



# DES Update: Current Information

*Developed in collaboration with the Centers for Disease Control and Prevention,  
Centers of Excellence in Women's Health (Department of Health and  
Human Services) for CDC's DES Update*



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## Objectives

- After completing this program, participants will be able to
  - Describe DES and its past uses
  - State the known adverse health risks associated with DES exposure
  - State health effects known to be unrelated to DES
  - Describe areas of ongoing research



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State the known adverse health risks associated with DES exposure

State health effects known to be unrelated to DES

Describe areas of ongoing research

## Objectives

- After completing this program, participants will be able to counsel
  - Women prescribed DES while pregnant
  - Women exposed to DES in utero (DES Daughters)
  - Men exposed to DES in utero (DES Sons)



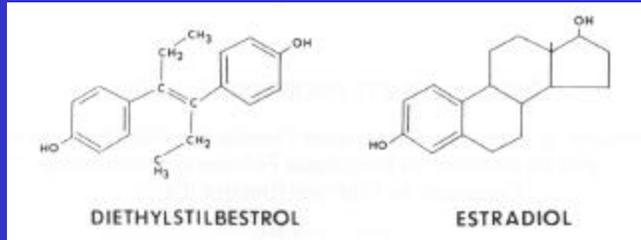
After completing this program, participants also will be able to counsel

Women prescribed DES while pregnant

Women exposed to DES in utero, also known as DES Daughters

Men exposed to DES in utero, also known as DES Sons

## Diethylstilbestrol (DES)



- Potent nonsteroidal estrogen
- First synthesized in 1938



Diethylstilbestrol (DES) was first synthesized by Sir Charles Dodds and his colleagues in 1938. In contrast to naturally occurring estrogens, DES does not contain a classic four-ring steroid molecule. DES is the most potent nonsteroidal estrogen. Its use in humans today is restricted to clinical trials for treatment of various hormonally responsive malignancies and in veterinary medicine.

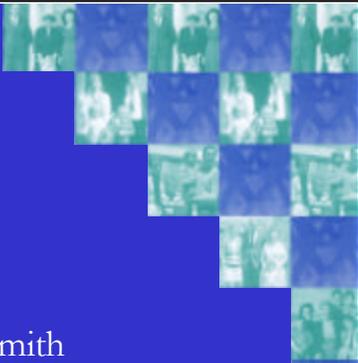
However, DES was used during 1938-1971 to enhance pregnancy outcomes.

# History

- 1940s
  - Olive Watkins Smith and George V. Smith
    - Noted that decrease in urinary estrogen and progesterone preceded adverse pregnancy outcomes
    - Postulated that administering estrogen might prevent adverse pregnancy outcomes



In the United States, use of DES increased because of research conducted by Olive Watkins Smith and George V. Smith. In the 1940s, Smith and Smith noted that various adverse pregnancy outcomes, including first and second trimester spontaneous abortion, toxemia, and premature labor, were preceded by a decrease in urinary estrogen and progesterone. They postulated that administration of exogenous estrogens might counteract these effects and allow continuation of a normal pregnancy.



- 1949
  - Reports of nonrandomized, nonblinded trials of DES by Smith and Smith published in
    - *New England Journal of Medicine*
    - *American Journal of Obstetrics and Gynecology*
  - Enthusiastically endorsed the use of DES

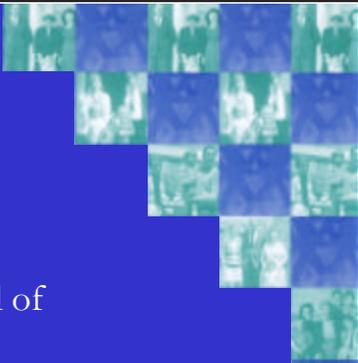


Smith OW, et al. *Am J Obstet Gynecol* 1949.  
Smith OW, et al. *N Engl J Med* 1949.



The Smiths tested their hypothesis in clinical trials by administering the new potent synthetic estrogen, DES, to pregnant women who started their prenatal care in the first half of their pregnancy. However, as was common practice at that time, study participants were not randomized to receive either the study medication or a placebo. Control patients for comparison were not selected at random, and the investigators were not blinded as to which patients were test subjects or controls when the data were analyzed.

In 1949, Smith and Smith published the results of their experiments in prestigious journals such as the *New England Journal of Medicine* and the *American Journal of Obstetrics and Gynecology*. These reports indicated that their hypothesis was correct and that administration of DES resulted in fewer spontaneous abortions, premature labor, or toxemia of pregnancy. They enthusiastically endorsed the use of DES to prevent common pregnancy complications, and many physicians caring for pregnant women adopted their recommendations.

- 
- 1953—Dieckmann et al.
    - Randomized double-blind trial of DES at University of Chicago
    - Included 1,646 patients
    - Found no improvement in pregnancy outcome
    - Would become a valuable source of future information on DES effects



Dieckmann WJ, et al. *Am J Obstet Gynecol* 1953.



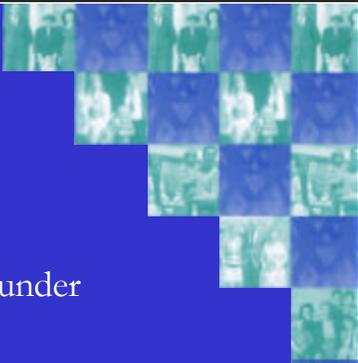
To better assess whether DES was truly effective in preventing adverse pregnancy outcomes, W. J. Dieckmann and colleagues conducted a large randomized, placebo-controlled, double-blind study of DES use in early pregnancy. This well-designed trial, involving 1,646 women, demonstrated the lack of any objective benefit from the use of DES.

This study was important in refuting the Smiths' reports of the effectiveness of DES, but it was not the only randomized trial to do so. The greatest contribution from this study was to come in future years, as the adverse effects of DES became more apparent. The conduct of such a large trial through one institution allowed for the eventual assembly of a cohort of women and their offspring who were randomized to receive either DES or placebo in pregnancy. This cohort, often referred to as the Dieckmann cohort or the Chicago cohort, was eventually followed for decades, and provided some of the most valuable information about long-term health risks associated with exposure to DES.

- 
- 1950s—Despite findings of Dieckmann et al. and similar studies, DES use continued because of
    - Different standards of medical practice than today
    - Lack of strict government regulation
    - No known ill effects



Despite the findings of Dieckmann and other researchers, DES continued to enjoy widespread use for several reasons. The standards of the practice of medicine were much different 40-50 years ago. Physicians often based their practice on what they perceived to be effective on the basis of personal experience, or what older and respected colleagues promulgated to be true. Objective evidence of clinical trials was sometimes rejected on the basis of personal experience that seemed to point to a contrary conclusion. In contrast to today, pharmaceutical companies did not have to provide strong proof of either safety or efficacy before manufacturing and marketing DES. Even if its efficacy was questionable, DES was not initially known to have harmful effects. Given the lack of other proven beneficial therapies for common complications of pregnancy, trying DES was not believed harmful. DES became especially tempting to try in situations where young mothers had recurrent miscarriages or otherwise were unable multiple times to complete a normal pregnancy. In such situations, a doctor, acting with the best of intentions, might suggest any therapy that might be effective.

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- 1938–1971—DES and similar nonsteroidal estrogens marketed under many brand names
    - Combined with progesterone
    - Combined with androgens
    - Vaginal creams and suppositories
    - Oral administration
    - Injections
  - Many different doses and regimens used



DES and similar synthetic estrogens were marketed under many brand names, often combined with other ingredients considered beneficial to the pregnancy. These ingredients might include androgens, progestins, or even vitamins. In addition to oral administration, vaginal creams or suppositories, and injections were employed. The doses of synthetic estrogens were not standardized and varied widely among brands and formulations.

**"Really?"**

Yes...  
**desPlex**  
 to prevent ABORTION, MISCARRIAGE and  
 PREMATURE LABOR

recommended for routine prophylaxis  
 in ALL pregnancies . . .

96 per cent low delivery with **desPlex**  
 in one series of 1300 parturients\*—  
 — bigger and stronger babies, too.\*\*

No gastric or other side effects with **desPlex**  
 — in either high or low dosage\*\*\*

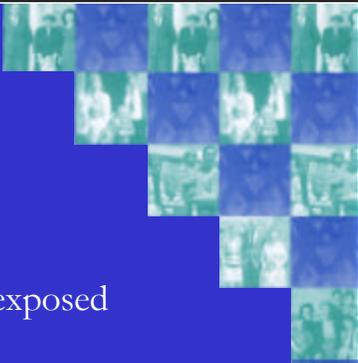
Each **desPlex** tablet starts with 25 mg. of diethylstilbestrol, U.S.P., which is then ultrasonicated to smooth and accelerate absorption and activity. A portion of this ultrasonicated diethylstilbestrol is also included in the tablet coating to assure prompt help in emergencies. **desPlex** tablets also contain vitamin C and certain members of the vitamin B complex to aid detoxification in pregnancy and the effective use of estrogen.

