DES Action® VOICE

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

Inside

A Focus on Diethylstilbestrol

FALL 2019 #162

Studies Investigate Plant Extracts' Effects on DES-Caused DNA Damage

While many researchers work on understanding the effects of DES exposure both on DES Daughters and DES Sons and on their subsequent generations, others are exploring ways to treat or even reverse the damage DES has already caused. Some of this research has investigated whether plant extracts can reduce the DNA damage caused by DES.

So far, this research is in its infancy: It's not possible right now to recommend any plant extract supplements with enough evidence to show they effectively reverse DES effects. But the research is fascinating and worth following to learn whether such extracts might eventually help reduce direct or multi-generational effects of DES.

Two recent studies look at two unrelated leaf extracts: edible fig leaf extract and dry olive leaf extract. Both, however, focus on similar goals: preventing or reducing the effect of the DNA damage resulting from DES exposure.

The Olive Leaf Study

The first, by a group of Serbian and Italian researchers, explored the effects of dry olive leaf extract on DNA damage caused by a specific estrogen, 17b-estradiol, and DES in human blood cells in a lab (DOI: 10.1016/j.mrgentox.2018.12.001). They note that estrogens can contribute to oxidative stress, which can damage DNA, and DNA damage can occur alongside development of cancer, though it's not clear if it causes it. Dry olive leaf extract has some antioxidant properties.

The researchers collected blood from five healthy women and one healthy man aged 18 to 40 years. No participants were smokers or drinkers or were taking any medications or supplements.

> The way cells react to a chemical in the lab does not always correspond to how they will react in the human body.

The researchers first added estradiol and DES to different samples of blood cells and found the chemicals each separately caused DNA damage in about 30% of exposed cells. Then they added dry olive leaf extract to the cells both before and after hormone exposure. When treated with the dry olive leaf extract, before or after hormone exposure, a smaller percentage of cells showed DNA damage.

The study could not show that taking dry olive leaf extract reduces DNA damage. The authors instead suggest that eating foods rich in antioxidants may help reduce oxidative stress, already a staple of nutritional advice. Foods rich in antioxidants primarily include fruits and vegetables.

The Fig Leaf Study

The second study, published in April 2019, investigated whether fig leaf extract would reduce breaking of DNA strands caused by DES in the cells of tissue lining the human breast.

In this study, the researchers exposed human breast cells to DES on its own, to fig leaf extract on its own and to both DES and fig leaf extract together.

DES caused breaks in DNA strands with any dosage, compared no similar breakage in cells treated with fig leaf extract or with nothing at all. However, the more fig leaf extract that was added to DES-exposed cells, the less breakage was seen in DNA strands.

The authors conclude that fig leaf extract might offer a way to help reduce the risk of cancer. However, they wrote that more research would be necessary "to identify relevant active ingredients, confirm the mechanism of action and further elucidate the therapeutic potential of fig leaf extract for early-stage breast cancer chemoprevention."

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Have You Thought About Joining One of Our Support Groups?

We have two members-only support/discussion groups, our long-established site for DES Daughters and a new one for DES Men (sons and grandsons).

The DES Daughters group has minimal moderation—it's really for members to discuss medical conditions and compare notes, or ask questions about something they may be experiencing related to their or their family's DES exposure. Community Manager Karen Calechman, a DES Daughter herself, does offer tips for finding answers to questions that are on the website or answers that have come up before. There is more functionality if you have a Yahoo email account, but you don't need one to join. Just log in on our home page, go to member's tab and scroll down until you see link requesting permission to join the group. As long as your DES Action membership is current, your membership to this discussion/support group will be approved, usually within 24 hours.

The DES Men's discussion/support group is hosted on Google and is similar to the DES Daughters group. It was created this year by DES Action at the suggestion of new member and DES Son Dan Rosenfield. The topics are specific to the side effects of DES exposure experienced by men, and the conversation can be detailed. To join the group, email karen@desaction.org.

amazonsmile

Did you know that when you buy something from Amazon, a few cents of your total can be donated to DES Action?

All you have to do is go to smile.amazon.com, and choose the nonprofit you'd like to help out.

