DES Action® VOICE

We identify, educate, empower and advocate for DES-exposed individuals

Inside

A Focus on Diethylstilbestrol

WINTER 2020 #163

DES Linked to Increased Testicular Cancer Risk

The evidence for gynecological cancer risks from DES is overwhelming, but less attention has focused on possible cancer risks to men from DES exposure. Now a new study has investigated what evidence exists for testicular cancer in DES Sons.

The new research suggests that an estimated three out of 250 DES Sons would be likely to develop testicular cancer, compared to the average rate of one out of 250 among men in the general population.

The study, published in June 2019 in the *Journal of the National Cancer Institute Cancer Spectrum*, is a systematic review and meta-analysis that brought together the findings of all previous research looking at testicular cancer and DES exposure (doi: 10.1093/jncics/pkz045).

A Meta-Analysis of Six Studies

The researchers combed through multiple databases of medical studies and found five that compared testicular cancer rates between DES Sons and unexposed men.

Then they analyzed the combined data from those five studies and from a sixth unpublished study conducted by one of the meta-analysis authors. Together, the studies involved 3,521 men, including 428 diagnosed with testicular germ cell tumors.

One of the studies was a randomized controlled trial of DES during pregnancy that had been done to test its effectiveness in preventing preterm birth. The other five looked specifically for harms after the negative effects of DES were understood.

> The odds of testicular cancer were three times greater in DES Sons than in unexposed men, meaning that three out of 250 DES Sons could be afflicted.

Most of the studies individually did find an increased risk of testicular cancer with prenatal DES exposure initially, but the findings did not reach statistical significance. In other words, the margin of error was so large that the results could have been due to chance.

Sometimes, however, a study may not reach statistical significance because the study does not contain enough participants. This is one reason the authors decided to combine the data from multiple studies that, together, included a larger number of people.

The combined analysis found that the odds of testicular cancer were three times greater in DES Sons than in unexposed men. The average risk of testicular cancer in the general population is one in 250, according to the American Cancer Society. Therefore, this study's findings mean that three out of 250 DES Sons would develop testicular cancer.

New Studies Are Unlikely

The authors note that it is unlikely more new studies can be done to investigate the link between testicular cancer and DES

continued on page 5

Does DES Cause Psychosis or Other Psychiatric Disorders?

In the Fall 2019 issue of the VOICE, we addressed the question of whether DES exposure might contribute to depression or anxiety. But those are only two mental health conditions among many, so could DES be linked to any other conditions, such as schizophrenia, bipolar disorder, anorexia or other psychiatric disorders?

As with depression and anxiety, the evidence is scant, and the evidence that exists sometimes provides contradictory results. Mental illness is definitely among the areas of health that are understudied in DES research.

Some of the better research comes from a paper we mentioned in the previous issue. A pair of French researchers published

continued on page 6

DES Action Updates

The CCA Registry

The Clear Cell Adenocarcinoma Registry has a new website. You can find it here: https://voices.uchicago.edu/ccaregistry/

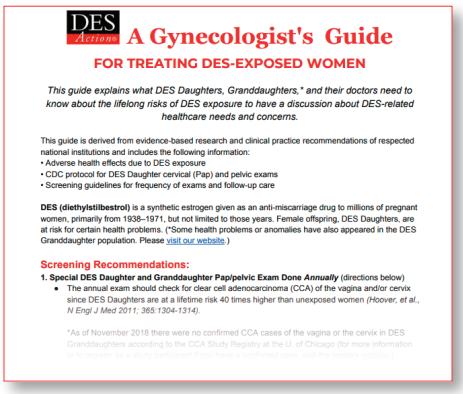
In case you haven't heard of it, here is the definition of the Registry, via their website:
"The Registry for Research on Hormonal Transplacental Carcinogenesis (the Registry) is an international research registry of cancer patients with clear cell adenocarcinoma (CCA) of the vagina and/or cervix or other specific gynecologic cancers who may or may not have been exposed to diethylstilbestrol (DES) or other synthetic hormones in utero (while still in their mother's womb). The Registry was established in 1971 at Massachusetts General Hospital by Dr. Arthur L. Herbst and colleagues to investigate the development of CCA of the vagina and/or cervix in young women born since 1940 and in 1976 it was moved with Dr. Herbst to the University of Chicago. The development of most of the vaginal tumors has been linked to the ingestion of DES during pregnancy. Because these tumors are rare in young women, the Registry was established to centralize data collection on this rare carcinoma. Varying amounts of information on the epidemiology, clinical aspects and pathology of these tumors has been obtained."