For further data and a general  
 trial supply of **desPlex**, write to:  
 Medical Division

REFERENCES  
 \* *Journal of the American Medical Association*, 167: 1000, 1957.  
 \*\* *Journal of the American Medical Association*, 167: 1000, 1957.  
 \*\*\* *Journal of the American Medical Association*, 167: 1000, 1957.

GRANT CHEMICAL COMPANY, INC., Brooklyn 26, N.Y.

This is an ad for desPlex from the June 1957 issue of *Obstetrics and Gynecology*. In addition to DES, each desPlex tablet contained “vitamin C and certain members of the vitamin B complex to aid detoxification in pregnancy.” The ad also stated that a portion of the tablet’s DES was in its coating “to ensure prompt help in emergencies,” implying that DES was helpful for impending problems such as threatened spontaneous abortions.

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- 1938–1971
    - Total number of women and exposed fetuses cannot be known with certainty
    - An estimated 5–10 million women and their fetuses exposed in the US



Guisti RM, et al. *Ann Intern Med* 1995.



However, an estimated 5–10 million women and their fetuses were exposed to DES in the United States. The precise number will never be known.

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- 1971
    - Arthur Herbst and Robert Scully reported a series of young women with rare clear cell adenocarcinoma (CCA) of the vagina
    - Case-control study demonstrated an association with DES exposure in utero

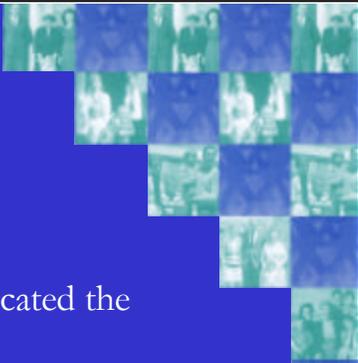


Herbst AL, et al. *Cancer* 1970.

Herbst AL, et al. *N Engl J Med* 1971.

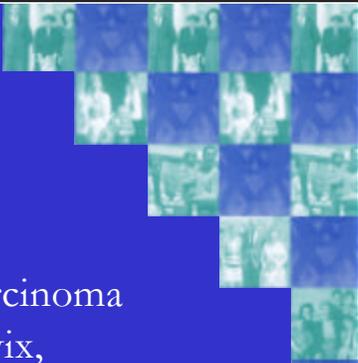


In 1971, Drs. Arthur Herbst and Robert Scully reported a series of young women with clear cell adenocarcinoma (CCA) of the vagina. This type of cancer was an exceedingly rare tumor that occurred predominantly in older women. A gynecologic oncologist would rarely ever see more than one or two cases of CCA of the vagina, let alone a series of cases in young women. Herbst and colleagues subsequently conducted a case-control study to identify a common risk factor. They showed that maternal ingestion of DES during pregnancy was associated with subsequent development of CCA of the vagina in female offspring.

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- 1971
    - FDA Drug Bulletin contraindicated the use of DES in pregnancy
    - DES remained available for other uses
    - DES remained available outside the US



On the basis of results of the Herbst study, in 1971 DES was the subject of an FDA Drug Bulletin contraindicating the use of DES during pregnancy. However, DES remained available for other uses in the United States, and it remained available outside the United States. Because not all physicians received notice, some men and women born after 1971 were exposed to DES in utero, particularly if they were born outside the United States.

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- After early reports of DES-associated clear cell adenocarcinoma (CCA) of the vagina and cervix, other possible effects investigated in
    - DES Daughters
    - DES Sons
    - Women Prescribed DES While Pregnant



After early reports of DES-associated CCA of the vagina and cervix, other possible effects were investigated in DES Daughters, DES Sons, and women prescribed DES while pregnant.

## Women Prescribed DES While Pregnant

- Population that has reached age of significant risk for malignancy
  - Most women now aged 50–90 years
- Most investigations have centered on risk for breast or other malignancies



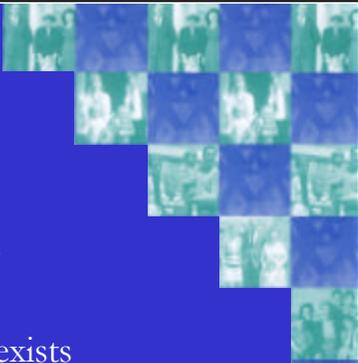
Most women prescribed DES while pregnant are now aged 50–90 years. Because this cohort of women is now reaching the age of rising baseline risk for malignancy, studies have addressed whether taking DES while pregnant may have increased the risk for malignancy above baseline, particularly in estrogen-responsive organs such as the breast.

## Numerous Studies Suggest an Increased Risk for Breast Cancer

- Many studies suggested a relative risk of approximately 1.3–1.4
  - Not all statistically significant
- No study found a dramatic increase in risk (relative risk >2)



A number of studies, including an initial analysis of participants in the Dieckmann trial, showed a modest excess of breast cancer in women prescribed DES while pregnant. Many studies suggested a relative risk for development of breast cancer of 1.3 to 1.4. However, because of the small size and limited follow-up of these early studies, these increased rates of breast cancer were not always statistically significant. Most studies found slightly increased risks for breast cancer. None reported dramatic increases, such as a doubling of relative risk.

- 
- Analysis of breast cancer risk difficult
    - Only one randomized cohort exists for retrospective analysis
    - Many potential confounding variables
      - Decreased parity
      - Socioeconomic status
      - Lead-time bias



Analysis of breast cancer risk in women prescribed DES while pregnant is difficult. Only one large randomized trial has analyzed subsequent breast cancer risk. Other studies must use a case-control or nonrandomized cohort design. The assembly of a satisfactory cohort of matched controls is difficult in breast cancer studies because of the large number of potential confounding variables. For instance, women prescribed DES while pregnant may have been more likely to have fewer children or they may have been from a higher socioeconomic background. Both of these variables are associated with an increased risk for breast cancer.

- 
- 1983—Vessey and colleagues
    - Randomized, double-blind placebo controlled trial at University College Hospital in London
    - 20-year follow up
    - Approximately half of the 1,310 women originally enrolled available for analysis
    - No difference in breast cancer risks

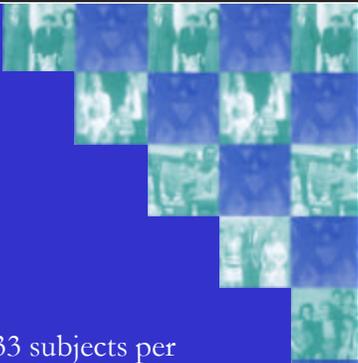


Vessey MP, et al. *Br J Obstet Gynecol* 1983.



Several studies in the literature are helpful in counseling patients.

Vessey and colleagues reported on the follow-up of women enrolled in a British study similar to the 1953 Dieckmann study at the University of Chicago. Approximately half of the original 1,310 women enrolled in the study were identified and available for follow-up 20 years after their original exposure to DES or placebo. No significant differences existed between the two groups in the incidence of breast cancer.

- 
- 1993—Colton et al.
    - DES Mothers Cohort
      - Retrospective cohort study (3,033 subjects per group)
      - Drawn from 3 academic centers and 1 private practice
    - 5,494 subjects (91%) available for follow-up
    - Over 100,000 women-years of follow-up



In 1993, Colton and colleagues updated the findings from an assembled cohort, known as the DES Mothers cohort. This study of over 6,000 women included women prescribed DES while pregnant and matched controls who delivered at the same hospitals. The study participants were drawn from three academic medical centers and one private practice. At the time of their report, over 90% of the cohort was still available for follow-up, with a total follow-up time of over 100,000 women-years each for cases and controls.

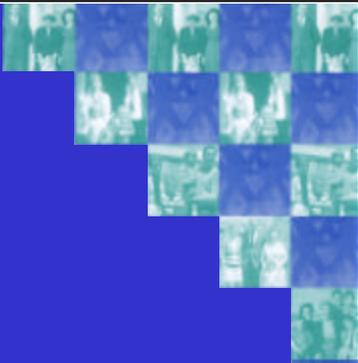
- 1993—Colton et al.
  - Relative risk for breast cancer 1.35
  - 95% CI 1.05-1.74
  - No indication of increasing risk over time



Colton T, et al. *JAMA* 1993.



