DES Action® VOICE

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

Inside

A Focus on Diethylstilbestrol

SPRING 2021 #168

What You Need to Know About COVID Vaccines

U.S. health experts have repeatedly stressed that getting as many people as possible vaccinated against COVID-19 is the best way to end the pandemic. However, members of the DES-affected community have better reason than most to feel uneasy about receiving a new pharmaceutical product. Here's what you need to know about the vaccines.

Will the mRNA vaccine work for me?

Yes, as well as it would in anyone without DES exposure. Here's why. DES interferes with the endocrine system, which uses hormones to send messages throughout the body. It's reasonable to wonder whether a "messenger" RNA vaccine will work in someone if their body's "messaging" system is compromised. Fortunately, these are different messaging systems.

The mRNA in the Pfizer and Moderna vaccines is a recipe for making a key protein on the coronavirus (called "spike"). But it doesn't require hormones to get the message to your body. Once the vaccine is injected, the mRNA makes its way into a cell, and it's within individual cells that the protein factories (called ribosomes) read the recipe and start making the protein.

The cells stop making the protein when the mRNA disintegrates, which happens within a few days (so your cells can't go out of control making nonstop proteins). When the immune system sees the proteins, it quickly begins to make antibodies to fight it.

But all this happens on the cellular level, within individual cells. The problems in the endocrine system caused by prenatal DES exposure happen on the system and tissue level. Even if your body's hormones don't function properly or don't get the right messages to the right places because of DES exposure, that won't affect how well your cells interpret the mRNA and make proteins. It also won't affect how well your immune system responds to the proteins. The vaccine will work as well in you as in anyone else of your age.

Were these vaccines really tested enough?

Yes. They went through the same trials that all vaccines must go through—a small phase 1 trial, a larger phase 2 trial of several hundred people and a huge phase 3 trial with tens of thousands of participants. The reason the testing hap-

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Cervical CCA Identified in One DES Granddaughter

The first evidence that DES exposure in the womb could cause harm to the children of mothers who were given the drug was a collection of eight cases of clear cell adenocarcinoma (CCA) of the vagina in young women in the Boston area in the late 1960s. Soon after that, a 1971 landmark study by Dr. Arthur Herbst, et al, confirmed that DES Daughters were at much higher risk for CCA than those not exposed to DES in utero.

Though researchers have learned much more about the health risks of prenatal DES exposure since then, they're now trying to learn more about Third Generation effects. A new case study on an 8-year-old DES Granddaughter with cervical CCA is raising questions about whether it's the first of more cases in this generation. It's important to note, however, that the case occurred 10 years ago, and no cases have been reported since.

The study, published online in the journal Human Reproduction in November 2020, should be viewed with caution since it describes a single case of CCA in a young girl (DOI: 10.1093/humrep/deaa267). One case could

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DES Annual Meeting in January

DES Action USA held its first online annual meeting on January 26, and we were thrilled to see all of you who were able to join us. Executive Director Suzanne Robotti opened the meeting with a presentation on the annual report.

Following this, VOICE Managing Editor Tara Haelle discussed the process of selecting stories for the VOICE, including how we select people for Q&As and the topics for the "Did DES Cause This?" column. Many of these suggestions come from you, our members.

We strive to feature a diversity of individuals in our Q&As, from DES Moms, Daughters and Sons to the Third Generation, from doctors and researchers to artists who find ways to continue raising awareness about the DES disaster and its ongoing repercussions.

Most of the "Did DES Cause This?" topics come from our members through phone calls, emails and online groups. If you have an idea for this column or any other DES stories, please email Tara at tara@desaction.org.

After Tara discussed how she reviews and analyzes the scientific studies she writes about in the VOICE, Community Manager Britt Vickstrom, also a DES Granddaughter, put out a call for volunteers and reminded members of the benefits of renewing memberships and donating. It's our members who keep us going!

If you missed the meeting, you can watch it on the DES Action website. Your incredible support continues to enable us to serve you and others in the DES-exposed community, and we are always eager to hear more from you about how this organization can best meet the needs of those impacted by DES.