The Gynecologist Guide

In 2019, we updated the important guide to take to your gynecologist visits. It's especially important to take this along to a gynecologist you haven't seen before to ensure that the doctor is familiar with DES and its side effects for DES Daughters and Granddaughters.

The new version has more information related to Granddaughters, and we will continue to update it as more studies are published.

You can find the guide on desaction.org, listed under Resources as: Print & Take to Your Gynecologist. The direct link is: https://www.desaction.org/wp-content/uploads/Gynecologist-Guide.pdf



DES Action

A Gynecologist's Guide

FOR TREATING DES-EXPOSED WOMEN

This guide explains what DES Daughters, Granddaughters, and their doctors need to know about the lifelong risks of DES exposure to have a discussion about DES-related healthcare needs and concerns.*

This guide is derived from evidence-based research and clinical practice recommendations of respected national institutions and includes the following information:
- Adverse health effects due to DES exposure
- CDC protocol for DES Daughter cervical (Pap) and pelvic exams
- Screening guidelines for frequency of exams and follow-up care

DES (diethylstilbestrol) is a synthetic estrogen given as an anti-miscarriage drug to millions of pregnant women, primarily from 1938–1971, but not limited to those years. Female offspring, DES Daughters, are at risk for certain health problems. (*Some health problems or anomalies have also appeared in the DES Granddaughter population. Please visit our website.)

Screening Recommendations:

1. Special DES Daughter and Granddaughter Pap/pelvic Exam Done *Annually* (directions below)
- The annual exam should check for clear cell adenocarcinoma (CCA) of the vagina and/or cervix since DES Daughters are at a lifetime risk 40 times higher than unexposed women *(Hoover, et al., N Engl J Med 2011; 365:1304-1314).*

*As of November 2018 there were no confirmed CCA cases of the vagina or the cervix in DES Granddaughters according to the CCA Study Registry at the U. of Chicago (for more information

Renew Your Membership

It's easier than ever to renew your membership. Just log into the site using the email you registered with and your password. If you don't remember your password, you can reset it.

If you no longer use the email you signed up with, send your new address to Karen Calechman at karen@desaction.org. She will set a temporary password for you.

Thank you for supporting DES Action USA with your membership.

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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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Third Gen Study Finds Higher Risk of Uterus Defects

The effects of DES exposure repeatedly show up most often in men's and women's reproductive systems. Most research has focused on DES Daughters' reproductive systems, with a small amount of research into DES Sons' systems.

Studies in rodents have shown that DES effects can be passed down through multiple generations, so researchers are increasingly exploring what reproductive effects might exist in DES Grandchildren.

Scientists have already identified an increased risk of hypospadias in DES Grandsons. Hypospadias is a condition in which the urethra opening on a penis is located somewhere on the shaft other than the tip. A new study investigated whether any reproductive birth defects occurred in the daughters of DES Daughters and Sons.

The main finding of the study, published in the journal *Therapies*, was that abnormalities in the uterus were more common among DES Granddaughters than in the general population. It's not yet possible to say definitively that prenatal DES exposure in their parents is the cause.

There is evidence from lab animal studies that it's possible for DES-caused changes in DES Daughters' genes to contribute to abnormal changes in their children's genes. But it is necessary to continue doing more research in DES Grandchildren before more solid conclusions about third generation effects can be determined.

Comparing DES Granddaughters

The new study, led by French researcher Anne Wautier of France's DES Association, involved analyzing questionnaires from 759 daughters of DES Daughters and Sons. They recruited DES Granddaughters through the French DES patients' association and through the media and health insurance mailings.