Because DES Action is under the umbrella of MedShadow Foundation, you have to select MedShadow as your charity name, but rest assured all DES Action donations will go to the right place. Thanks!

Renew Your Membership

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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.

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

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Does DES Cause Depression or Anxiety?

Being a DES Daughter or Son can come with plenty of stress managing the health effects of exposure, worrying about added risks or wondering if new symptoms are related to exposure. But can DES exposure increase depression or anxiety risk beyond what's related to other health problems?

Research on DES exposure and mental illness is contradictory and inconsistent, as is much research in general related to understanding how environmental exposures might affect cognitive and psychiatric health.

No individual study can ever be considered conclusive. Scientists look for patterns so they can draw conclusions based on results that occur repeatedly. Unfortunately, that consensus doesn't exist in studies on DES exposure and psychological diagnoses.

The most comprehensive review on DES and mental illness is a 2012 paper in the *The World Journal of Biological Psychiatry* by two French researchers (DOI: 10.3109/15622975.2011.560280).

They combed through four research databases to identify all 10 studies from 1960–2010 that examined psychiatric conditions and DES. We are focusing here only on anxiety and depression findings; the next VOICE will discuss psychosis-related disorders.

Because studies' quality and conclusions varied, the authors concluded the "role of prenatal exposure to DES as an environmental risk factor for psychiatric disorders requires more evidence before any conclusions can be drawn."

In the research review, a 1983 survey of 530 DES-exposed and unexposed participants found the risk of depression and anxiety was doubled in DES Children. This study was based on questionnaires and did not control for distress related to physical health conditions.

Five very small studies from the 1980s-90s compared major depression rates between DES-exposed and unexposed participants. In three studies, both participant groups had abnormal Pap smears (for women) or urological problems (for men), and major depression rates were similar between DES-exposed and unexposed groups but higher than in the general population. That suggests the depression could be related to the health condition rather than specific to DES exposure.

The role of prenatal exposure to DES as an environmental risk factor for psychiatric disorders requires more evidence before any conclusions can be drawn.

Two studies involving men found higher rates of major depression in DES Sons than in the unexposed comparison group. But one of these found higher overall rates of major depression, alcohol use disorder and other psychiatric symptoms among all participants — DES Sons and unexposed brothers — compared to the general population.

Finally, a 2010 American study with over 76,000 women, including 1,612 DES Daughters, found DES Daughters had a 1.4 times greater risk of depression.

Since that review, a September 2019 study in the journal *Epidemiology* surveyed nearly 5,000 DES-exposed and over 2,700 unexposed participants in the NCI's DES Combined Cohort Follow-up Study (DOI: 10.1097/EDE.0000000000001048).

Among women, 26% of DES Daughters and 23% of unexposed women reported depression, and 17% of both DES Sons and unexposed men reported depression. The researchers found no statistically significant increased risk of depression in DES Children, even when limited to those taking antidepressants. They controlled for various factors, including physical health problems, but not family history of depression.

However, the authors did find a weak association between DES and depression for only DES Daughters with a low exposure dose or exposure before 8 weeks gestation: They were 1.2 times more likely to have depression than unexposed women. Interestingly, the depression diagnoses weren't related to whether the DES Daughters had abnormal findings in the vaginal lining or any other DES-related problems.

Overall, the researchers concluded that depression didn't appear any higher in DES Daughters or Sons than in similar people not exposed to DES, with the possible exception of a weak association in DES Daughters exposed early in development or with a low overall dose.

Together, this research shows that a link between DES exposure and depression cannot be completely ruled out, but there isn't enough evidence to suggest depression is any more likely in DES Daughters and Sons than in the general population. This is likely true for anxiety as well, though fewer studies focused specifically on anxiety. But those findings refer primarily to increased risk as a direct biological result of DES exposure. It's still possible that DES Children may experience more depression or anxiety due to other DES-related health problems they must manage.