We hope to see you at next year's meeting! -TH

Have You Changed Your Email? Current Emails Requested

We have a number of old emails in our database for members. This prevents us from keeping you up to date. Also, if your old email is connected to your membership record, it may prevent you from logging in and accessing the website. If your email has changed, please email Britt@desaction.org with your new email. -BV

Correction

In the Fall 2020 VOICE, we mistakenly wrote that Claire Cagney is from Massachusetts. She lives in Wisconsin. We regret the error.

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 Britt Vickstrom at britt@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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Q&A With Miriam Mackovic, MD, PhD

Miriam Mackovic, MD, PhD, is a private practice OB-GYN in Long Beach, Calif. But she isn't your ordinary OB-GYN. In addition to staying particularly up to date on knowledge about DES, Dr. Mackovic is the founder and CEO of Complete Women's Care, the nation's first—and currently still the only—freestanding gynecological and early pregnancy emergency care center, open every day around the clock.

Dr. Mackovic also holds two patents, including one for a device she invented to minimize blood loss during cesarean deliveries. Every three minutes, a woman dies while giving birth because of blood loss, and cesarean deliveries typically involve about double the blood loss of vaginal deliveries, she said. Her device is about to enter clinical trials. We spoke with Dr. Mackovic to learn why it's important to her to keep up with the latest science and healthcare related to DES.

Why did you enter OB-GYN, and why did you want to learn more about DES as a clinician?

When I entered medical school, I felt at that time that women are best understood by women and that we can really give that extra touch. [She graduated from medical school in 1982.] Men can be great physicians and great surgeons, but women also need emotional support and empathy, and that was not so common then. I felt that by entering that field, I could contribute to women's well-being and safety and improve how women have access to care and how they are treated by the system.

While I was doing my oncology rotation at Cedar-Sinai Beverly Hills, I truly was moved when I met a brilliant attorney in her 30s who was dying because she had developed adenocarcinoma of the vagina. DES was not so well recognized then. She died while I was there, and I thought what a loss of a brilliant woman that should not have happened. My heart went out to her and her family. I started reading about DES when I met that patient. It was a really profound event for me.

From a clinical perspective, what is most important when caring for patients with DES exposure?

They have more frequent visits, they more frequently need cytology samples [such as pap tests], and if needed, biopsy samples of the cervix and the vaginal wall. I'm looking for any vaginal symptoms, and I make sure patients are aware of the need for more frequent visits.

I've treated patients who I suspected were exposed to DES, but they didn't know. An example is women who were born premature. I ask them to go back and ask if their mothers were prescribed DES during pregnancy or look for her medical records. Sometimes they come back and say, "Oh my God, my mom told me that she was given DES during pregnancy." I provide them information, inform them about DES Action, talk about the health risks [of DES exposure] and do additional testing and follow-up.

What surprises you most about the story of DES?

It surprises me that it is not more known, because one life lost is one too many. Some think, "Oh, that's such a minor issue." It might be minor to the general population, but to the person it happens to, it's 100%. Awareness is very important to me, because when you're aware, you can be proactive and take care of your patients. And many times patients don't know. A patient can pay a huge price with her health and sometimes with her life.

Do you think it's possible another pharmaceutical disaster like DES could happen again?

Yes. For instance, there's the opioid crisis. Opioids are very dangerous and very addictive, and pharmaceutical companies knew that, but they did not warn physicians or patients. Now we know that even using opioids for seven days, some people can get addicted. Many, many people paid with their lives. Is it going to happen again? Do we as physicians and as the public have to be conscious about it? Do we need to request information? Yes, we do. It will

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Q&A with Miriam Mackovic MD, PhD

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happen. It happened with DES, it happened with opioids. Is it going to happen in the future? Yes.

I think if we would be more strict with pharmaceutical companies about consequences, and if consequences would be severe enough, then disclosure would be better. For example, if a pharmaceutical company willingly omits information about a drug's harmful side effects for financial reasons, and patients pay with their lives, the company, or at least the department responsible, should be shut down, you will not be able to profit anymore. Small financial punishment is a slap on the wrist. We should have some system in place where we have an independent organization that reviews [medications] besides the FDA. There should be no lobbying from pharmaceutical companies, because they reach the government, reach the FDA, reach so many areas, and things don't happen as they should.