Most of the Granddaughters were daughters of DES Mothers, but 76 Granddaughters were daughters of DES Sons, and 11 had both a DES Mother and DES Son as parents. Their average age was 18, but 7% of them were over age 30.

The researchers compared DES Granddaughters' genital and reproductive characteristics to those of the general population of France, of DES Daughters, and of two groups of DES Daughters' daughters from previous research.

Overall defects of the uterus occurred more often in DES Granddaughters aged 18 and older than in the general population: 3.2% of 380 Granddaughters had uterine abnormalities, compared to 0.17% in the general population of fertile women. Infertile women in the general population have a rate of 3.5%. (The researchers did not report on defects in those under age 18.)

However, the researchers noted that "these findings must be considered carefully because we could not acknowledge the existence or absence of other risk factors for uterine anomalies in our population." In other words, they were not able to learn about other risk factors the women had which may have also contributed to risk of uterine defects.

Types of Uterine Defects

Three specific types of uterine defects were identified. Three Granddaughters (0.8%) had Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, in which the vagina and uterus are underdeveloped or completely absent even while the outer genitals look the same as in other women. MRKH usually occurs in one of 4,500 women (0.02%).

"This high incidence of MRKH syndrome and new mechanisms described for this malformation suggest a hypothetic link between DES and MRKH syndrome," the researchers wrote.

continued on page 7

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Q&A: Matthew Jeffers, DES Grandson and Actor

Matthew Jeffers is a DES Grandson and actor who played roles in the television shows "The Blacklist," "New Amsterdam" and "Exit Interview." He has recently completed a screenplay about a family grappling with a family secret involving DES. Here he shares a bit about his life and his screenplay.

Tell us about how you first learned about your exposure to DES.

Unfortunately I don't have a specific memory, but around 2014, I have a vague memory of my father floating this factoid that my grandma took a drug to help with pregnancy complications, and that she blamed herself for my rare dwarfism and my first cousin's rare knuckle disorder, where she's missing the middle knuckle in her fingers and toes. I don't remember really receiving the information. It was presented in too casual a light for me to grasp the gravitas of what my father was telling me. But certainly subconsciously, that truth became branded in my psyche, because a year or so later, when I was co-writing a script with a friend, DES surfaced out of the depths of my memory. My friend and I researched it together, and that's when I began to educate myself on DES.

In what ways might you have been affected by exposure to DES?

It is unclear whether or not my rare form of dwarfism is linked to DES. If so, obviously that would be a major impact. Most every facet of my life has been shaped from my dwarfism. I know that DES can have impacts on sexual functioning and complications with sexual organs.

Between 2010–2014, I landed in the hospital on four occasions due to complications with severe pain during sexual activity with my partner. I'm not sure if this was linked to DES, but I wouldn't be surprised.

Matthew Jeffers

Tell us about the screenplay you've written that involves DES.

Oh, how much space do we have! It's a behemoth of a story, spanning three generations and 80 years. It tackles faith, family, drug abuse, the medical community…all the fluffy things.

One of the common critiques has been that the script may be juggling more than it can juggle, but I'm firm on keeping the thread of DES.

It begins with a mother in 1939 taking DES to help with pregnancy. The story enters a new plane when the main character, in the present day, realizes this family secret, and how he grapples with the conflict between science and his long-held family tradition of faith and acceptance. I'm interested in exploring transgenerational effects, the domino effect of how a decision made in 1939 can have a profound impact on the life of a millennial in 2019.

Why did you choose to use DES exposure as a device in your screenplay?

I was on the subway recently eavesdropping on a nearby conversation, which is one of my favorite things to do in the city. This woman was explaining how bored she was with the storylines of TV shows and movies these days, how they are largely recycled plots that have become quite stale, especially with our rapidly evolving social structure.

Certainly DES is not going to be the savior of original storytelling, but I do think it offers that freshness that the subway woman was yearning for. I'd argue very few people on the street would know much about DES, yet most people are supremely interested in the ways science and medicine affect their lives.

Adding a tablespoon of religion, I think, helps create a zesty, spicy, uncomfortably close portrait of a lot of people today: who do we believe in, why do we believe in it, and is it killing us or saving us?

