by then, my obstetrician was gone from Denver. He'd moved to the West Coast, and then I learned that he had died, so I never had an opportunity to go back to him and talk to him about it.

Q: How did you respond to the news of DES's health effects?

A: Well, of course I was concerned, and I immediately called my daughter since the dangers were identified as cancer. Since she was not a person with other symptoms that we could link to DES, we discussed her checking in with her own gynecologist, which I believe she did. I haven't really talked to her about this. It was a long time ago for sure.

Q: Did you look into the findings about DES more or do any additional research?

A: I only read about it when there was publication of studies or information in the newspaper. I didn't go after the studies since we thought we really didn't have anything at that point to be concerned with. Although, who knows what's ahead?

Q: Did learning about DES's effects influence your attitudes or behaviors toward the medical industry and/or toward pharmaceutical companies?

A: I don't think my behavior changed, though maybe it should have as I'm taking more medications. Perhaps my skepticism should have been increased. My work has been in the medical field since I was at one time a speech pathologist, so I tend to feel positively about the profession. But I felt a little bit betrayed and that I should be not so trusting.

Q: In what ways, if any, has your own DES exposure or that of your children affected your lives?

A: I have not had any problems that I can relate to that, and I don't think my daughter Julie has. My son and his wife had fertility issues, though I'm not sure if it was related. I don't even know if they would know. [Elinor added that she is currently fighting lung cancer, but she is responding well to the drug Opdivo and doesn't have reason to believe it's linked to her DES exposure.]

A Conversation with DES Daughter Chris Winberry

Chris Winberry, from Lynchburg, Virginia, found out about her DES exposure and its possible effects around age 17. Now age 60, Winberry recalls having horrible periods starting at age 12. They involved vomiting, fainting, and horrendous pain and caused her to miss school two days every month. She is the only girl among her siblings, and two of her three brothers were also exposed. Chris's mother was on bedrest during her pregnancy with Chris and took DES from early pregnancy until premature labor at 32 weeks, when Chris was born.

Chris Winberry (left) with her children and two nieces (right).

Q: Tell us about your experience of learning about your DES exposure and its possible effects.

A: My mother happened to pick up a *Woman's Day* magazine that had an article on DES. My mom had 9 miscarriages between my oldest brother and my next oldest brother. We really didn't talk about it much—you just didn't discuss stuff back in the day like that. But she said, you're having these horrible periods, so maybe you should get it checked out.

Thankfully, we went to the gynecologist who delivered me. She was treating my mom, and I'd never had a pelvic exam. She did a Pap smear, and that came back class 2 with severe dysplasia, so they wanted to do a D&C and cold knife conization. All I knew was these doctors were going to go into an area I wasn't comfortable with when I was 17.

The dysplasia was precancerous for clear cell adenocarcinoma, and its removal led to hemorrhaging after Chris returned home from the hospital. It felt awkward, she said, to go through all this while in high school and dating a guy. The treatment did not improve her periods, so she took Demerol (a narcotic pain reliever), Tylenol and ibuprofen every month for years. She was fortunate to receive treatment at the DES Center at Long Island Jewish Hospital in New York because they understood DES exposure better than nearly anywhere else at the time.

Q: What kind of additional research did you do into DES exposure?

A: I became a nurse and landed a job with the gynecologist that had given my mother the DES and delivered me. I had no idea how important that decision was going to be. I was able to get my mother's records and assisted with colposcopies and biopsies, and I wanted all the information I could get. The more I read, the more scared I became. It was knowing too much. I would go for my checkup and they'd always do biopsies when I went in. My Pap smears were always abnormal up until I married. It never came back cancerous, always severe dysplasia.

Q: What kinds of effects have you experienced as a result of your DES exposure?

A: The DES caused a bunch of health problems for me. [After marriage, Chris and her husband had fertility problems, which tests showed were not related to her husband.] It was a very difficult time for us. The emotional roller coaster was just awful, and every month without a baby just crushed you to the core. I went on fertility drugs, and they did an x-ray where they put dye in the fallopian tubes. There was a blockage in the tubes. The doctor said if you don't get pregnant in the next two months, there was no point. We couldn't do in vitro because we didn't have that kind of money. By some miracle, I did get pregnant the last month I was on it.

Q: How did the pregnancy and birth go?