One of DES Action's current concerns is use of the drug Makena. Can you offer thoughts on that?

I have been following the research. Makena is a progesterone. Can Makena cause damage? We really don't know, but the evidence is that its help is minimal, and these types of medications that don't have clear benefits should not be used. Further clinical trials would be required to settle the issue.

Again, we should have a separate body, such as watchdog or public advocates, that have the ability to keep the FDA, politicians and pharmaceutical companies liable. There have to be consequences. When pharmaceutical companies submit something, they may not know [a safety problem] is there initially, but once the evidence is there, if the information is not disclosed, there should be severe consequences. If there were feedback and consequences for wrongdoing, then wrongdoing would happen less often. There is such a large amount of money involved that bad things can and do happen—if you want to find a crime, follow the money.

How did learning the history of DES affect how you perceived the medical or pharmaceutical industry?

It affected me in that I take everything with a grain of salt. Many times whatever is considered evidence-based medicine and firm belief today is nonsense five or ten

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What You Need to Know About COVID Vaccines

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pened so much more quickly than with other vaccines is not because corners were cut. It's because the companies had the money to move from one step to the next immediately without having to wait for funding approvals along the way.

The vaccine data was also reviewed by the same committee of independent experts—separate from FDA employees and uninfluenced by pharmaceutical interests—before being reviewed by the FDA as a whole.

DES exposure had extremely long-term effects that took years to discover. Could that happen with these vaccines?

It's extremely, extremely unlikely. It's impossible to say 100% no, but it's more than 99.9% no. It is possible for vaccines to have longer-term effects, but "longer term" refers only to several weeks or months after the vaccine. No U.S.-approved vaccine has ever shown side effects a year or more after the vaccine in more than 80 years of vaccine history.

It's now been almost exactly a year since the first study participants received the mRNA vaccines, and no long-term effects have shown up in any of them.

So what side effects do I need to know about?

The most serious reaction that has been reported from the mRNA vaccines is a severe anaphylactic reaction in a very small number of people who have a history of severe anaphylaxis. An early CDC report estimated the reaction occurred in about 11 per 1 million people.

So far, all reported cases of these reactions were marked by full recovery following immediate treatment. When people get the vaccine, they are asked to remain for up to 15 minutes afterward so someone is available if they have a reaction. If you have a history of anaphylaxis, talk to your doctor about the vaccine.

The other side effects are common ones for vaccines: soreness or swelling at the injection site, fatigue, sleepiness, headache, nausea, diarrhea, fever, chills, aches or a delayed skin rash at the injection site. Not all of these side effects happen to all people.

Some people have no effects. Others have several. Older adults tend to have fewer side effects than younger adults. The second shot of mRNA vaccines tend to cause stronger effects than the first shot. The effects can last from a few hours to a couple days.

To learn more about how many people experience each of these effects for the mRNA and Johnson & Johnson vaccines and information on extremely rare adverse events, visit MedShadow's COVID-19 Vaccine Side Effects Tracker at medshadow.org/covid19-vaccine-side-effects. –TH

Q&A with Miriam Mackovic MD, PhD

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years down the line or completely wrong. Our knowledge is evolving. I don't think that pharmaceutical companies and Big Pharma are 100% evil. They're not. They help tremendously, but after learning about DES, I'm much more careful about taking for granted what I hear from pharmaceutical representatives. I look at the National Institutes of Health library and look at articles published on what they talk to me about.

What is your hope for the future, considering what happened with DES?

It is a tragedy for too many people. I really hope that the pharmaceutical companies and physicians and patients will be more aware and more cautious about what we administer and what we take—more aware about what pharmaceutical companies put on the market and what physicians believe, and I hope that patients would be their own advocates. I would like patients to read and be empowered by knowledge.

What else would you like DES Action members to know?