People want to learn something about what it's like to be in someone else's shoes but still have the same shoe size. They want to learn, but they also want to relate—that's the recipe for empathy, and I think DES can be a great vehicle for this philosophy.

What is your hope for the future as a DES Grandson?

I think a lot of people are searching for the whys and the hows. It is my hope that as science continues to progress, truths

can be firmly planted where faith sometimes wavers and offer people answers to those questions, for better or worse. I'm on the same journey. I have a lot of questions that I've been throwing against my faith in the past few years, and it's no longer sticking the way it did when I was younger. DES is just one part of a very, very large canvas of question marks and how we're all indelibly tethered to them, whether it's a 28-year-old woman in 1939 or a 32-year-old man in 2020.

Tell us how DES Action USA has helped you.

Searching online led me to DES Action, and it proved quickly to offer the most useful information and resources. I am eternally grateful to Karen Calechman for our phone conversations. She read multiple drafts of the script in a very short period of time, and some of the most exciting revelations of key plot points came from our conversations.

We did it! We earned Great Nonprofits' Top-Rated status again!

The daily work in my position of Community Manager at DES Action can sometimes be very emotional as I take calls from people who were just diagnosed with a DES-linked condition. All of the other tasks I do are important, but the calls and emails I answer are the most important. As DES Children we understand the fear, anxiety, sleepless nights, and lifetime of vigilance our DES exposure has caused for us and for our families. I am not writing this to receive any gratitude. We all help each other. We learn from each other. However, when I read the reviews it was a reminder of why I do my job, and why the tough days are worth it. We are truly a family, watching out for one another. Where would we be without DES Action?!

— Karen Calechman

DES Linked to Increased Testicular Cancer Risk

continued from page 1

exposure because of the average age of DES Sons. Testicular cancer is typically diagnosed between ages 15-45. Since DES prescriptions ended in 1971, the youngest DES Son would be about 48 years old.

The authors looked for other possible factors that might explain the increased risk besides prenatal DES exposure, but it's not likely other factors contributed enough to cancel out the association.

Some Unknowns

Because the data came from multiple studies with different designs, the authors were not able to determine whether testicular cancer risk was affected by the dose of DES or the trimester(s) of exposure.

The authors did, however, explore what biological mechanisms could potentially explain how DES could contribute to the development of testicular cancer. They describe studies in rats where DES given during pregnancy crossed the placenta and accumulated in the reproductive tract.

In this research, the exposed newborn male rats had abnormalities in their sex organs. One of these problems was undescended testes. Having undescended testes has been linked to a higher risk of testicular cancer in humans.

A Strange Chromosonal Phenomenon

Another study of prenatal DES exposure in hamsters found that the male newborns had an abnormal number of chromosomes in some of their cells even though those cells did not have DNA damage. That same phenomenon—abnormal chromosome number without DNA damage—is seen in the nucleus of testicular tumor cells.

Even though these studies were conducted in rodents, not in humans, they reveal how DES might influence fetal development in male mammals more broadly.

The authors conclude that it is likely that prenatal exposure to DES, and other chemicals like DES, could contribute to the development of testicular cancer cells in males.

The research was funded by the National Cancer Institute, the U.S. Public Health Service, the California Cancer Research Program and the University of Southern California Keck School of Medicine.

No pharmaceutical company funding was involved in the study, and the authors did not have any conflicts of interest or links to the pharmaceutical industry.

Does DES Cause Psychosis or Other Psychiatric Disorders?

continued from page 1

a paper in 2012 in the *The World Journal of Biological Psychiatry* that reviewed the evidence on psychiatric conditions in DES-exposed people in 10 studies from 1960-2010 (doi: 10.3109/15622975.2011.560280).

Two Studies Found No Increased Prevalence of Mental Illness Among the DES-Exposed

Three of those studies looked at conditions beyond depression and anxiety. Two of these, an American study of 5,686 women (mostly DES Daughters) and a French study of 3,127 women (1,680 DES Daughters and their 1,447 unexposed siblings), found no increased prevalence of mental illness among those exposed to DES.

