



# 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 or to register as a study participant if you have a confirmed case, visit the registry [website.](#))

While a rare disease, even for DES Daughters, this population is aging and CCA can occur after menopause.

Researchers are watching DES Granddaughter cohort. For this reason we recommend the same exam for DES Granddaughters as we do for DES Daughters.

- 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

- These need to be done because of ongoing studies continuing to explore an increased risk compared to 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; Troisi, et al. *Environmental Molecular Mutagenesis*:14 October 2017 DOI 10.1002/em.221552017; )

- Annual breast screenings
- Yearly clinical breast exams
- Attention to breast health by DES Daughters and Granddaughters who report changes

## Treatment Considerations:

### 1. Treatments for DES Daughters and Granddaughters are the same as for unexposed women in most areas

- **The exception is for gynecologic procedures** because cervical stenosis is a concern in the DES daughter 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.

*\*To date the research on DES granddaughters is ongoing. Since that cohort population is generally between the ages of 20 and 40 years, many have not tried to have children and the possible impacts on their health are being watched as they age. We suggest DES Granddaughters tell their doctors about their and their mothers’ exposures and remain vigilant in following up on anything that may be a concern or questionable since it could potentially be a medical problem in the Granddaughter population. Animal studies indicate a higher rate of tumor growth in DES Grandson and Granddaughter mice compared with unexposed animals. But researchers caution that more studies are needed to prove conclusively that this finding in DES-exposed mice also occurs in humans. This is being closely watched in the grandchildren population. Therefore, we recommend DES Granddaughters receive the same kind of thorough exam as DES Daughters.*

## DES Daughters and Granddaughters Should Have Annual Paps

Current cervical cancer screening guidelines released in August 2018 by the US Preventive Services Task Force (USPSTF) specify that some women can skip years between Paps, but **not DES Daughters**.

See the [Clinical Considerations section](#) for the relative benefits and harms of alternative screening strategies for women 21 years or older. This live link states:



**“This recommendation statement applies to all asymptomatic individuals with a cervix, regardless of their sexual history. This recommendation statement does not apply to women who have been diagnosed with a high-grade precancerous cervical lesion or cervical cancer, women with in utero exposure to diethylstilbestrol, or women who have a compromised immune system (eg, women living with HIV).”\***

*\*Please note, DES Granddaughters were eggs in their mother’s fetal body, so were exposed as well. Studies continue to see what the impacts on the DES Granddaughters are.*

Arthur L. Herbst, MD, Director - University of Chicago CCA Study, who first discovered the link between prenatal DES exposure and vaginal or cervical clear cell adenocarcinoma, recommends: “Even in the absence of a pap smear, the DES exposed woman should have an **annual pelvic exam** where her physician fully views the vagina and cervix.” Even if the pap smear isn’t done annually, the pelvic exam is the greater priority for these women. It is important that they have these exams annually. Additionally, he says, “we do not have enough data to definitively say or support that there is no upper age limit on CCA diagnoses. Since it is not known yet, this should lead to the continuation of annual exams.”

**The USPS Task Force recommends:** “Certain considerations may also support screening in women older than 65 years who are otherwise at high risk. (ie, women with a history of high grade precancerous lesions or cervical cancer, in utero exposure to diethylstilbestrol or a compromised immune system.) Women with these risk factors are not included in this recommendation, and should receive individualized follow-up. Women at increased risk of cervical cancer (ie, women with a history of cervical cancer, a compromised immune system, or diethylstilbestrol exposure) may need to be screened more often.”

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 and granddaughters. 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 Fact Sheet](#), Diethylstilbestrol (DES) and Cancer, number 9: “[What should DES-exposed daughters do?](#)”

## **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 (and Granddaughters, as their eggs) 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.**



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.

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)



## Insurance Codes for DES-Related Medical Visits

Many DES Daughters have asked us what codes their doctors should use to ensure their insurance company and/or Medicare appropriately pays for the visit and does not leave them with a big bill. No specific code exists for DES exposure since exposure affects people differently, but several codes can be used for the problems associated with exposure. Special thanks to Karen Fernandes, DES Daughter and registered nurse, who provided these codes to us. No ICD-10 code is yet available for the third generation.

- 755 Malignancy, female reproductive system with cc
- 756 Malignancy, female reproductive system without cc/mcc

- C52 is applicable to female patients.
- ICD-10-CM C52 is grouped within Diagnostic Related Group(s) (MS-DRG v34.0):
- 736 Uterine and adnexa procedures for ovarian or adnexal malignancy with mcc
- 738 Uterine and adnexa procedures for ovarian or adnexal malignancy without cc/mcc
- 739 Uterine, adnexa procedures for non-ovarian and non-adnexal malignancy with mcc
- 740 Uterine, adnexa procedures for non-ovarian and non-adnexal malignancy with cc
- 741 Uterine, adnexa procedures for non-ovarian and non-adnexal malignancy without cc/mcc
- 754 Malignancy, female reproductive system with mcc





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## **Annual Exam Guidelines for DES Daughters and Granddaughters**

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