Two things. I really have devoted my life to improving women's health. I would like to license the device that minimizes blood loss during cesarean sections, use the profits to make reusable devices, and send them to developing countries for free and save lives. The second thing is that I hope to have made an impact by replicating the first freestanding early pregnancy and gynecologic emergency centers in multiple locations, so a woman can walk in any time, 24/7, and get complete care for a much lower price and in a much more appropriate environment.

From simple uterine infections to life-threatening bleeding and ectopic pregnancies, our specialized OB-GYN team in our emergency center can take care of everything. It's a vertically integrated system, and I would like to build more of these throughout the United States so that we can save more lives and provide much better care for women. –TH

Cervical CCA Identified in One DES Granddaughter

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be an unfortunate anomaly rather than the start of a pattern. Still, given how incredibly rare CCA is in young women, the study also means it's important for researchers to continue closely monitoring DES Granddaughters and Grandsons to learn about possible health issues.

It has long been shown that multigenerational effects of DES exposure appear in mice and other animals in lab studies. In addition, several conditions have been linked to Third Generation DES exposure, such as hypospadias—a defect on the penis—in DES Grandsons. Until now, however, no evidence had linked any cancers to Third Generation exposure.

The study states that the girl was admitted to the emergency department after two days of severe vaginal bleeding. She did not have abdominal pain, had no evidence of being abused or of early puberty, and her pelvic ultrasound was normal. The doctors diagnosed her with an early start to her period.

Six months later, as she continued to have episodes of bleeding, she underwent a vaginoscopy that showed a tumor beginning to grow at the opening of her uterus. The doctors learned her grandmother had had six miscarriages and subsequently was prescribed DES for her entire pregnancy with the young girl's mother.

The girl's mother needed two thirds of her left ovary removed when she was 12 years old due to a cyst, but she did not have any other health issues. The girl's 11-year-old brother had a micropenis, which has been possibly linked with Third Generation exposure.

A biopsy led the doctors to conclude that the girl had cervical CCA. She underwent procedures to preserve her future fertility and then underwent surgery to remove the tumor. She then received radiation to reduce the likelihood of the cancer returning.

Over the next 10 years, she did not experience any recurrence of the cancer, and she had begun having a normal period at age 11. She began taking estrogen-containing oral birth-control pills to prevent pregnancy.

Outside of people exposed in utero to DES, only eight girls in the world have ever been reported in the medical literature to have CCA between the ages of 1 and 10 years old, reported from 1996 to 2020.

The authors note one other case of a 15-year-old DES Granddaughter with small-cell carcinoma of the ovary. A 2008 study of 463 DES Granddaughters did not find any higher risk of cancer overall in the group, but they did have a higher-than-average number of ovarian cancers specifically. However, that finding was based on only three cases of ovarian cancer (DOI: 10.1097/EDE.0b013e318163152a).

"A direct causal link between the grandmother's treatment with DES and the development of CCAC in our patient cannot be demonstrated and thus remains speculative," the authors wrote. "Yet it is nevertheless possible that this prepubertal CCAC was the result of a multigenerational effect of DES." –TH

DES Research Featured at Beyond Genes Conference

In December, a discussion about DES was featured at Beyond Genes, an online conference on non-genetic inheritance in human disease. Non-genetic inheritance refers to changes in gene expression—what turns genes on and off—and other contributions to disease that are not in our actual genes but which can be inherited, just as the effects of DES exposure have been documented in subsequent generations.

The conference took place on six Fridays across two months, and the December 4 session focused on heritable impacts of DES and other endocrine disruptors.

During the session, moderated by Executive Director Suzanne Robotti, Dartmouth scientist Linda Titus presented research from the Ongoing NCI Multi-Generational DES Follow-up Study.

Dr. Titus found that DES Granddaughters were more likely to have irregularities in menstruation. DES Granddaughters also had a possibly higher risk of ovarian cancer, but that was based only on three cases—too few to rule out that chance caused the higher case numbers.

Most importantly, Dr. Titus's research highlighted the importance of continuing to study DES Granddaughters and whether they have any fertility or other reproductive problems as they grow older.

Columbia scientist Marianthi Kioumourtzoglou shared her research on ADHD in DES Grandchildren. In a population of 47,540 women, including 861 DES Daughters, she found that children of DES Daughters were 1.3 times more likely to have an ADHD diagnosis. They were 1.6 times more likely to have ADHD if their mother's DES exposure was in the first trimester.