Both studies were based on questionnaires, and one included the largest group of DES Daughters of all the studies. The studies looked at rates of depression, anxiety, psychosis, anorexia, bulimia, suicide, psychiatric hospitalization and overall mental illness. Psychosis refers to hallucinations and can occur in multiple different disorders.

One Study Finds a Dramatic Increase in Mental Disorders

Another American study of 2,630 women in 1991 found that DES Daughters were nearly six times more likely to have lost weight over their lifetimes, but the study did not directly ask about a diagnosis of anorexia or any other eating disorder.

But more research has been published on psychosis-related disorders and DES exposure since that review. A 2016 French study compared 740 DES Children to their unexposed siblings. Among the unexposed siblings, 180 had been born before their mother ever took DES, and 262 were born after their mother had a previous DES-exposed pregnancy. Mothers filled out the questionnaires (doi:10.3109/09513590.2015.1063604).

The results were dramatic: The mothers reported no psychiatric disorders or suicide attempts among first-born unexposed children. But they did report mental health disorders or suicide attempts in 83.8% of DES-exposed children and 6.1% of non-first-born unexposed siblings.

The study has many problems, however, that make the results less reliable than we'd like. First, the participants all came from an advocacy-based patient support group, so it's a selective group that cannot represent the broader DES-exposed population.

(Members of advocacy groups differ from non-members in ways that might affect percentages. For example, people with known health issues are more likely to be members of an advocacy group than people without known health conditions, so health conditions can often be over-represented among members.)

In addition, the researchers did not confirm diagnoses in medical records and did not take into account other health conditions, including ones that could increase the risk of psychiatric conditions. It's possible that mothers, especially ones in a support group, noticed more possible problems in their DES-exposed children than in unexposed children after learning about DES risks.

The numbers themselves are also extraordinary enough to raise red flags: It's very unusual to see absolutely no mental health problems at all in 180 people. The high numbers seen among those exposed to DES—including 23% with schizophrenia, 11% with eating disorders and 15% with behavioral disorders—have not been reported in any other studies of DES Children. Again, these rates probably resulted from including only mothers in the advocacy-based support group, where the rate of health problems would be expected to be higher.

The rate of suicide attempts was 85% in DES-exposed children and 11.5% in unexposed siblings born after a previous exposed pregnancy, compared to a general population rate of 0.3%.

It's unclear why the unexposed group had such a high rate, and the exposed group's rate is far, far higher than what any other study has reported. Again, however, this higher rate probably exists because the participants came from a support group (which would primarily include people already seeking help for known problems). Without other stronger studies with similar results, it's hard to judge the reliability of these findings.

Another French study in 2017 compared questionnaire answers from 2,566 DES Daughters and 2,967 unexposed comparison women of the same age (doi: 10.1007/s00737-016-0711-8). DES Daughters were 1.7 times more likely to report a severe mental health disorder or to have consulted a psychiatrist.

Not Connecting the Health vs. Mental Health Dots

Unlike the siblings study, this research did take into account other DES-related physical health problems that might increase mental health risks. Unfortunately, it did not distinguish between those who reported an actual diagnosis and those who visited a psychiatrist, so it doesn't help us know if DES specifically increased the risk of any diagnosis or a particular type of diagnosis.

Finally, the authors of the large French review collaborated with other researchers on a 2017 paper that looked for biological explanations for how DES might affect the brain (doi:10.1371/journal.pone.0174783).

They compared DNA in 37 DES Children and 32 unexposed siblings to see if changes had occurred that would affect gene expression. Gene expression refers to turning a gene on or off. Among the DES Children, seven were diagnosed with psychosis, based on criteria in the Diagnostic and Statistical Manual Fourth Edition (DSM-IV) for psychiatric disorders, and 30 did not. None of the unexposed participants had psychosis.

Differences related to gene expression did exist between those with and without psychosis in the DES-only group. However, the researchers didn't compare DES-exposed people with psychosis to unexposed people with psychosis, so the finding does not tell us anything about possible DES involvement.

The researchers did not find any DNA differences between the DES-exposed group and unexposed group in general that might affect gene expression.

Together, these studies present a complicated picture. Those showing an increased risk of psychosis had substantial problems in the study design that make it difficult to assess how reliable they are.