A: I was really cautious. [Chris found a high-risk OBGYN at Stony Brook University.] At 11 weeks, my cervix was dilating to 3 cm, so I was already about to lose the pregnancy, and I was carrying twins. My doctor put a cerclage in so it was total bedrest from 12 weeks on. He would not do an internal exam because he was afraid. I went into premature labor at 35 weeks. I delivered my son at 4 lbs., 4 oz. and daughter at 4 lbs., 12 oz., but the placenta became embedded. I hemorrhaged so badly, I lost almost all the blood in my body. [The body typically expels a placenta within 30 minutes after giving birth. If it doesn't, the woman has a retained placenta, a life-threatening pregnancy complication where the placenta remains attached the uterus, often causing severe internal bleeding.]

We had just delivered two babies—it's supposed to be a high point—and life just came crashing down. We were alone at the hospital in the middle of the night, and I was bleeding to death. I wound up going into shock, and they took my husband out of the delivery room. The doctor said, "I don't know if we can save her." I had multiple blood transfusions, and they were able to stop the bleeding. But then I developed a nasty infection in the uterus which required antibiotics, and I was in the hospital 9 days for a vaginal delivery. I really should have not survived that.

I got pregnant with my daughter a year later and had to have a cerclage and do bedrest, which I couldn't do because I had toddlers. I went into labor at 39 weeks and hemorrhaged again because the placenta became embedded again. I found out this is very common in DES Daughters, which really surprised me. If it was so prevalent, why didn't my OBGYN know about it?

Q: How did these experiences influence your attitudes and beliefs toward the medical industry?

A: I was always very trusting in the medical profession and had a lot of respect for the drug companies until everything with DES started. It really changed my attitude. I was angry the more that I found out about the drug companies and how they did it only for profit. I think because we were women, we didn't question it. I think if it were guys, maybe it would be different. You think of all the millions of women who were given this drug.

In my mom's time, DES was considered a breakthrough medicine. Then, you just worshipped the ground your doctor walked on. You didn't question them. They were God in your eyes, or my mother's eyes at least. I think [her doctor] gave it in good faith back then.

I see all these research studies now and read stories online about what other women have experienced, and I feel like women back then were guinea pigs. The only suits that have occurred were settled out of court with small minute amounts compared to what these women should be compensated with, and the drug companies have never apologized.

Q: What occupies your thoughts now, and how do you cope and find support?

A: I'm really concerned about my future. What's going to happen with this second wave of breast cancer? It's always in the back of your mind. I did wind up having a hysterectomy at age 42 [due to severe pelvic pain, especially during ovulation, that no other procedures successfully treated].

Our genes are messed up from DES. What's going to happen after my kids have their kids? Is this going to be a continuing trend? Is it going to be passed down from generation to generation? And why does everyone want to hush it up? Younger doctors today don't know anything about DES.

I find support from other women through DES Action, where I don't feel like I'm alone. People I talk to on an everyday basis haven't heard of DES, so you feel isolated. I love reading others' stories. We need to be heard and to know what each of our sisters and brothers are coping with in their lives due to this nasty drug.

Higher Risk of Birth Defects

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of girls and 7.9% of boys. Among children of unexposed mothers, 2.6% had birth defects, including 2.2% of girls and 3% of boys. Five children of unexposed mothers had multiple birth defects, compared to 31 of the DES Grandchildren.

Six types of birth defects occurred more frequently among DES Grandchildren, in decreasing risk: esophagus defects; other digestive defects; male genital tract anomalies (especially undescended testicle(s) and hypospadias); cleft lip/palate; musculoskeletal anomalies; and congenital heart defects. The researchers did not find an increased risk of birth defects in DES Granddaughters' genital tracts.

"This study provides a new reassuring message for the daughters of women exposed in utero," the researchers wrote, referring to the lack of genital tract anomalies. Still, they recommended continuing follow-up research because half the Granddaughters were under age 18, so some problems may not be detected until later.

The researchers also did not find an increased risk for any kind of cancer, including breast, uterine and ovarian cancers, in DES Grandchildren. Again, though, the children were still young, and cancer may not appear until they get older. The researchers did find a greater likelihood of cerebral palsy among DES Grandchildren that corresponded with a higher rate of preterm birth in the DES-exposed group. Four children in the unexposed group (two preterm) had cerebral palsy, compared to 26 DES Grandchildren, 20 of whom were preterm.

This study was funded by the nonprofit DES France Network and the French equivalent of the Food and Drug Administration.

DES and Psychosis

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DNA methylation differences between exposed and unexposed individuals. But they did find a higher risk of psychosis in those exposed to DES, and the DES Daughters and Sons with psychosis did have methylation differences.

What's Methylation?

