

A Focus On Diethylstilbestrol

FALL 2013 #138

DES Action Health Survey

Most DES Daughter Issues Not Reported In Large Numbers For DES Granddaughters

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In 2012, DES Action USA asked VOICE subscribers and other DES-exposed people to complete a questionnaire about various health problems they may have experienced (see details in VOICE issue 137, summer 2013). The current article provides additional details about responses from DES Daughters and DES Granddaughters from the United States.

Many conditions, already known or suspected to be associated with DES exposure, were reported in high frequency by DES Daughters. For some of these conditions, i.e., clear cell cancer, the number was higher than expected even for the DES exposed. This is an example of reporting bias—those

with health problems are more likely to respond to surveys.

What has not been widely reported are the prevalence of these conditions in DES Granddaughters. As can be seen in the table, most conditions are reported more frequently by DES Daughters than Granddaughters. This suggests that DES is more likely to have an affect on those directly exposed (DES Daughters) than those indirectly exposed (their children).

Keep in mind that DES Granddaughters are still young (mean age 28 years) and many have not yet attempted pregnancy (only 37% have ever been pregnant), so prevalence of some conditions in DES Granddaughters may increase over time.

However, some of the conditions are rare and/or were not expected to be in increased frequency in DES

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Bra Sizes May Help Explain DES Link to Breast Cancer

“Prenatal DES exposure in relation to breast size,” Julie R. Palmer, et al. *Cancer Causes & Control*. 2013 Sep; 24(9): 1757-61.

Reviewed by Kari Christianson

DES Daughters: Do you remember what bra size you wore when you were 20 years old?

Participants in the National Cancer Institute (NCI) DES Follow-up

Study were asked this question about bra size. They were asked to report both their chest circumference and their bra cup size.

Julie R. Palmer, Sc.D., Professor at the Slone Epidemiology Center at Boston University and a principal investigator with the DES Follow-up Study, and her colleagues were seeking more information about how DES influences the risk for breast cancer in

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DES Daughter Toolkit Inside!!

Here it is—an exciting benefit of DES Action USA membership. Our new Toolkit will help DES Daughters advocate for the health care they need.



Years of DES research and official clinical guidelines have been collected into a single document for DES Daughters to easily share with their doctors.

We now hear frequently of the retirement of providers who knew about DES—but their replacements lack current knowledge and experience. This first-of-its-kind Toolkit addresses our on-going health concerns by providing DES information in a format that is user-friendly for doctors.

- As a DES Action member you get a free Toolkit inside this VOICE.
- **Extra copies are available at two for \$5**, which includes shipping. Send a check to:
DES Action USA
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Jupiter, FL 33468.

Feel empowered—hand this Toolkit to your provider and let it do the explaining about DES for you!



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Yes!—I want to join DES Action to stay informed and support a cause I believe in.

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Please make checks payable to **DES Action.**

I am a: ☐ DES Daughter ☐ DES Son ☐ Other ☐ DES Granddaughter or Grandson
☐ DES Mother of a: ☐ Daughter ☐ Son

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Online Support Group for DES Daughters

Want to be in touch, via e-mail, with other DES Daughters? As a benefit of being a DES Action member, you can join the DES Action Daughters Online Support Group. That way you can ask questions and share experiences common only to those of us who are DES-exposed.

To join the DES Action Online Support Group simply send a blank e-mail to:

DESActionDaughters-subscribe@yahoogroups.com

You'll receive an e-mail back from Yahoo! Groups confirming your request to join. It offers two registration options and the easiest is Option 2. Click "Reply" so the note is sent back.

Once we've checked to be sure you are a current DES Action member, you'll receive a welcome to the group letter explaining how to send messages. Then you can participate in the e-mail conversations, or just quietly read and enjoy the learning experience.

Have You Considered Planned Giving?

Think about including DES Action USA in your estate planning, trusts and wills. Speak with your estate planning attorney to ensure your wishes are correctly put in place.

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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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DES DAUGHTER TOOLKIT

A PHYSICIANS' GUIDE

What DES Daughters and their doctors need to know about the lifelong risks of DES exposure to have a discussion about DES health care needs and concerns.

This toolkit is derived from the evidence-based research and clinical practice recommendations of respected national institutions and includes the following information:

- Adverse Health Effects due to DES Exposure
- CDC DES Daughter Pap/pelvic Exam Protocol
- Screening Guidelines for frequency of exams or 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.