This study demonstrated a statistically significant elevated incidence of breast cancer among women prescribed DES while pregnant. The relative risk was 1.35, similar to the findings of earlier, smaller studies. The study also had adequate power to exclude, with 95% certainty, a relative risk  $>1.75$ .

- 
- 2001—Titus-Ernstoff et al.
    - Update of:
      - Dieckmann cohort
      - DES Mothers cohort
    - Examined relation between DES exposure and all types of cancer



Titus-Ernstoff L et al., *Br J Cancer* 2001.

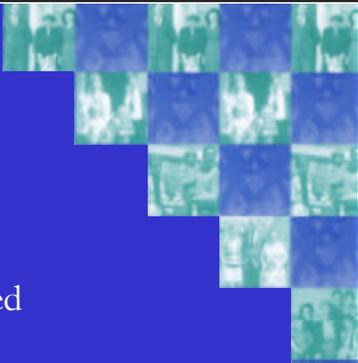


Most recently, Linda Titus-Ernstoff and colleagues updated the findings in both the Dieckmann cohort and the DES Mothers study cohort. Analyzing each study both separately and combined, this report examined the association between DES exposure and the incidence of all types of cancer.

- 2001—Titus-Ernstoff et al.
  - Breast cancer risk
    - Both groups combined
      - RR 1.27
      - 95% CI 1.07-1.52



When both groups were combined, the incidence of breast cancer remained modestly but statistically significantly elevated at a relative risk of 1.27.

- 
- 2001—Titus-Ernstoff et al.
    - No evidence of DES-associated increased risk for
      - Ovarian cancer
      - Endometrial cancer
      - Other malignancies



Titus-Ernstoff and colleagues also investigated the rate of other cancers in women prescribed DES while pregnant. They found no evidence of increased incidence of ovarian, endometrial, or other malignancies among women prescribed DES while pregnant. In addition, Titus-Ernstoff and colleagues found no evidence of interaction and DES exposure relative to increased risk for breast cancer.

## Women Prescribed DES While Pregnant

- Most studies identified a modestly increased risk for breast cancer (RR ~ 1.3)
- Retrospective studies of 2 randomized cohorts failed to show a statistically significant increased risk
  - Power to exclude small increased risk limited because of study size

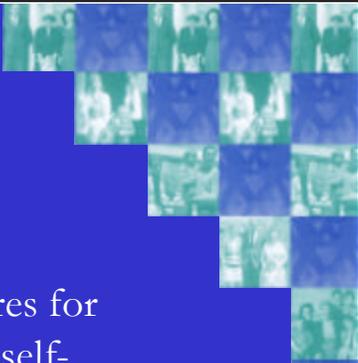


In summary, most studies identified a small increased risk for breast cancer in women prescribed DES while pregnant. These studies usually showed a relative risk of approximately 1.3. Some of these studies are limited by either small size, limited follow-up, or the limitations inherent in a retrospective cohort study design. Retrospective analysis of the two cohorts who were randomized to receive either DES or placebo failed to show a statistically significant increased risk for breast cancer. However, the power of these two studies to definitively exclude a small increased risk for breast cancer is limited by their sample size.



- No study has demonstrated a clinically significant increased risk ( $RR > 2$ )
- No evidence exists of increased risk for other malignancies

Fortunately, no study has even suggested an increased incidence that might be large enough to alter current clinical recommendations for breast cancer screening.



## Summary

- Promote preventative measures for breast cancer screenings and self-exams
  - National Cancer Institute  
([www.cancer.gov](http://www.cancer.gov))
  - American Cancer Society  
([www.cancer.org](http://www.cancer.org))



Providers should promote preventative measures for breast cancer to their patients as recommended by the National Cancer Institute or the American Cancer Society.

## DES Daughters

- First group in whom DES-related adverse effects identified
- Numerous potential DES-related effects investigated



DES Daughters were the first group found to experience adverse effects from the use of DES during pregnancy. They have been the most extensively studied group, and numerous potential DES-related effects have been investigated.

## Increased Health Risks

- Malignancy
- Cervical dysplasia
- Congenital anatomic abnormalities
- Infertility
- Spontaneous abortion
- Other adverse effects



These risks include increased incidence of cancer, precancerous lesions, genital malformations, infertility, and spontaneous abortion.

- 
- Clear cell adenocarcinoma (CCA) of the vagina and cervix
    - Rare malignancy before exposure to DES
    - Series of cases reported by Herbst and Scully in 1971 led to establishment of the Registry for Research on Hormonal Transplacental Carcinogenesis—University of Chicago



As previously discussed, CCA of the vagina was the first known adverse consequence of in utero exposure to DES. This type of cancer also can originate from the cervix, and CCA of the cervix may be related to DES exposure. The need to characterize the DES-associated form of this heretofore rare malignancy led to the establishment of the Registry for Research on Hormonal Transplacental Carcinogenesis, currently at the University of Chicago.

- 
- CCA of the vagina and cervix
    - 750 cases reported to the Registry
      - 60% DES-exposed
      - 10% exposure status unknown
    - Estimated risk for clear cell adenocarcinoma in DES Daughters ~ 1 per 1,000

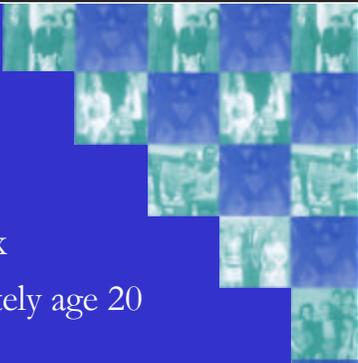


Herbst AL. *Gynecol Oncol* 2000.

Trimble EL. *Obstet Gynecol Surv* 2001.



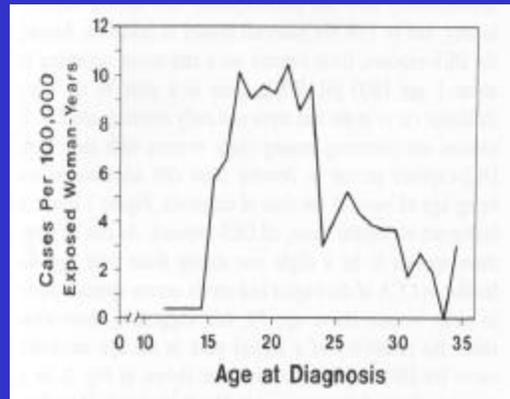
As of May 2002, approximately 750 cases of CCA had been reported to the registry; 60% of these cases were known to have occurred after in utero DES exposure, and 30% were known to have occurred in women definitely not exposed. The exposure status in the remaining 10% was unknown. The risk for CCA of the vagina and cervix in a DES Daughter is approximately 1 in 1,000.

- 
- CCA of the vagina and cervix
    - Incidence peaks at approximately age 20 years
    - Rare after age 30, but age at onset as high as 48
    - In women not exposed to DES, generally occurs in the 6<sup>th</sup>-9<sup>th</sup> decade of life
    - Future risk for DES Daughters unknown



In the Registry for Research on Hormonal Transplacental Carcinogenesis, the peak incidence of CCA occurs at 20 years of age. Cases after age 30 are rare, although cases have been accessioned into the registry as late as 48 years of age. Previously, CCA in non-DES-exposed women was reported to generally occur after age 50. Because the oldest DES Daughters are just now reaching such an age, their risk of developing CCA in the later decades of life is unknown. As a result, screening for CCA in DES Daughters has no upper age limit.

## Estimated Age-Specific Incidence of CCA in DES Daughters



Melnick S, et al. *N Engl J Med* 1987.