Methylation refers to a chemical change in a DNA strand. DNA makes up the genes that make up chromosomes. The building blocks of DNA are called nucleotides. How these nucleotides are strung together determines the genetic instructions in that DNA. Four types of nucleotides exist: cytosine, guanine, thymine and adenine, often abbreviated C, G, T and A. Cytosine always pairs with guanine (C-G), and thymine always pairs with adenine (T-A).

Methylation means that a compound called a methyl group (one carbon atom and three hydrogen atoms) attaches to the DNA strand, most often to a ring of carbon atoms in cytosine. When this methyl group attaches itself to the DNA strand, it can change the way the genetic instructions are delivered or interpreted. Methylation can affect the expression of specific genes, or how a gene is "turned on" or "turned off." If DES exposure causes changes to DNA methylation, then that would explain one way the drug might flip certain genes on or off, and that action can control risk of cancer and many other health effects.

The study's results also mean that risk of schizophrenia and similar mental health disorders is greater in those exposed to DES, based on this small population.

So far, however, most studies on DES and DNA methylation have not found much evidence that DES does cause methylomic changes. Since there is still very little research in this area, scientists are continuing to study it. Current studies have only looked at possible methylation differences in a small fraction of the whole genome.

What Did the New Study Find?

The study, published in the peer-reviewed journal *PLOS ONE*, took place in France and was funded by the French equivalent of the National Institutes of Health. It involved 69 siblings from 30 different families. Among all the participants, 37 were exposed to DES in utero, including 25 DES Daughters and 12 DES Sons, confirmed through their mothers' medical records. The 32 unexposed siblings included 20 women and 12 men. The researchers took blood samples and extracted DNA to look for differences in methylation. They did not find any major differences between DNA methylation patterns in those exposed to DES and in the unexposed brothers and sisters of DES Daughters and Sons.

Then the researchers compared mental health diagnoses between the two groups. The rate of depression, anxiety disorder and bipolar disorder were similar between those who were and were not exposed to DES. There were slightly higher rates of depression and anxiety in those exposed to DES, but the statistical calculations suggested these differences were more likely due to chance. (Past studies have shown a higher risk of depression and anxiety in DES Daughters and Sons. This study had too few participants for the researchers to adequately compare small differences.)

The rate of schizophrenia or schizophrenia-related disorders, however, was much higher among DES Daughters and Sons than among their brothers and sisters. Out of the 37 DES-exposed individuals, seven of them (6.7%) had a schizophrenia-related disorder, but none of the 32 siblings had a schizophrenia-related disorder or any other mental health condition that causes psychosis. Worldwide about 1–1.5% of the population is diagnosed with schizophrenia. This finding was statistically significant, which means it was not likely due to chance.

Then the researchers compared the DNA of DES Daughters and Sons with psychosis and those without. One gene on chromosome 6 (called ZFP57) did show 15% more methylation in those with psychosis. "Overall, our results suggest that in exposed individuals, ZFP57 methylation may be associated with psychosis," the authors wrote.

What Does This Mean?

The researchers could not compare methylation differences between both DES-exposed and unexposed individuals with psychosis because none of the unexposed people in the study had a schizophrenia-type disorder. Therefore, it's not possible right now to know whether the methylation difference in those with psychosis existed only because of the psychosis, or if it was related to the DES exposure. It's possible that anyone with psychosis would show that methylation difference compared to people without psychosis.

However, it's also possible that only people who were exposed to DES and have a schizophrenia-type disorder have those methylation differences. Several others studies looking at DES and DNA methylation differences are ongoing, so additional research will hopefully help explain the findings seen here. The study's results also mean that risk of schizophrenia and similar mental health disorders is greater in those exposed to DES, based on this small population.

Looking Toward Future Research

A study in 2012, published in *The World Journal of Biological Psychiatry*, reviewed the findings of 10 studies looking at psychiatric conditions in people exposed to DES versus those who weren't exposed. The quality of these studies varied greatly, though. The two largest studies found opposite results. One of them found that the risk of anorexia nervosa was higher in DES Daughters, but the other study found no differences between exposed and unexposed women.

Similarly, two other studies with participants drawn from the general population had contradictory results. The rate of depression was higher in DES Daughters than unexposed women in one of the studies, but the other study did not find any differences between the two groups.

"The role of prenatal exposure to DES as an environmental risk factor for psychiatric disorders requires more evidence before any conclusions can be drawn," the researchers concluded. One challenge of doing these studies is finding enough DES Daughters and Sons for research that studies have enough participants to draw solid conclusions. The fewer people that are in a study, the weaker the statistical analysis of the findings.