Q&A with Dr. Alisa Suen

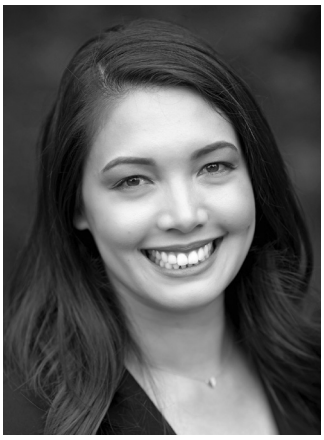
Most of the Q&A features we include in the VOICE share the stories of people exposed to DES. This time we took a different direction by learning more about the research and experience of an early-career DES researcher, Alisa Suen, PhD, at the National Institutes of Health.

Q. Tell us about your academic journey to studying DES.

I became interested in environmental health science and women's reproductive health research after watching the documentary *Blue Vinyl* by Judith Helfand in my college American Studies class. The documentary focused on the effects of vinyl chloride exposure in plastic industry workers, but I was particularly moved by the sub-story about DES exposure. Ms. Helfand had been prenatally exposed to DES, developed vaginal clear cell adenocarcinoma, and needed a hysterectomy at age 25.

I was shocked to learn that millions of mothers had been exposed to DES in the United States and that these maternal and prenatal exposures led to a wide spectrum of diseases, many of which we are still learning about today. The more I dug into DES history and research, the more I learned how little is known about the underlying disease mechanisms.

My interest in DES research drove me to complete a PhD in Toxicology and conduct dissertation research using animal models to understand how DES exposure during development leads to endometrial cancer. Using animal models helps control the window of development when exposure occurs—as we now know, timing of the exposure matters. We can also target specific biological pathways that may contribute to disease development. I hope this research will help us learn how these exposures affect people long-term and contribute to identifying and developing better treatment options.



Dr. Alisa Suen

My experience studying DES and speaking with DES Daughters helped me realize that I want to work directly with patients and contribute to healthcare innovations. I am now applying to medical school so that I can support patients by providing direct care, leading clinical trials and performing fundamental research that supports healthcare. I hope my dual roles as a physician and principal investigator will allow me to provide patients with more options.

Q. What do you find most interesting or fascinating about researching DES?

I was drawn to DES research because I wanted to positively impact a large group of people through health policy, education and medicine. In the time I have spent studying mechanisms of estrogenic chemical-induced cancer, speaking about it at conferences and corresponding with women exposed to DES, I find myself asking these questions: What research can I do to help patients and physicians better identify disease risk factors and make more informed healthcare decisions? How can I help characterize disease development and progression to support personalized treatment and identification of therapeutic targets? How can I help prevent similar exposures from happening in the future? I continue to push this research forward because I believe I can make an impact in these areas.

Q. Tell us a bit more about your research.

I performed my PhD dissertation research under the direction of Dr. Carmen Williams at the National Institute of Environmental Health Sciences (NIEHS). Dr. Williams' lab studies genomic and epigenetic biomarkers of early-life estrogenic chemical exposures that predict later-life susceptibility to female reproductive diseases. My research focuses on the biological function of a protein called sine oculis homeobox 1 (SIX1) and its role in mediating endometrial cancer after early-life DES exposure in mice.

To summarize our thought process, we exposed mice to DES, SIX1 appeared in the tissue, and then the mice developed cancer. These findings led us to ask whether the abnormal presence of SIX1 is the biological link between DES exposure and disease. But correlation does not equal causation—just because SIX1 is present doesn't mean it is actually contributing to the disease. To learn more, we had to ask more questions.

Before we dove deeper into the relationship between DES and SIX1 in mouse endometrial cancer, we needed to learn if SIX1 was relevant to human endometrial cancer. Mice aren't tiny humans, but they are a very good model for studying female reproductive tract development and hormonally induced diseases. They can help us understand what might be happening in humans.

We found that SIX1 was not present in normal human endometrial tissue samples but was expressed in a subset of endometrial cancers in

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Dr. Alisa Suen's Research Offers Insights into DES Mechanisms

As DES Children age, DES-related medical studies have slowed down compared to earlier decades, when physicians and researchers tried to learn as much as possible about the health risks DES Daughters and Sons faced.

The apparently dwindling research is discouraging for those exposed to the drug and concerned about its effects. However, it's encouraging that researchers continue to study DES and other endocrine disruptors in Petri dishes and lab animals. This work is also vital to understanding how DES interferes with various body systems and how to ensure no similar tragedies occur in the future.