"Our study provides evidence that DES use is associated with multigenerational neurodevelopmental deficits," Dr. Kioumourtzoglou said.

After the presentations, Su moderated a discussion on Third Generation effects with former DES Action research director Kari Christianson, independent researcher Scott Kerlin and biochemistry professor Subhrangsu Mandal from the University of Texas at Arlington. -TH

Does Des Cause Uterine Cancer?

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cer. However, none of the DES-exposed mice born to mothers eating a healthy diet showed signs of developing cancer.

Both these studies suggest that prenatal DES can contribute to uterine/endometrial cancer, but not by itself. There needs to be a trigger.

A report that reviewed all the evidence available in 2005 noted, "Prenatal and perinatal exposure to DES increases the predisposition to uterine developmental abnormalities and cancer in the daughters and granddaughters of exposed pregnant mice." (DOI: 10.1093/hmg/ddi103)

Clearly, the mechanism for DES to contribute to uterine cancer in tandem with some other kind of environmental or biological trigger in a mouse exists. The question is whether that translates to humans, since not all DES research on mice does translate to humans.

The only research that offers much evidence to consider is a 2019 study on the DES Combined Cohort Follow-up from the National Cancer Institute team. That study looked at prenatal DES exposure and all types of cancer (DOI: 10.1002/em.22155).

Surprisingly, that study found that DES Daughters had a lower risk of endometrial cancer than the unexposed daughters, and the finding was statistically significant, which means it was less likely to be due to chance.

However, the unexposed daughters in the study strangely had a higher risk of endometrial cancer than the general population. It's possible that DES Daughters appeared to have a much lower risk of endometrial cancer simply because the comparison group had a higher-than-expected risk.

Still, DES Daughters had a lower risk of endometrial cancer compared to the general population too. Then again, DES Daughters tend to have higher rates of hysterectomies.

"[The finding] could be due to more hysterectomies in exposed women compared with the general population," Dr. Rebecca Troisi, the study's lead author, told the *VOICE*. Obviously it's not possible to develop cancer in an organ that's been removed.

Meanwhile, none of these studies looked at uterine sarcoma, and it's far more difficult to get data on that disease since cases are already extremely rare.

So, what's the verdict? It appears that the potential for DES to contribute to uterine/endometrial cancer risk—most likely if some other trigger is involved—could exist in DES Daughters, but so far, there is no evidence of it in the ongoing DES Daughter Follow-up Study. -TH

Better Education on Annual Cancer Screenings Needed for French DES Daughters

Not enough DES Daughters appear to be getting annual screening exams for cervical and vaginal cancer, according to a new study from France. More than a third of women had not received a Pap test in the past year, found Michel Tournaire and his colleagues from the University of Paris and the DES Research Association of France.

Although the findings are specific to DES Daughters living in France, it's likely that a study of women in the U.S. would have similar findings. In fact, it's possible even more U.S. DES Daughters are not getting annual exams since France's universal healthcare removes the blocks that women in the U.S. face with healthcare cost and access limitations.

Most concerning is that the findings are based on a survey of women who know their DES exposure status and are conscientious enough to be a member of a DES association.

The results "are encouraging but show a need to improve the dissemination of information to all DES daughters and health professionals," the authors wrote.

It's impossible to say how many DES Daughters not involved with a DES-related association are not receiving annual screenings. Those women who don't know of their DES exposure aren't aware of their higher risk and extra need for screening.

The researchers conducted a survey of 570 DES Daughters with the help of the Association Réseau DES France (sister organization to DES Action USA). The nonprofit sent out a physical questionnaire and posted an electronic one on their website and social media. The survey asked about preventive care women were receiving related to DES-caused cancer.

Nearly all the women (94%) were aged 45-64. More than half of respondents (64%) said they were following the recommendations for annual Pap tests and had received one within the past year. A quarter had received one within the past three years, and about one in ten women (11%) had not had a Pap in the last three years—or had never had one.