Screening Recommendations:

1. **Special DES Daughter Pap/pelvic Exam Done Annually** (directions inside)
 - to 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)
 - While a rare disease, even for DES Daughters, this population is aging and CCA can occur after menopause
 - An important aspect of the special exam is *palpation of the vagina* to check for cancerous lumps under the surface
 - *Even after a hysterectomy* or menopause DES Daughters should continue with this annual exam to screen for vaginal cancer
2. **Vigilance in Breast Cancer Screenings as DES Daughters Age Past Forty**
 - because of an increased risk that is almost twice the risk of unexposed women (Palmer, et al. *Cancer Epidemiology Biomarkers* 2006; Aug 15(8): 1509-1514 and Hoover, et al. *N Engl J Med* 2011; 365: 1304-1314)
 - Annual breast screenings
 - Yearly clinical breast exams
 - Attention to breast health by DES Daughters who alert providers to changes

Treatment Considerations:

1. **Treatments for DES Daughters are the same as for unexposed women in most areas**
 - **The exception is for gynecologic procedures** because *cervical stenosis* is a concern in this population, especially from cryosurgery and cone biopsy, which the researchers suggest should be approached cautiously (Cervical Stenosis Following Minor Gynecologic Procedures on DES-Exposed Women,” *Obstetrics & Gynecology* 56:33, Sept. 1980)
 - DES knowledgeable providers are favoring LEEP for DES Daughters, understanding the least invasive but diagnostically correct procedure is the goal

DES Daughters Should Have Annual Paps

Current cervical cancer screening guidelines released in March 2012 by the U.S. Preventive Services Task Force (USPSTF) specify that some women can skip years between Paps, but *not* DES Daughters.



The third paragraph under USPSTF Recommendations spells out that:

“This recommendation statement does not apply to women with in utero exposure to diethylstilbestrol.”

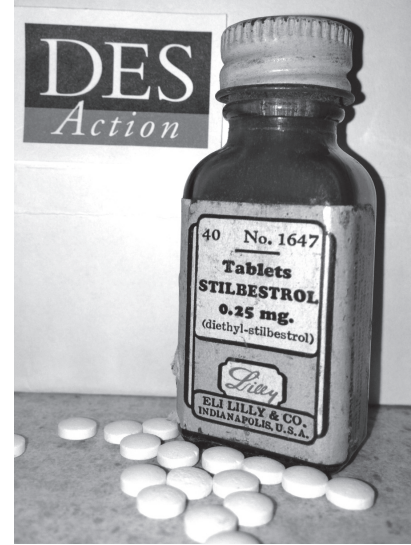
However, we are watching the evolution of screening protocols and detect a movement toward potentially allowing DES Daughters over age 70 to lengthen the time between cervical cancer screenings, if there has been no previous diagnosis of cancer or recent cervical or vaginal biopsies or changes. If new Pap recommendations are issued, yearly visits to a gynecologist would still be needed, even without a yearly Pap or cervical cancer screening. Even after hysterectomy it's prudent for DES Daughters to be checked for vaginal cancer. DES Action will keep members informed of official guideline changes, to pass along to providers.

In early years of caring for DES Daughters **colposcopy exams** were routinely performed. Some DES Daughters continue to have them. However, thinking has evolved now so providers generally employ colposcopy primarily as a diagnostic tool:



“A routine cervical Pap test is not adequate for DES Daughters. The Pap test must gather cells from the cervix and the vagina. It is also good for a clinician to see the cervix and vaginal walls. They may use a colposcope to follow-up if there are any abnormal findings.”

“National Cancer Institute FactSheet, Diethylstilbestrol (DES) and Cancer, number 9: “What should DES-exposed daughters do? <http://www.cancer.gov/cancertopics/factsheet/Risk/DES>”



Menopause and Hormone Replacement Therapy

NCI DES Follow-up Study research indicates that DES Daughters may begin menopause slightly earlier than unexposed women. However, it appears their experiences are no different from unexposed populations.

Studies have not been done specifically concerning DES exposure and HRT use. But since DES Daughters were exposed to a synthetic hormone in utero, and knowing of current studies on HRT concerns, **it may be considered prudent to use the lowest dose for the shortest period of time IF symptom relief is absolutely needed.**



Department of Health and Human Services

Centers for Disease Control and Prevention

Annual Exam for DES Daughters

Although health effects of DES exposure differ among DES Daughters, health care providers should monitor these women for abnormal genital tract structures, particularly for clear cell adenocarcinoma (CCA) of the vagina and cervix.