Alisa Suen, PhD, is among the researchers who focus on DES and similar endocrine disruptors. In addition to the Q&A with Dr. Suen on the previous page, we explain some of the research she's already published as she works to learn more about how DES disrupts normal physiology.

One of her earliest studies, published in *Molecular Cancer Research* in 2016, investigated the role of a specific protein in endometrial cancer (DOI: 10.1158/1541-7786.MCR-16-0084). The protein, SIX1, had already been implicated in several other cancers, but Dr. Suen expanded on that research by studying how endometrial cancer developed in mice exposed at birth to DES, and what role SIX1 might play in disease development.

DES does not cause endometrial cancer in DES Children, but the type of cancer it does cause — clear cell adenocarcinoma (CCA) — does not usually occur in mice. Ideally, learning about the mechanisms that lead to endometrial cancer in mice might shed light on similar mechanisms related to how DES causes CCA in people.) One goal of the research was to find out whether SIX1 could be used as a biomarker for endometrial cancer in people. That is, would it be useful to create a test for SIX1 that would help doctors identify better courses of treatment?

Dr. Suen and her colleagues compared human endometrial tissue samples from women with and without endometrial cancer. (Their DES status was unknown.) The SIX1 protein wasn't expressed in normal tissue samples, but it did occur in a subset of cancer patients' samples, particularly from people with later-stage disease.

SIX1 could, therefore, potentially indicate the presence of endometrial cancer and might predict if the cancer would act more aggressively. Studies like these might contribute to earlier identification of gynecological cancers and help doctors understand how exposures to endocrine-disrupting chemicals like DES cause cancer, possibly informing prevention or treatment.

Dr. Suen was also involved in a study last year seeking to understand how DES exposure affects the "epigenome" of a mouse uterus (DOI: 10.1093/nar/gky260). If the genome is like the human body's instruction manual, then the epigenome is all the punctuation marks that help the reader understand how the instructions should be read and their relative importance.

Chemical exposures can also alter the epigenome, and changes to the epigenome can affect which proteins are expressed, when they are expressed and how they are passed down to an organism's offspring.

Studies like these are essential for helping scientists learn how epigenetic changes caused by DES exposure might affect the grandchildren, great grandchildren and other DES descendants.

Even though Dr. Suen's research does not look at multigenerational effects, it is crucial to overall research because she investigates the early changes DES exposure makes to the epigenome and how this leads to altered normal development of the uterus.

Dr. Suen's most recent paper, published in *Toxicologic Pathology* in July 2018, also used mice to better understand the relationship between DES exposure and uterine cancer (DOI: 10.1177/0192623318779326). Dr. Suen exposed mice to DES and observed how the lining of the uterus changed over time as the mice grew.

She documented how three separate groups of abnormal cells appeared in the endometrial lining of the mouse uteri. All the mice developed uterine cancer containing those abnormal cell types. Suen and her colleagues concluded that DES exposure disrupted normal cell programming in early development and established patterns of cell development linked to later cancer risk.

Dr. Suen's passion for investigating endocrine-disrupting chemicals and their effects on the body means important DES lab research will continue, hopefully helping us understand enough to treat or prevent problems that would otherwise occur in future generations.

DES Action VOICE

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patients who were also more likely to have late-stage disease. These findings identified SIX1 as a disease biomarker—like a "red flag" for future disease development—and suggested that SIX1 may play a role in endometrial cancer development in both mice and humans.

It is important to note that we don't know if the women who donated their tissue for us to study were exposed to DES. Therefore, we can't specifically link DES, SIX1 and endometrial cancer in humans. However, we can say that SIX1 might be useful in understanding human endometrial cancer in general and may contribute to developing future tools or screens to support physicians and patients as they make healthcare decisions.

Going back to our animal model helped us understand what SIX1 is doing in DES-induced endometrial cancer. One question we asked was if SIX1 was absent altogether, would DES still be able to cause cancer? So, we removed the gene for SIX1 in the mouse uterus and found that DES exposure still caused cancer. Although these results were initially disappointing, we were surprised to find that, without SIX1, the cancer changed in its appearance and the mice developed cancer earlier in life.