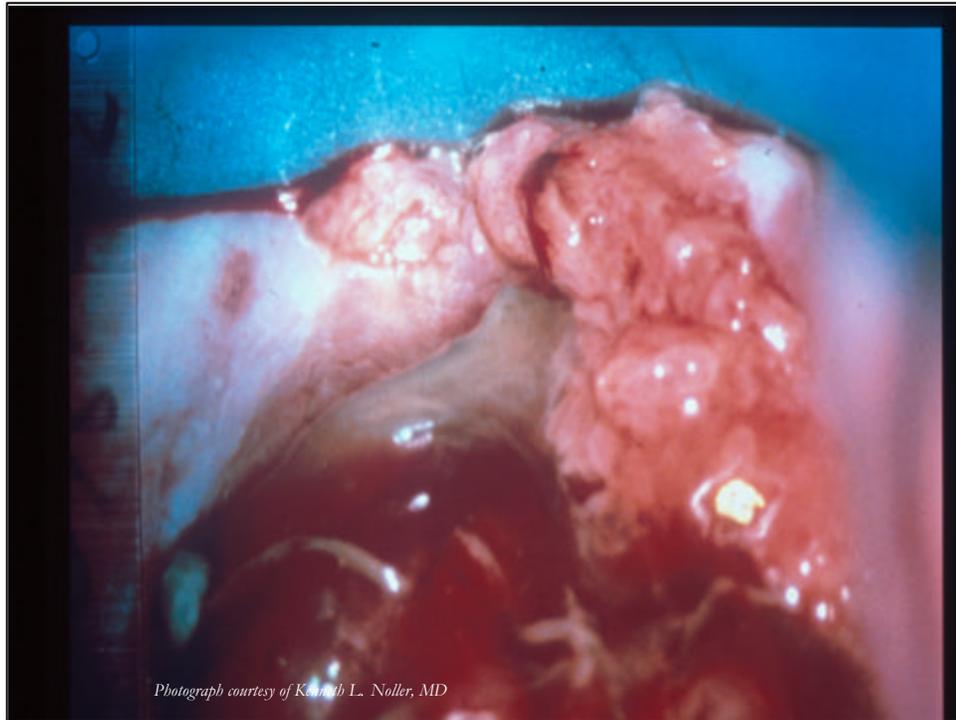


As you can see, most CCA cases occur before age 30 years. Since use of DES in pregnancy was contraindicated by the FDA in the United States in 1971, most DES Daughters are now beyond the age of known high risk for CCA. Nonetheless, DES Daughters should continue to be screened for CCA of the vagina and cervix throughout their lives.

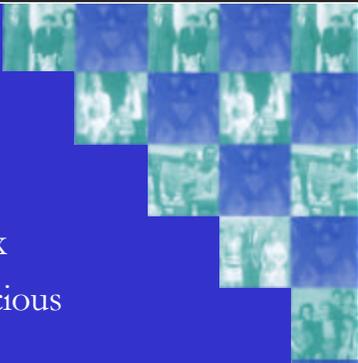
- CCA of the vagina and cervix
  - Presents with abnormal vaginal bleeding or discharge, gross lesion on the vagina or cervix
  - No known premalignant lesion
    - No known role for Pap smear or other screening methodology



CCA often presents with either abnormal vaginal bleeding or an abnormal vaginal discharge. All women with such symptoms should routinely undergo a thorough pelvic examination, including careful inspection of the vagina and cervix by speculum exam. Once symptoms occur, a red, fleshy grossly evident lesion can usually be identified in the vagina or on the cervix. There are anecdotal reports of CCA detection by Pap smear, and some authorities have recommended obtaining separate four-quadrant vaginal smears in addition to the routine cervical smear when examining women at high risk for CCA. However, the utility of Pap smear screening in preventing cervical cancer is based on the existence of a premalignant lesion for the most common type of cervical cancer, which is squamous cell carcinoma. The premalignant lesion associated with squamous cell cancer, known as squamous dysplasia, may take many years to develop into a cancer. This usually allows ample time for detection of squamous dysplasia when a Pap smear is performed annually. When the dysplasia is treated, the subsequent formation of a cervix cancer is prevented. No such premalignant form of CCA is known to exist. Once a CCA forms, it usually grows rapidly. Detection of a CCA on Pap smear when it is still too small to cause symptoms or be seen on speculum exam of the vagina probably would be serendipitous. Therefore, the benefit to performing Pap smears specifically to detect CCA of the vagina or cervix is uncertain, and the utility of altering standard Pap smear screening in women at high risk for CCA is also unknown. However, palpation of the vagina to check for subdural nodules is an essential part of the DES exam.



This is a colposcopic view of the of the red, fleshy appearance of a CCA, seen in the lower half of the slide.

- 
- CCA of the vagina and cervix
    - Diagnosed by biopsy of suspicious lesion
    - Therapy managed by a gynecologic oncologist
    - Survival related to stage at diagnosis



CCA of the vagina and cervix is diagnosed by biopsy of any grossly apparent lesions. All patients with CCA of the vagina or cervix should be managed by a gynecologic oncologist. Treatment usually entails radical surgical resection or radiation therapy. As with most malignancies, the chances for cure are inversely proportional to the stage at diagnosis.



This is the gross appearance of a CCA of the vagina after radical hysterectomy and radical vaginectomy.

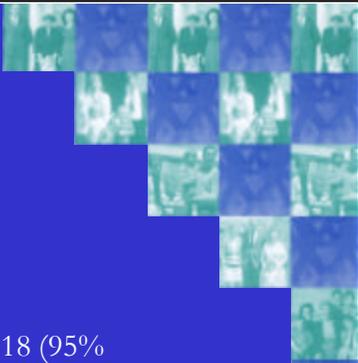
- Risk for other malignancies
  - 1998 Hatch et al.
    - Combined study of 3 research cohorts
    - 4,536 DES-exposed
    - 1,544 controls



Hatch EE, et al. *JAMA* 1998.

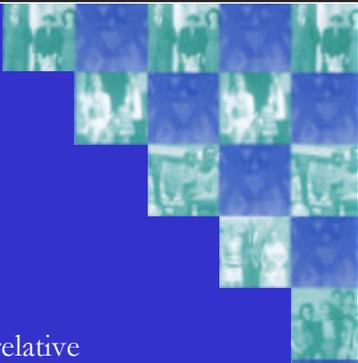


To determine whether DES Daughters are at increased risk for malignancies other than CCA of the vagina and cervix, Elizabeth Hatch and colleagues combined data from three previously reported DES research cohorts. The combined study examined over 4,500 DES Daughters and over 1,500 case-matched controls.

- 
- Risk for other malignancies
    - 1998 Hatch et al.
      - Relative risk for breast cancer 1.18 (95% CI 0.56-2.49)
      - No increased risk for any cancer other than CCA of the vagina and cervix
      - Average age at last follow-up only 38 years
        - Further surveillance required



The study found no statistically significant increased incidence of any malignancy other than CCA of the vagina and cervix. However, the average age of most recent follow-up in the study was only 38 years. To exclude an increased risk of malignancy in later years of life, when most cancers develop, further surveillance is required.



- Risk for other malignancies

- 2002 Palmer et al.

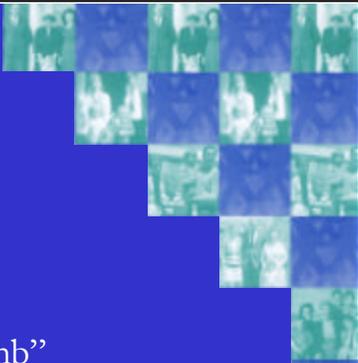
- Overall, DES Daughters had a relative risk for breast cancer of 1.4 (95% CI 0.7-2.6)
- DES Daughters over 40 had a relative risk of 2.5 (95% CI 1.0-6.8)
- Findings are considered preliminary



Palmer JR, et al. *Cancer Causes Control* 2002.



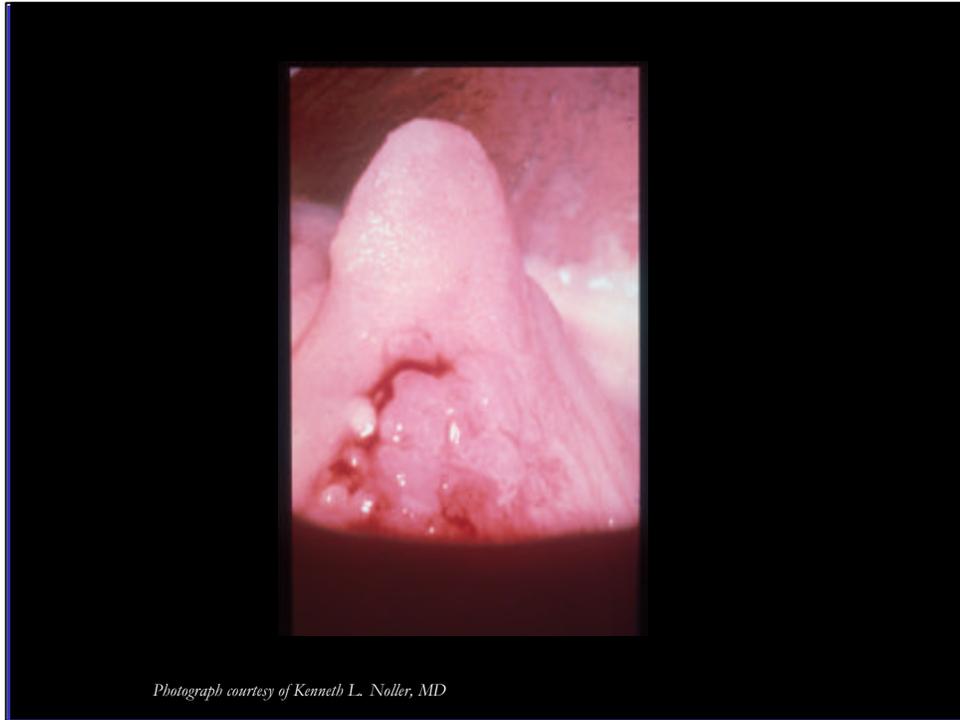
A recent study provides initial results linking exposure to DES before birth with increased rates of breast cancer. The study found that among study participants, DES Daughters were more likely to experience breast cancer than were unexposed women. Overall, DES Daughters had a relative risk of 1.4. However, the findings were not statistically significant. In participants over 40, DES Daughters were two-and-a-half times more likely than unexposed women to be diagnosed with breast cancer. Findings for DES Daughters over 40 were statistically significant. DES Daughters under 40 years of age did not experience an increased risk of breast cancer. The findings from this study are considered preliminary until confirmed and refined by other research.