- **Clinical breast exam**
- **Vulvar inspection**
- **Vaginal and cervical inspection**
 - Inspection of epithelial surfaces of vagina
 - Rotation of speculum to view anterior & posterior walls of vagina
- **Cytology**
 - Separate specimens from vagina fornices and cervix — all specimens placed on one slide or in liquid media
- **Palpation of vagina and cervix (an essential part of the exam)**
 - Palpate entire length of vagina, including fornices
 - Note ridges or structural changes
- **Bimanual rectal-vaginal exam**
- **Biopsy**
 - Areas of thickening or induration found during vaginal and cervical palpation
 - Palpable nodules
 - Discrete areas of varied colors or textures
 - Atypical colposcopic findings
- **Colposcopy**
 - If abnormal findings on Pap smear
- **Iodine staining of vagina and cervix**
 - To confirm boundaries of epithelial changes
 - Use Lugol's solution (half strength)
- **Frequency of follow-up visits**
 - Determine on individual basis
 - Focus on changes since initial evaluation — include: palpation, inspection, cervical & vaginal cytology
 - Colposcopy, iodine staining, biopsy as needed
 - Ask about interval bleeding or abnormal vaginal discharge



DES DAUGHTER TOOLKIT



Researchers with the **National Cancer Institute (NCI) DES Follow-up Study** outlined twelve known adverse health impacts for DES Daughters in the October 6, 2011 issue of the *New England Journal of Medicine* ("Lifetime burden of adverse health outcomes among women exposed in-utero to Diethylstilbestrol (DES)," Hoover et al. *N Engl J Med* 2011; 365:1304-1314)

Risks for DES-exposed Daughters Compared to Non-DES-exposed Daughters

Outcome	Increased Risk
Clear cell adenocarcinoma	40 times higher
Neonatal death	8 times higher
Preterm delivery	4.7 times higher
Loss of second trimester pregnancy	3.8 times higher
Ectopic pregnancy	3.7 times higher
Stillbirth	2.4 times higher
Infertility	2.4 times higher
Early menopause	2.4 times higher
Cervical intraepithelial neoplasia	2.3 times higher
Breast cancer	1.8 times higher
First trimester miscarriage	1.6 times higher
Preeclampsia	1.4 times higher

(Table from the March 2012, Number 44 issue of *Linkage*, a publication of the NIH National Cancer Institute Division of Cancer Epidemiology and Genetics)

Higher Incidence Percentage in DES Daughters and DES Sons Compared with Unexposed Population

Condition	DES-Exposed
Diabetes	21%
High Cholesterol	12%*
Hypertension	14%*
Coronary Artery Disease	18%
Myocardial Infarction	28%
Stroke	55%
All CVD	27%*
Osteoporosis	24%
Fractures	30%

*Difference between exposed and unexposed is statistically significant (i.e., unlikely to be due to chance) but doesn't prove DES was causal.

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

DES research continues with additional health issues now possibly linked to exposure. At this time there are no special screenings or treatments identified, just the need for awareness of potential increased risks.

("Medical Conditions Among Adult Offspring Prenatally Exposed to Diethylstilbestrol," Troisi et al. *Epidemiology*; Vol. 24, No. 3, May 2013)



Health Survey *from page 1*

Granddaughters. For example, polycystic ovarian syndrome occurs in 5-10% of women of childbearing age but is reported by 14% of DES Granddaughters.

These findings will be shared with the research community for more rigorous investigation to determine if it is a real increase or another example of reporting bias.

Of course most of these conditions occur in non-DES exposed women as well. Without well-controlled studies, it is not possible to prove that any of these conditions are higher than expected.

In a future article we will present more information on DES Sons and Grandsons. Thanks to everyone who completed the survey, which may provide clues to scientists who are investigating the long-term health consequences of DES exposure.

Editor's note: In the next VOICE issue Dr. Wingard compares more of the conditions listed to the occurrence rates in unexposed women. Special thanks to our DES Action members and friends who shared their health experiences for this important anecdotal survey.