These results have taken us in a completely different direction than we initially thought and suggest that, at least in the mouse uterus, SIX1 redirects cells down a pathway that delays cancer development. This research is currently under review for publication and I am working to further explore these findings.

Q. What is most surprising to you, if anything, about the DES story?

Whenever I think about the first time I heard about DES, I am still surprised that I didn't know about it sooner. I've tried to reflect on why it isn't a more well-known event in U.S. history, and I think one of the major contributing factors is that reproductive health and disease are taboo subjects in the U.S. My impression is that, for the vast majority of people, DES exposure is a forgotten event in history. I think the quote "those who fail to learn from history are condemned to repeat it" is pertinent for chemical exposures. I want DES Daughters and Sons to know that I haven't forgotten about them and that I will continue to study DES effects.

Q. Do you think it's possible for "another DES" to occur in some form in the future with a different drug, or have the right lessons been learned?

I think there will always be a push and pull between the development of new chemicals which are functionally valuable in one area (i.e., plasticizers, flame retardants, pesticides etc.) and the ability to make sure these chemicals are safe for human health and the environment. As an environmental health scientist, I am particularly interested in preventative medicine, how research impacts health policy and providing information that enables individuals to educate themselves.

Asking the right research questions helps us understand if specific chemical exposures can contribute to diseases. Gathering this information helps us take a proactive approach by preventing these exposures from occurring and identifying biomarkers that help people who have been exposed access the healthcare they need earlier.

Q. What is your hope for the future as it relates to DES?

Most of the science that reaches the media only highlights leaps and bounds in progress. However, the reality is that science usually progresses in slow, small steps with many twists and turns. Biology is complicated, and it is often very challenging to tease apart small changes at specific points during an organism's development, and then build an understanding for how these changes fit into the larger picture. My hope for the future is that we find some mechanistic answers to support the health of DES Daughters and Sons, and that we prevent exposures like this from happening again. DES VOICE

Help DES Action With a 5-Star Review

We're proud of our Top-Rated designation from Great Nonprofits. Help us keep it going. Fresh reviews are needed by October 31 for us to achieve Top-Rated status for 2019. If you have a few minutes, please go to https://greatnonprofits.org/org/des-action-usa or just search Great Nonprofits and you'll find DES Action on their search easily. Please post a review, it only takes five minutes. Let the nonprofit community know why you support us with your membership. Your words will tell potential members and sponsors they can trust us.

Note that the EIN for DES Action USA is the same as for our parent organization, MedShadow Foundation. But all reviews stay with DES Action in the Great Nonprofits site.

Why is this so important? As its website says, "GreatNonprofits Top-Rated Awards is the one and only people's choice award where volunteers, donors, and people served by nonprofits are asked to share stories of inspiration, express their appreciation, and potentially help nonprofits earn a spot on the prestigious GreatNonprofits Top-Rated Nonprofits List."

Olive and Fig Leaf Extracts

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It's worth noting that this study appeared in a publication, *Journal of Bioequivalence & Bioavailability*, that is not indexed in PubMed. PubMed, a database of medical studies maintained by the National Library of Medicine, typically includes all reputable medical journals.

Being excluded from PubMed does not mean a study or journal is disreputable or unreliable, but it can be a red flag suggesting that the journal is not regarded as a serious or high-quality journal.

Both the fig and olive leaf studies are interesting because they suggest that these two types of plant extracts can lessen the DNA damage caused by DES—at least in a lab.

However, the way cells react to a chemical in the lab does not always correspond to how they will react in the human body. In fact, cells often react to various substances in a Petri dish in a lab, but don't react at all when exposed to the same substance in the body.

More Research Needed

Each of these studies is also a stand-alone study. After one group of researchers has published a paper like these, other researchers will ideally conduct the same experiments to see if they get the same results. The findings must be replicated several times before they can be considered reliable.

Once scientists establish that cells might react to a particular substance in the lab, the next step is for them to see if the cells react similarly in an animal model, such as zebrafish or mice.