The most common reason women had not gotten a recent Pap test is that they or their doctor (or both) did not know it was recommended: 38% of women said their practitioners were not aware of the recommendations, and 30% of respondents said they weren't aware of them either.

Even among women who were following the recommendations, 9% said they had had difficulty getting their annual screening because their doctor was not aware of the recommendations.

Other reasons are familiar to many women. For example, a third of those surveyed said they hadn't received a test because they felt fatigued, and 15% were apprehensive about an exam.

A substantial proportion of women cited difficulty with accessing care as the reason they hadn't been tested: 29% said it was difficult to get an appointment, and 28% had trouble finding a doctor. Either they lived too far from their healthcare provider, their doctor had retired, or they had trouble finding someone who was adequate.

Only 6% said cost of care was a reason they hadn't been screened, but French residents have universal access to care that costs much less than in the U.S. It's therefore likely more U.S. women would find cost to be a barrier. The Affordable Care Act requires insurance to cover preventive care, but not everyone has insurance, and some insurance companies still fight to avoid paying for annual exams for DES Daughters, or require repeated attempts to bill.

Interestingly, women who learned about the questionnaire through Association Réseau DES France's newsletter were much more likely to receive annual screening than women who learned of the questionnaire through social media. That finding suggests that those who regularly read the French equivalent of the DES VOICE were more likely to know about and follow the screening recommendations.

The authors noted that screening recommendations for DES Daughters in France include an annual exam of the cervix and vagina as well as cytological testing (cell cultures) from cervical and vaginal tissue. They also wrote that women should continue to receive these annual screenings past age 65, even if they have had a hysterectomy.

In the survey, half the women who were over 65 years old had stopped screening, as did three quarters of the women who had had a hysterectomy.

Current screening recommendations that include 3- to 5-year gaps between screenings are based on the fact that nearly all cervical cancers are caused by human papillomavirus (HPV). However, cervical and vaginal clear cell adenocarcinomas are not related to HPV. The screening recommendations need to account for the additional risk factors in women who have a risk of cervical or vaginal cancer independent of HPV risk. -TH

Study DOI: 10.1016/j.jogoh.2020.102042

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Does DES Cause Uterine Cancer?

DES Daughters have a greatly increased risk of cervical and vaginal cancer because of DES exposure, but those are not the only types of gynecological cancers. Others include ovarian, uterine/endometrial, and vulvar cancer. This column looks at evidence for any possible effects from DES exposure on uterine cancer.

First, it's important to clarify what uterine cancer includes. Endometrial cancer is a cancer in the lining of the uterus and is frequently called uterine cancer. Indeed, uterine cancer and endometrial cancer are the same disease—uterine adenocarcinoma, the most common cancer of the female reproductive system.

However, another much rarer cancer in the uterus is called uterine sarcoma, which is different from endometrial/uterine cancer. Uterine sarcoma has different risk factors, symptoms and treatments than endometrial/uterine cancer.

Endometrial/uterine cancer occurs in the tissue lining the uterus, and uterine sarcoma develops in the uterine muscle.

So, is either of these cancers in the uterus potentially related to DES exposures? Frustratingly, the evidence can't answer this question satisfactorily.

Experimental evidence in mice suggests a possible relationship, and epidemiological data from the DES Daughters Follow-up Study that suggests there is no relationship. Neither is definitive.

A study in 1990 administered DES to newborn mice in the first 1 to 5 days of their life and followed them for 18 months (PMID: 2174729). Most of the mice developed uterine adenocarcinoma, and those receiving the largest DES dose developed it sooner.

Among mice that received the highest dose, 90% developed uterine adenocarcinoma. None of the unexposed mice developed cancer.

However, if the mice had their ovaries removed before reaching puberty, they never developed uterine tumors. The development of uterine cancer depended on a trigger of estrogen during puberty.

Other mouse studies found similar effects. One from 2018 looked at how maternal diet influenced development of uterine cancer in mice exposed to DES in utero.

Among the DES-exposed mother mice that ate a high-fat/high-sugar diet, half their offspring developed early-stage endometrial hyperplasia, which is a precursor to uterine can-

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