- 
- Genital tract abnormalities
    - Vaginal adenosis
    - Cervical “collar” or “cockscomb”
    - Strictures of the Müllerian-derived structures
    - T-shaped appearance of uterine corpus

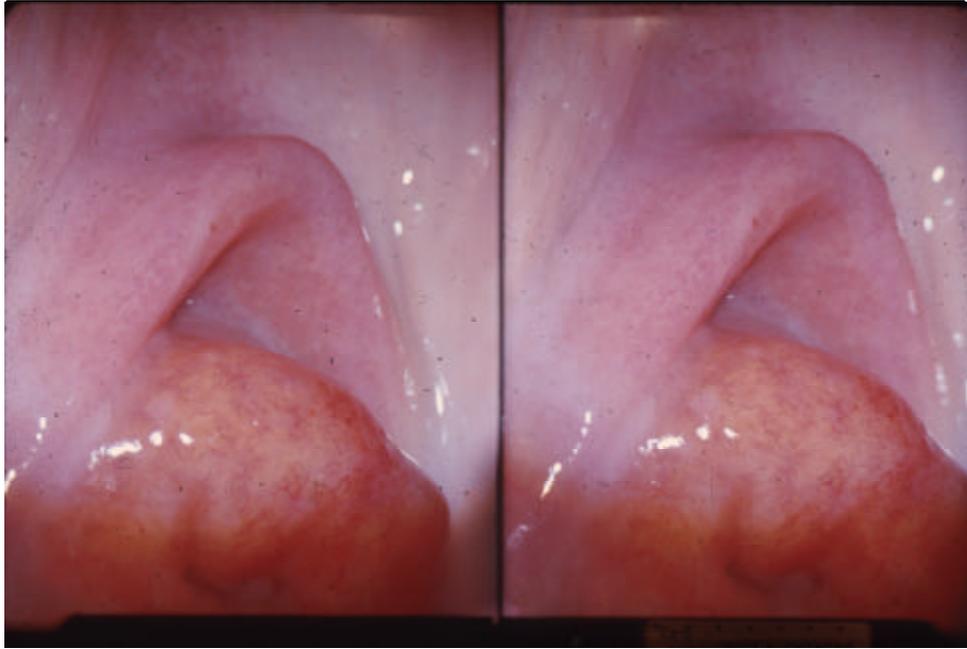


In the female fetus, two tubules form from the coelomic epithelium in the lower abdominal cavity. These tubules, known as the Müllerian ducts, fuse at their most inferior ends to form a Y-shaped structure. The upper branches of the Y become the fallopian tubes, and the fused base of the Y becomes the uterus, cervix, and upper two-thirds of the vagina.

DES Daughters reportedly to have increased rates of various genital malformations along the entire portion of the genital tract derived from the Müllerian tubules. These include vaginal adenosis, cervical abnormalities, strictures in the vagina or endometrial cavity, or abnormally shaped endometrial cavities. In particular, a T-shaped appearance of the uterine corpus on hysterosalpingogram has been reported in association with in-utero DES exposure.



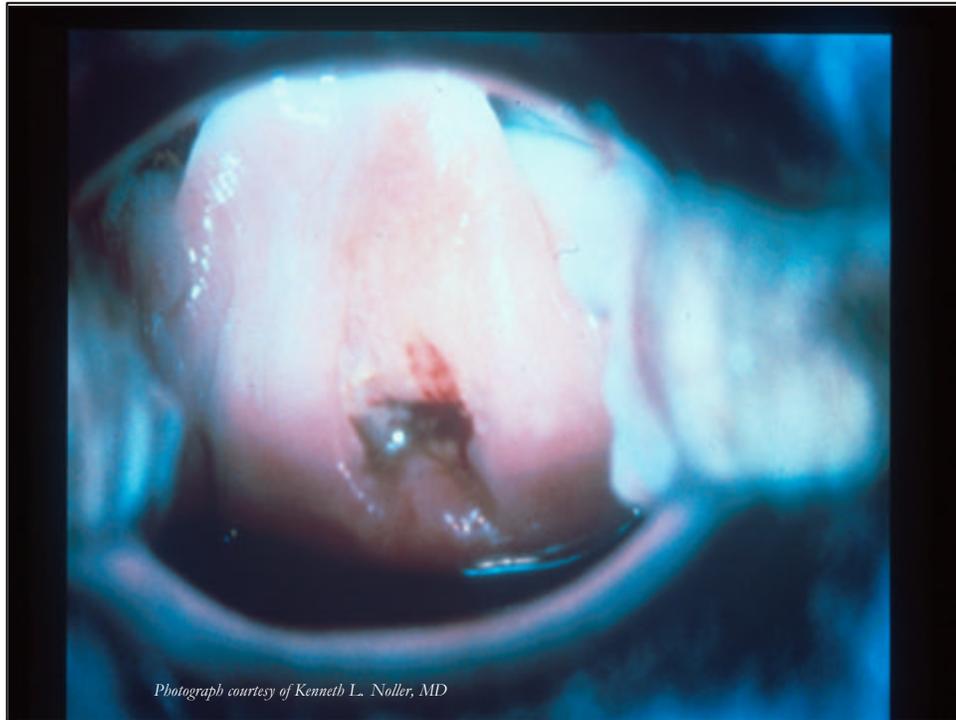
This is a typical cockscomb, a small ridge that may form on the cervix in a DES Daughter.



This is a similar abnormality known as a “cervical hood.”



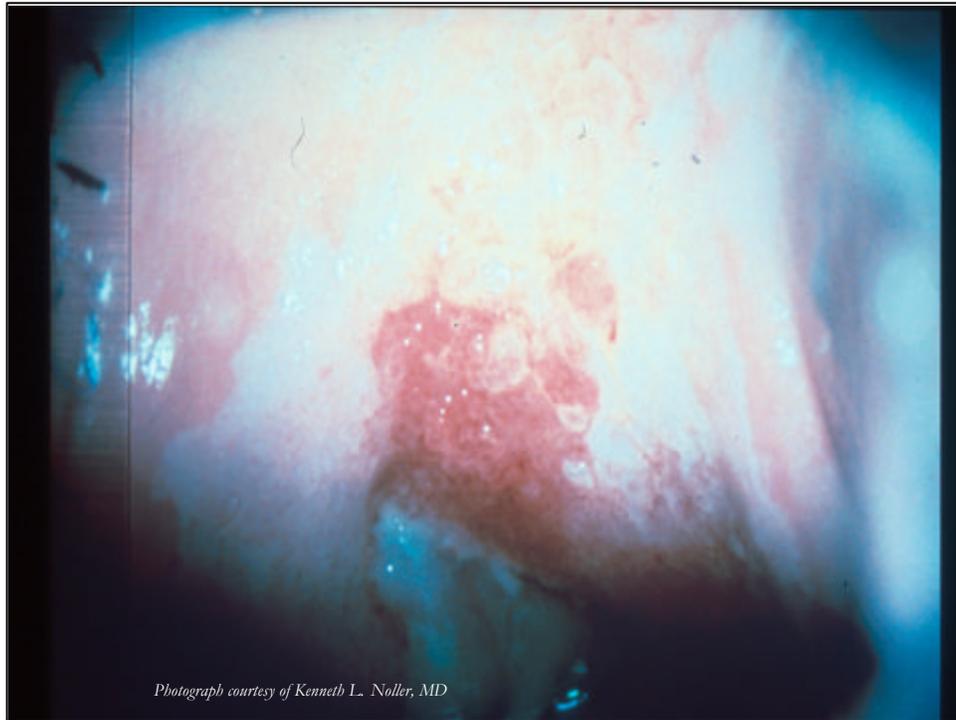
This is an abnormally developed cervix that appears to have a collar around a smaller central area.