However, if more evidence—such as this new study—continues to suggest a link between DES exposure and mental health conditions, the researchers mentioned several ways that DES could cause this risk. One way is through epigenetics, which refers to changes in how genes are expressed (how they are turned on or off) instead of changes in the genetic code itself. Methylation is a mechanism that affects epigenetics. It's possible, then, that this new study on psychosis offers an early piece of a puzzle that scientists will continue putting together when they have more data about DNA methylation in those exposed to DES.

Screening Recommendations for DES Daughters

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gynecologists use) to look for enlarged glands or glandular tissue in the vagina. Second, the doctor will use his or her hand to palpate, or press, on the vagina and cervix to check for structural abnormalities. Sometimes, this manual physical exam may be the only way the doctor finds evidence of CCA, the cancer DES Daughters are at highest risk for.

Third, instead of a standard Pap smear or the HPV test which has become common, DES Daughters should receive a "four-quadrant sampling" of the upper vagina since a standard Pap smear cannot detect CCA. So samples of cells are taken from each of the four sides of the upper vagina and sent for lab analysis (cytology). Last, if the doctor finds particularly unusual changes in tissue, he or she should take cell samples from the middle and lower thirds of the vagina to send for analysis. If any of the cytology analyses come back abnormal, the recommendations state that a specialist with experience in evaluating and treating DES Daughters should study them. Abnormal findings during any of these exams and tests means a biopsy and/or colposcopy is necessary. It's not clear whether iodine staining of the vagina and cervix, previously recommended when DES Daughters were in their young adulthood, is still necessary.

It's also unclear whether all these aspects should still be recommended today when DES Daughters are peri- or postmenopausal. CCA peaks at age 20 in the general population. After age 30, a CCA diagnosis is extremely rare, even among DES Daughters. Yet DES Daughters should still be screened for it because at least two cases have been identified in DES daughters over age 70, which is certainly troubling.

"Routine" cervical cancer screening today also differs from screenings in the early 2000s. Today, most women receive an HPV test and may not even get a Pap smear. Yet, "some of the few cervical cancers that we see that are not caused by HPV are in DES-exposed women," said Brawley. He added that "the majority of DES women who get dysplasia and cancer [is] due to HPV, but they are the one group who end up having cervical cancer for reasons other than HPV."

Therefore, DES Daughters going for cervical cancer screenings would want to be sure they receive a Pap smear and probably the four-quadrant Pap smear, depending on their doctor's advice, in addition to an HPV test. The CDC document noted other female reproductive cancers that researchers should look for, such as endometrial cancer, but so far, no increased risk of those have been found.

Meanwhile, no major medical organizations publish official screening recommendations for DES Daughters: we lack data on future risk of disease, and data on past risk may not offer insights for future risk.

"A guideline is supposed to be based on data and not based on opinion," Brawley said. "It actually ends up being opinion influenced by data in most instances. This would be opinion influenced by no data whatsoever. That's the major issue."

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Higher Risk of Birth Defects in Third Generation

A recent study has found that DES Grandchildren have an increased risk for six different types of birth defects as well as cerebral palsy. Cerebral palsy is a neurological disorder resulting from some kind of injury or related problem that happens in a child's brain while it's developing. No increased risk for cancer was found for DES Grandchildren, but researchers cautioned that the children were still relatively young, before most people develop cancer.

The study, published in the September 2016 issue of the journal *Pharmacoepidemiology*, was led by Michel Tournaire, MD, an OBGYN with the Hospital of Paris, Paris Descartes University and DES France Association Network. Previous research has shown an increase among DES Grandsons in hypospadias, a condition where the opening to the urethra is not at the tip, where it should be, but instead on the underside of the shaft or somewhere else along the penis or scrotum. Hypospadias typically occurs in one of every 250 male births in the general population, and it frequently involves an underdeveloped foreskin and downward bend of the penis as well.

Tournaire's research team compared 4,409 children of 3,436 DES Daughters with 6,203 children of 3,256 women not prenatally exposed to DES. The data came from questionnaires sent in 2013 to DES Daughters throughout France who were certain of their mothers' exposure, either with medical records or consistent details about the exposure.

The comparison group of unexposed women were born between 1950 to 1977, the period when DES was prescribed in France. The surveys were retrospective—asking questions after the exposure instead of following people forward in time—and relied on self-reporting. Both these study aspects could introduce some bias to the results.

The average age of children at the time of the study was 15 years for DES Grandchildren and 17 years for children of unexposed women. The researchers found that DES Grandchildren had more than double the risk of birth defects compared to unexposed women's children and to Europe's general population. Among DES Grandchildren, 6.2% total had some kind of birth defect, including 4.5%

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