The research with stronger study design showed little or no increased risk of psychosis from DES exposure. Frustratingly, this means we just don't have the firm answers that the DES community needs.

We need additional, stronger studies to show more clearly whether DES exposure can contribute to schizophrenia, bipolar disorder or other psychiatric conditions. It's encouraging that some scientists have taken these concerns seriously, but it's clear that more high-quality research would provide better answers.

Third Gen Study Finds Higher Risk of Uterus Defects

continued from page 3

Three Granddaughters (0.8%) had doubling of the uterus, in which the two tubes that are supposed to join and create a single uterus during development do not properly connect and instead create two separate uterine spaces.

Women with a doubled uterus can still have children, but they may have a higher risk of miscarriage or preterm birth. In the general population, a doubled uterus is estimated to occur in one of 3,000 women (0.03%).

Six Granddaughters (1.6%) had a bicornuate uterus, which is a heart-shaped uterus that is similar to a partly joined double uterus. The rate for a bicornuate uterus in the general population ranges from 0.1% to 0.6%.

DES Granddaughters did not appear to have an increased risk of unexplained infertility, T-shaped uterus or hypoplastic uterus.

Contradictory Pregnancy Outcomes

The results were more complicated when it came to pregnancy outcomes. The three groups of DES Granddaughters the researchers compared—one group from this study and two from previous studies—had a total of 121 pregnancies. All these Granddaughters were daughters of DES Daughters.

In the group surveyed for this new study, rates of early miscarriages (19.8%) and late miscarriages (2.5%) were higher than the rates in the general population. However, the other two groups of DES Granddaughters from past research did not show an increased rate of miscarriages.

Six Granddaughters (1.6%) had a bicornuate uterus, which is a heart-shaped uterus that is similar to a partly joined double uterus. The rate for a bicornuate uterus in the general population ranges from 0.1% to 0.6%.

No increased risk for preterm birth or ectopic pregnancies was seen among any of the DES Granddaughters.

It is not uncommon to have inconsistent findings from multiple groups in research. This is especially true when the individual groups are not very large, as in the case of this study and many others related to DES Grandchildren.

It requires multiple studies of thousands of people over time to gather the evidence necessary to draw conclusions about the likely effects caused by DES exposure, whether second- or third-generation.

One limitation of this study is that it drew primarily from people associated with the French DES organization. Members of DES organizations are often more likely to have health problems because a health problem is often what leads them to seek out an organization. (People without known health problems may be less likely to become involved with DES organizations.)

Therefore, the researchers note, it's possible the rates seen in this study are slightly overestimated, but it's hard to know how much, if at all. Hopefully, as more research is conducted in the third generation, the picture will become clearer regarding how DES exposure in their parents might affect DES Grandchildren.

The research was funded by the French Drug Agency, and the authors had no conflicts of interest. (doi 10.1016/j.therap.2019.10.004)

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DES Community Calls to Remove Pregnancy Drug from Shelves

In the Fall 2019 issue of the VOICE, we shared research about a progesterone drug called Makena that can be prescribed to allegedly reduce the risk of preterm birth in a select group of women at risk. However, as the latest study from Makena's manufacturers showed, the drug doesn't appear to actually reduce preterm birth risk. Although current studies have not found evidence of harm from Makena in mothers or their children so far, all drugs come with some risks and side effects. Right now, that means people who are prescribed Makena are vulnerable to the side effects and unknown future risk of harm without receiving any clear benefit.

That's the reason DES Action USA called for the FDA to remove Makena from shelves and asked for members' support in signing the petition. And you delivered!

"Bravo to our DES Action USA members!" said DES Action USA Executive Director Su Robotti. "Our small base of 600 members drove our petition awareness and support to gain more than 500 signatures in only two weeks." This result was amazing, but it wasn't surprising, Robotti said. "We who have lived with the consequences of DES exposure are and will always be quick to demand proof that a drug is necessary in pregnancy, and we will be slow to accept the risks of ineffective drugs."

The petition was delivered to the FDA on December 3, so now we must wait to hear what the agency decides.