This cervical abnormality has been described as a pancake cervix.

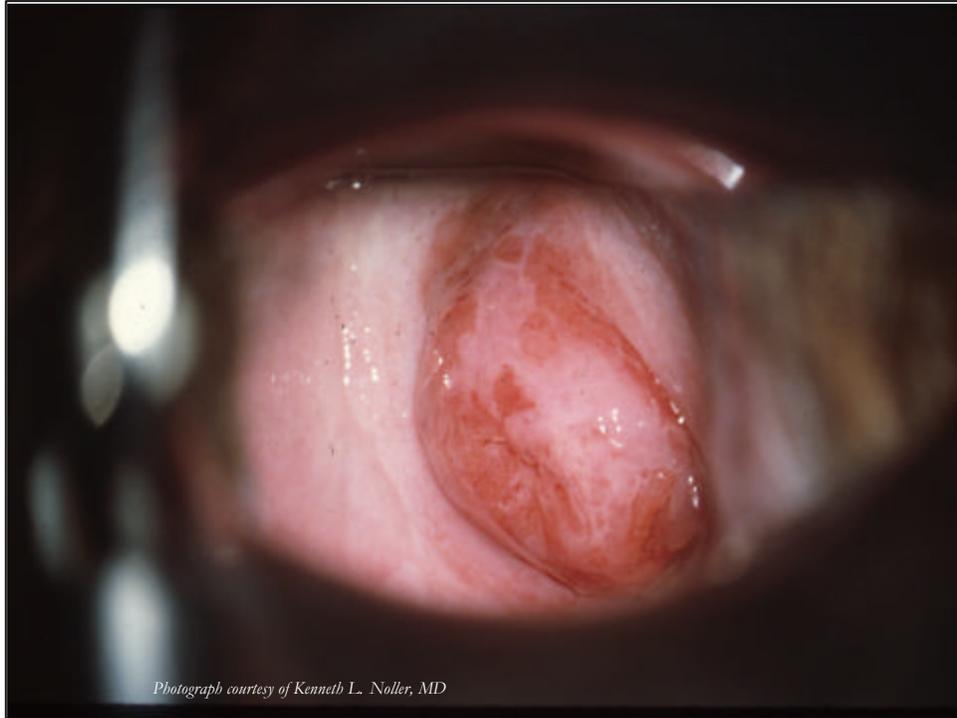


Its thin, flat appearance is best appreciated after being deviated with a cotton swab in this photo.



In the normal adult woman, columnar glandular epithelium lines the endocervical canal and often migrates outward onto the external vaginal portion of the cervix. As it migrates onto the outer cervix, this columnar epithelium changes into the squamous epithelium that normally covers the outer cervix and vagina. This is a normal process known as squamous metaplasia. The area at the cervical opening where squamous metaplasia occurs is known as the transformation zone. However, while squamous metaplasia is a normal and benign process, cells in the transformation zone that are undergoing metaplasia are more susceptible to precancerous changes, a process known as dysplasia. Most dysplasia, and thus most cervical cancers, start in the transformation zone.

This photograph demonstrates vaginal adenosis. Vaginal adenosis denotes a condition where the columnar glandular epithelium of the endocervix spreads out over the external cervix or even onto the walls of the vagina. The red or white “grape-like” tissue that emanates from the endocervix should terminate just outside the endocervical canal. In this photo, the glandular tissue extends well onto the ectocervix. In more extreme cases, it can extend across the entire ectocervix and involve the vaginal fornices or even the sides of the upper two-thirds of the vagina.



*Photograph courtesy of Kenneth L. Noller, MD*

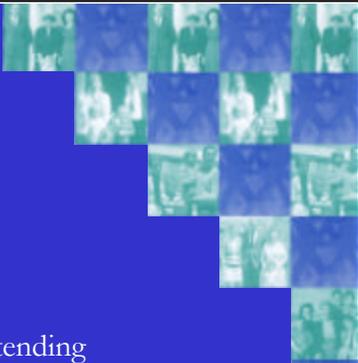
In this photo of vaginal adenosis, the red glandular areas involve multiple portions of the cervix and begin to extend onto the vagina.



The red glandular areas can take on a raised appearance.

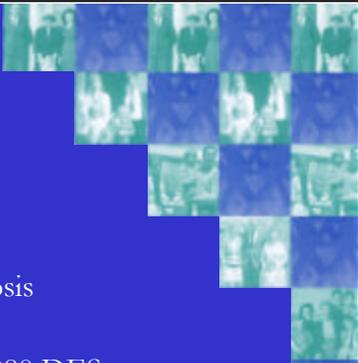


Here the areas of glandular tissue involve the entire cervix and spread onto the adjacent anterior vagina.

- 
- Cervical dysplasia
    - Vaginal adenosis
      - Area of glandular epithelium extending from endocervix onto vaginal mucosa
      - Undergoes squamous metaplasia
      - Increased risk for dysplasia?

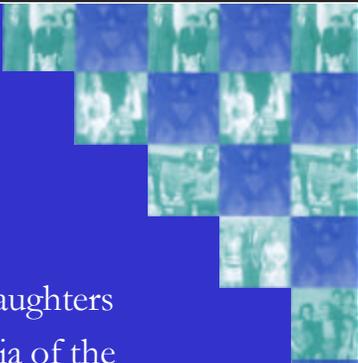


Because some DES Daughters develop vaginal adenosis and thus have a larger transformation zone undergoing squamous metaplasia, questions arise about the possibility of increased risk for dysplasia.

- 
- 1984—Robboy et al.
    - National Collaborative DES Adenosis Project
    - Retrospective cohort analysis of 3,980 DES Daughters and 744 controls
    - Higher incidence of dysplasia in DES Daughters
      - 15.7 vs. 7.9 cases of dysplasia per 1,000 woman-years
    - Limited additional data

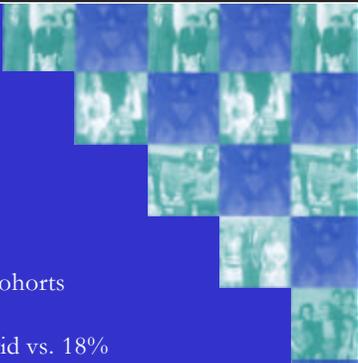


In 1984, Stanley Robboy and colleagues reported data from the National Collaborative DES Adenosis Project. This retrospective cohort study of almost 4,000 DES Daughters showed that the risk for dysplasia nearly doubled, from 7.9 to 15.7 cases per 1,000 woman-years. However, most cases of dysplasia were low-grade dysplasias.

- 
- 2001—Hatch et al.
    - RR 2.12 (95% CI) for DES Daughters
    - High-grade squamous neoplasia of the genital tract



The relation between in-utero DES exposure and increased risk for cervical intraepithelial neoplasia is uncertain. In 2001, Hatch and colleagues found a relative risk of 2.12 among DES Daughters for high-grade squamous neoplasia of the genital tract. The study also found a dose-response relation between timing of exposure and risk, with higher risks associated with earlier exposure in gestation. Unfortunately, few data on this subject exist in the medical literature.



- Infertility

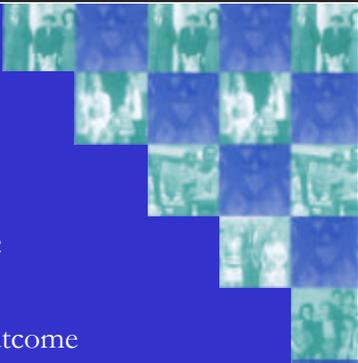
- Analysis of the Dieckmann and DESAD cohorts shows significant risk for infertility
  - 24% of DES Daughters were nulligravid vs. 18% of nonexposed women (RR 1.3, 95% CI, 1-1.5)
  - 28% of DES Daughters tried to become pregnant for 12 months without success vs. 16% of nonexposed women (RR 1.8, 95% CI, 1.6-2.1)
  - DES exposure associated with primary infertility (RR 2.5)
  - DES exposure associated with secondary infertility (RR 2.0)



Palmer JR, et al. *Am J Epidemiol* 2001.