If the cells do respond in multiple replicated studies, then researchers eventually progress to testing the substance in humans. This process can take many years before scientists might discover that a particular substance can actually be used as a treatment in people.

Right now, there is no evidence suggesting that taking dry olive leaf or fig leaf extract supplements would improve health or reduce any DNA damage in a person. These studies look at the effects of the extracts on human cells in a lab, but they do not otherwise involve people.

Nevertheless, it's encouraging to know that some plant extracts have shown these initial weakening effects on DNA damage caused by DES, especially if it inspires other researchers to replicate these experiments or to explore possible therapeutic effects from other plant extracts.

It's also reassuring to know that scientists are investigating a wide range of possible research pathways to better understand how to offset or prevent negative effects caused by DES. DES VOICE

Qualifying for Social Security Disability Benefits with Cervical Cancer

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being unable to work for at least a year before qualifying. Your condition must be considered severe, and it must affect your ability to perform work-related duties.

Disability Determination Services will evaluate the details of your case and determine if your condition meets the criteria established in the cervical cancer impairment listing. To qualify for disability benefits using the listing for this specific cancer, your cancer must have extended outside the cervix into the vagina, organs or pelvic wall, or it must have recurred after chemotherapy.

If your specific condition doesn't fall into one of those categories, the evidence that you supply will be reviewed along with vocational factors to determine if you would be able to perform some job and earn a living. Even if Disability Determination Services determines you cannot return to your previous job because of your condition, they must also determine if there is some other kind of work that you are able to do. Your educational level, work experience, transferable skills and age are all considered when they determine if there is work you would be able to do to earn a living.

Applying for Social Security Disability Benefits with Cervical Cancer

If you have cervical cancer and it has left you unable to work, you will want to get your application underway for disability benefits so you can be approved and have some financial assistance. You can start your application online at the SSA website, www.ssa.gov, or you can call 1-800-772-1213 to start your application over the phone or to schedule an appointment at your local SSA field office.

Documentation is essential for a successful disability claim. Be sure to include any doctor's notes that indicate how you are affected by cervical cancer, including any symptoms that you suffer and side effects that are caused by the cancer treatments themselves.

Resources:

Cervical Cancer: https://www.disability-benefits-help.org/blog/cervical-cancer-and-social-security-disability

Qualify: https://www.disability-benefits-help.org/content/do-you-qualify

Local SSA Office: https://secure.ssa.gov/ICON/main.jsp

Disability Determination Process: https://www.ssa.gov/disability/determination.htm

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Qualifying for Social Security Disability Benefits with Cervical Cancer

When you've been diagnosed with cancer, the last thing you want to think about is your finances, but it's unfortunately often the first thing many people have to worry about. A variety of programs can help with cancer-related costs, but those sources are less helpful if you cannot continue to work as a result of your diagnosis or treatment.

Fortunately, some people diagnosed with cancer are eligible for Social Security Disability benefits — if you know the process for applying. Cendy Moliere, from the organization Disability Benefits Help, has helpfully provided a straightforward guide to applying for disability benefits for DES Daughters diagnosed with cervical cancer. Disability Benefits Help aims to assist people of all ages in receiving Social Security disability benefits. This guide may also apply to other types of cancers if the applicant meets the criteria. If you have any questions on how to qualify with cervical cancer or about the disability process in general, feel free to reach out to the Disability Benefits Help team at help@ssd-help.org.

At one time, cervical cancer was the leading cause of death among women in the United States. But thanks to medical advances, those numbers have decreased significantly during the last four decades. The American Cancer Society reported that about 13,170 new cases of cervical cancer will be diagnosed during 2019 and about 4,250 women will die from this specific cancer.

Cervical pre-cancers are diagnosed more frequently than the invasive cancer, so treatment can get underway before the condition becomes too devastating. Most often, women diagnosed with cervical cancer are between the ages of 35 and 44. If you have been diagnosed with cervical cancer and the cancer is advanced enough to be disabling, or the treatments have left you unable to work, you may qualify for Social Security Disability benefits.

Qualifying for Disability with Cervical Cancer

A cervical cancer diagnosis alone isn't usually enough to qualify for disability benefits. You must meet specific medical criteria, including

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