DES VOICE

Condition	DES Daughters	DES Granddaughters
Painful periods (dysmenorrhea)	58%	49%
Irregular periods	43%	45%
Cervical anomalies (hoods, ridges)	52%	8%
Adenosis	45%	10%
T-shaped uterus	42%	6%
Uterine fibroids	32%	8%
Endometriosis	26%	16%
Pelvic inflammatory disease (PID)	10%	4%
Cystic (lumpy) breasts	47%	12%
Ovarian cysts	42%	29%
Polycystic ovarian syndrome	8%	14%
Paraovarian cysts	6%	0%
Dysplasia	34%	8%
Breast cancer	11%	0%
Cervical/vaginal cancer	8%	2%
Uterine Cancer	4%	2%
Other cancer	14%	2%
Ever pregnant	72%	37%
Number pregnancies	2.9	2.2
Number live births	1.4	1.2
Infertility	48%	20%
Miscarriages	35%	21%
Ectopic pregnancies	12%	2%
Preeclampsia	5%	8%

Bra Sizes *from page 1*

DES Daughters. She writes, "If there is indeed a causal relation between prenatal DES exposure and breast cancer risk, one mechanism may involve DES effects on the total number of mammary gland cells formed during gestation."

DES May Increase Mammary Gland Cell Formation—Hence Larger Cup Sizes

One way to determine the number of mammary gland cells or breast volume is by bra cup size. Palmer explains, "Bra cup size has been shown to be a more accurate measure of breast volume among women who have a small chest circumference than among all women considered together." That is why chest circumference was a focus in this study.

Chest circumferences of the women were grouped as 35" or higher, 34",

33", or 32" or less in this analysis. A large cup size was C or larger.

This study has been following the same women for decades. Weight and height information was taken in-person at the study screening centers in the 1970s and has been updated on questionnaires every five years. But participants had never been asked about bra size in the past.

Palmer found no association between DES exposure and bra cup size in women with 34" or higher chest circumference. But when she analyzed the responses of women with the smallest chest circumference (32" or less) who also reported being thin at age 20, there was a significant difference in the bra cup size among the DES-exposed women.

Palmer writes, "We found that these DES-exposed women had an estimated 45% greater prevalence of

large bra cup size and that the increase was even greater among women who were lean at age 20." Among those lean at age 20 DES-exposed women, there was an 83% greater prevalence of a C or larger bra cup size.

The researchers also reviewed the birth weight and total DES exposure of the lean women to further analyze the findings. Women with the highest doses of prenatal DES exposure had the larger bra cup size. No association with birth weight was found.

As Palmer concludes, "The present findings provide support for the hypothesis that in utero DES exposure may result in greater mammary mass. Taken together with the previous research on bra size and breast cancer risk, these findings suggest a mechanism for the possible association of in utero DES exposure with increased risk of breast cancer."

DES VOICE

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DES Daughter Toolkit**

DES Breast Cancer Litigation Settlements

A long, drawn-out emotional and exhausting legal battle finally wrapped up this fall.

But, as is common in situations where there are settlement agreements, it is stipulated they are private and cannot be made public.

This lawsuit had been an uphill battle from the start. The 14 drug makers named in the suit forced a Daubert Hearing in an effort to stop a trial. They claimed scientific evidence linking DES to breast cancer was flawed. But the plaintiff's lawyers vigorously disputed that and successfully proved a DES link to breast cancer is scientifically rigorous enough to withstand courtroom scrutiny. So the trial began in Boston Federal Court.

During opening arguments earlier this year, jurors were told that Eli Lilly failed to test the effect of DES on fetuses before promoting the drug to pre-



vent miscarriage. But jurors didn't get the chance to render a verdict because Lilly abruptly settled with the four DES Daughters in this first case, and therefore did not have to admit guilt.

After that there was hope and anticipation the remaining cases would be settled quickly. But months passed without success until the judge brought both sides back to the negotiating table in June, where serious talks began.

This resolution of these pending breast cancer cases ends the lawsuits filed in Boston and also in Washington D.C. Superior Court. For some the experience and how it ended was disappointing.

One DES Daughter had tears in her eyes. "Those who wanted to file suit but didn't qualify due to missing medical records or other technicalities did not miss out on anything except dashed hopes."

Says another DES Daughter breast cancer survivor, "I'm glad to have been involved. Now I can put this chapter behind me and move on to educate others facing the health issues DES exposure brought to us."

While this particular litigation now is finished, the court system continues to be where drug makers can be held accountable for harms caused by DES exposure.

DES VOICE