The literature strongly indicates that DES Daughters have increased rates of infertility, most likely related to genital tract malformations. Analysis of the Dieckmann cohort in 1984 showed that 33% of DES Daughters experienced primary infertility, compared with only 14% of controls. In 2001, Palmer and colleagues analyzed results from Dieckmann and DESAD cohorts and found 24% of DES Daughters were nulligravid compared with 18% of nonexposed women. Twenty-eight percent of DES Daughters had tried for 12 months to become pregnant without success compared with 16% of nonexposed women. DES Daughters had a relative risk of primary infertility at 2.5 and of secondary infertility at 2.0.

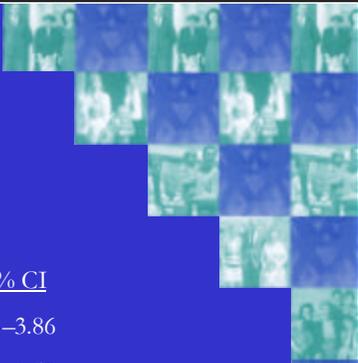
- 
- Adverse Pregnancy Outcome
    - 2000—Kaufman et al.
    - Combined analysis of pregnancy outcome
      - Dieckmann cohort
      - National Collaborative DES Adenosis cohort
    - 88% of eligible women responded to questionnaire
      - 3,373 DES Daughters and 1,036 controls



Kaufman RH, et al. *Obstet Gynecol* 2000.



Not only do DES Daughters have higher rates of infertility, they also have higher rates of adverse pregnancy outcomes than unexposed women. The likely mechanism is genital tract malformations. Raymond Kaufman and colleagues analyzed pregnancy outcomes in women from both the Dieckmann cohort and the National Collaborative DES Adenosis cohort. The combined groups included over 4,400 women available for analysis.



<u>Outcome</u>	<u>Relative Risk</u>	<u>95% CI</u>
Preterm birth	2.93	2.23–3.86
1 <sup>st</sup> trimester abortion	1.31	1.13–1.53
2 <sup>nd</sup> trimester abortion	4.25	2.36–7.66
Ectopic pregnancy	3.84	2.26–6.54



Kaufman found statistically significant increased risks for premature birth, first and second trimester spontaneous abortion, and ectopic pregnancy.



- Kaufman et al.
  - Overall outcome still good in most cases
    - Approximately 85% of pregnancies in DES Daughters resulted in a live-born infant



Despite these findings, most DES Daughters who desire a child still have a good outcome. The majority of such women do not experience primary infertility, and those who do usually eventually conceive. Once pregnant, the outcome is also usually good. Despite the increased risks for adverse outcomes, 85% of the DES Daughters in Kaufman's study who became pregnant delivered a live-born infant.

## Management Steps from the National DES Education Program, NCI

- Annual Exams for DES Daughters
  - Clinical breast exam
  - Vulvar inspection
  - Vaginal and cervical inspection
    - Inspection of epithelial surfaces of vagina
    - Rotation of speculum to view anterior and posterior walls of vagina
  - Cytology
    - Separate specimens from vaginal fornices and cervix



Kaufman RH, et al. *NCI* 1995.



Although health effects of DES exposure differ among DES Daughters, health care providers should monitor these women for abnormal genital tract structures, particularly for CCA of the vagina and cervix. Recommendations published by members of the recent National DES Program included the following steps: clinical breast exam; inspection of the vulva; and inspection of the vagina and cervix, paying careful attention to the epithelial surfaces of the vagina and rotating the speculum to view the anterior and posterior walls of the vagina. Cytology should include separate specimens from the vaginal fornices and cervix. All specimens are placed on one slide or in liquid media.



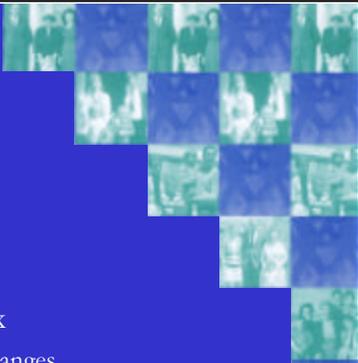
- Palpation of vagina and cervix
  - Palpate entire length of vagina, including fornices
  - Note ridges or structural changes
- Bimanual rectal-vaginal exam
- Biopsy
  - Areas of thickening or induration found during vaginal and cervical palpation
  - Palpable modules
  - Discrete areas of varied colors or textures
  - Atypical colposcopic findings



Kaufman RH, et al. *NCI* 1995.



Careful palpation of the cervix and the entire length of the vagina is recommended, including fornices, noting any ridges or structural changes. Bimanual rectal-vaginal exam also is recommended. Biopsy any of the following: areas of thickening or induration during vaginal or cervical palpation; palpable modules; discrete areas of varied colors or textures; or 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)



Kaufman RH, et al. *NCI* 1995.



Colposcopy is recommended if any abnormal findings appear on Pap smear.  
Iodine stain of the vagina and cervix can confirm boundaries of epithelial changes.

## Recommended Follow-Up for DES Daughters

- Frequency of follow-up visits
  - Determine on individual basis
  - Focus on changes since initial evaluation
  - Include
    - Palpation
    - Inspection
    - Cervical and vaginal cytology
    - Colposcopy, iodine staining, biopsy as needed
  - Ask about interval bleeding or abnormal vaginal discharge



Kaufman RH, et al. *NCI* 1995.



Recommended follow-up for DES Daughters, including the frequency of visits, should be determined on an individual basis. Visits should focus on changes since the initial evaluation and should include palpation, inspection, cervical and vaginal cytology and colposcopy, and iodine staining and biopsy as needed. Patients should be asked about interval bleeding or abnormal vaginal discharge.

## Recommendations for Pregnant DES Daughters

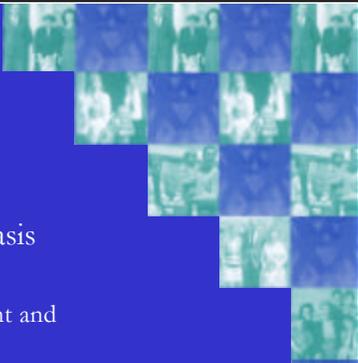
- Pregnancies of DES Daughters should be considered high risk and managed as such
  - As soon as pregnancy is diagnosed, monitor for ectopic pregnancy until intrauterine pregnancy is confirmed
    - Run serial serum HCG titers every 48 hours
  - If bleeding or pain occurs
    - Draw blood immediately for HCG level
    - Ultrasound



Kaufman RH, et al. *NCI* 1995.



Kaufman and associates also included recommendations for DES Daughters who are pregnant. The youngest DES Daughters are in their early 30s, still in their childbearing years. Pregnancies of DES Daughters should be considered high risk and managed as such with the following recommendations: As soon as the pregnancy is diagnosed, monitor for ectopic pregnancy until intrauterine pregnancy is confirmed with a serial serum HCG titers every 48 hours. If bleeding or pain occurs during pregnancy, draw blood for an HCG level immediately and perform an ultrasound.



- Starting 12<sup>th</sup> week, on a biweekly basis
  - Inspect cervix
  - Palpate, looking for cervical effacement and dilation
- Starting 3<sup>rd</sup> trimester
  - Counsel patient for signs of preterm labor



Kaufman RH, et al. *NCI* 1995.



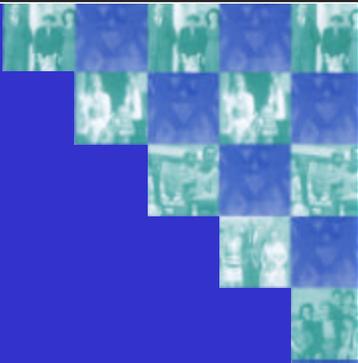
Starting the 12<sup>th</sup> week, on a biweekly basis, inspect the cervix and palpate looking for cervical effacement and dilation. Starting the third trimester, counsel the patient for signs of preterm labor.

## DES Sons

- DES effects have been reported in men
  - Epididymal cysts
  - Other genital abnormalities (microphallus, undescended testicles)
  - Decreased sperm count
- Concerns
  - Infertility
  - Cancers of reproductive system



Men exposed to DES in utero, also called DES Sons, have also experienced DES-related health risks. However, this group has not been as well studied as DES Daughters. Studies of DES Sons have documented a number of increased health risks. The most consistent finding has been increased incidence of epididymal cysts. Smaller numbers of studies have reported increased incidence of other genital abnormalities and decreased sperm count.

- 
- 1977—Bibbo et al.
    - Reported on DES Sons from Dieckmann cohort
    - Study participants examined by physicians blinded to their DES-exposure status
    - Subset of participants underwent semen analysis



Bibbo M, et al. *Obstet Gynecol* 1977.



Researchers at the University of Chicago identified a cohort of men whose mothers participated in the original Dieckmann study. Men who agreed to participate in a study underwent a urologic examination by physicians blinded to the subjects' DES-exposure status. A subset of study participants also underwent semen analysis.

- 1977—Bibbo et al.

	<u>DES Exposed</u>	<u>Controls</u>
Total examined	163	168
Epididymal cysts	22 (13%)	8 (5%)
Hypoplastic penis	4 (2%)	0



P<.01



A total of 331 men participated in the study. Compared with unexposed men, DES Sons had a statistically significant higher rate of epididymal cysts, hypoplastic penis,

- 1977—Bibbo et al.

	DES Exposed	Controls
Total examined	163	168
Hypotrophic testis	12 (7%)	2 (1%)
Capsular induration	5 (3%)	1 (0.6%)



P<.005



hypotrophic testis, and testicular capsular induration.

- 1977—Bibbo et al.

	DES Exposed	Controls
Total examined	163	168
Any abnormality on genital examination	41 (25%)	11 (6.5%)



P<.0005



Overall, one-quarter of DES Sons had some type of urogenital malformation, compared with just 6.5% of non-DES exposed controls.

- 1977—Bibbo et al.

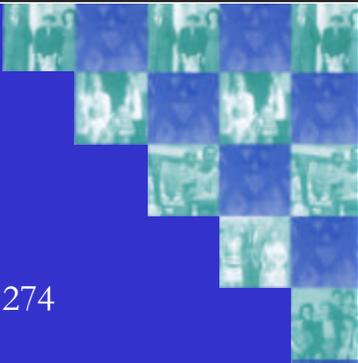
	DES Exposed	Control
Total undergoing semen analysis	39	25
Abnormal	7 (18%)	3 (12%)
Very abnormal	11 (28%)	0



P<.05



In the 64 men who underwent semen analysis, almost half of the DES Sons had abnormal semen analysis scores. In contrast, only three of 25 controls had abnormal scores, and none of these were highly abnormal.

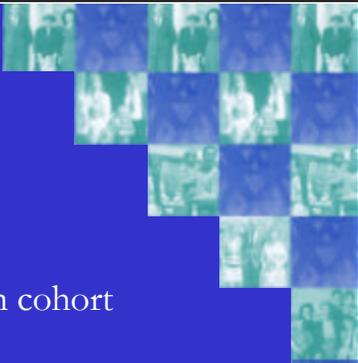
- 
- 1984—Leary et al.
    - Examined 265 DES Sons and 274 controls
    - Found no increased risk for genitourinary abnormalities
    - Found no increased risk for infertility



Leary FJ, et al. *JAMA* 1984.



However, data conflict in the literature. In a larger study of 539 men, Frank Leary and colleagues found no increased risk for genitourinary malformations and no increased rates of infertility among DES Sons.

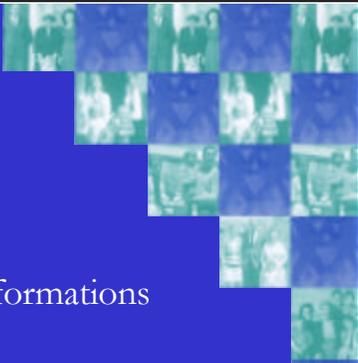
- 
- 1995—Wilcox et al.
    - Re-evaluated same Dieckmann cohort reported by Bibbo in 1977
    - Surveyed participants by telephone



Wilcox AJ, et al. *N Engl J Med* 1995.

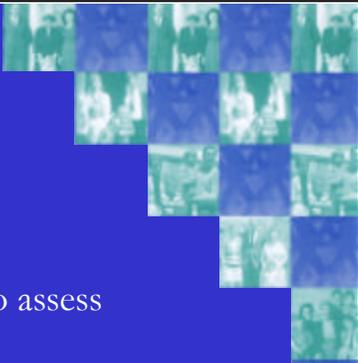


Allen Wilcox and colleagues reported on a recent re-analysis of the DES Sons identified from the Dieckmann cohort. In this study, participants from the original trial were questioned in a telephone interview about their history of having impregnated a woman. The interviewers were blinded to the DES exposure status of the study participants.

- 
- 1995—Wilcox et al.
    - More self-reported genital malformations in DES Sons (15% vs. 5%)
    - No difference in overall ability to impregnate a woman
    - No difference in length of time to conception
    - No decrease in fertility among men with genital malformations



Consistent with the findings of the original study, more DES Sons self-reported a history of genital malformation. However, no differences existed between the DES-exposed and non-DES exposed men in their overall ability to impregnate a woman or in the length of time to conception when a pregnancy was planned. In addition, fertility among men who reported a genital malformation did not appear to decrease.

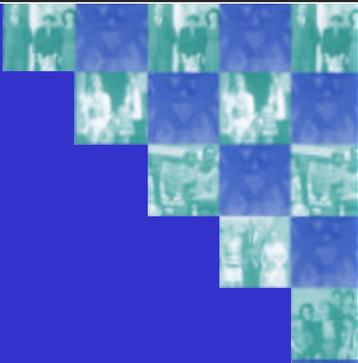
- 
- Testicular cancer
    - DES-related effects difficult to assess because of low prevalence
    - Depue et al. found
      - 108 cases with matched controls
      - RR of 8.0 associated with DES Sons



Depue RH, et al. *J Natl Cancer Inst* 1983.

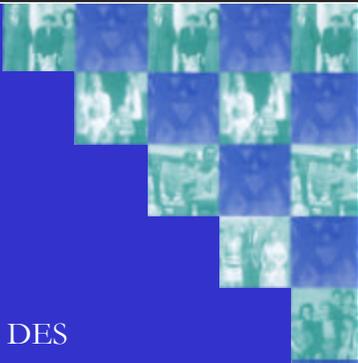


Researchers have also examined the risks for testicular cancer in DES Sons. However, because of the low incidence of testicular cancer, any DES-related effects is difficult to detect. R. H. Depue and colleagues found that DES Sons had a relative risk of 8.0 for developing testicular cancer.

- 
- Testicular cancer
    - Moss et al.
      - 273 cases and matched controls
    - Gershman and Stolley
      - 79 cases and matched controls
    - No increased risk for testicular cancer from DES exposure shown by either study



However, a larger study by A. Moss and colleagues, as well as an additional small study by S. F. Gershman and P. D. Stolley, failed to find any significant association between DES exposure in utero and risk for development of testicular cancer.

- 
- Testicular Cancer
    - Strohsnitter et al.
      - Comprised of 3,613 men whose DES exposure status was known
      - Drawn from 4 previously studied cohorts
    - No overall increased risk for cancer
    - No statistically significant difference in risk for any type of testicular cancer (RR 3.05, 95% CI 0.65–22.0)



Strohsnitter WC, et al. *J Natl Cancer Inst* 2001.



In the largest published study, Strohsnitter and colleagues combined four previously studied DES cohorts to analyze cancer risk in 3,613 men whose prenatal DES exposure status had been ascertained. The study showed no increase in the overall risk of cancer among DES Sons. Of the nine cases of various types of testicular cancer over the 16-year study period, seven were in DES Sons. However, this difference was not statistically significant.

## Third Generation

- Effects
  - Some DES Sons and Daughters have expressed concern about possible “third-generation” effects
  - Animal studies have reported DES-related changes in the offspring of mice exposed to DES in utero



Some DES Sons and Daughters have expressed concern about possible “third-generation” effects. This refers to possible adverse effects on the offspring of DES Daughters and Sons. These concerns are based largely on animal studies that reported DES-related changes in the offspring of mice exposed to DES in utero.

## Third-Generation Human Studies

- 1995—Wilcox et al.
  - No evidence of altered age at menarche
- 2002—Kaufman et al.
  - No incidence of genital structural abnormalities in granddaughters
- 2002—Klip et al.
  - Increased incidence of hypospadias



Wilcox AJ, et al. *Am J Obstet Gynecol* 1995.  
Kaufman RH, et al. *Obstet Gynecol* 2002.  
Klip H, et al. *Lancet* 2002.



Three studies in humans have been published that examine possible effects of third-generation DES exposure. However, Wilcox and colleagues found no difference in age of onset of menarche among DES Granddaughters. Kaufman and Adam found no incidence of genital structural abnormalities in DES Granddaughters. Klip and colleagues found an increased incidence of hypospadias among DES Grandsons.

The children of DES Sons and Daughters are still young. Further study by the National Cancer Institute will determine what, if any, DES-related effects may emerge as the third generation ages.

## Future Directions

- No additional adverse effects of DES exposure known to exist
- Most DES Sons and Daughters are aged 30–50 years
- Risk for many common reproductive tract malignancies does not begin to rise until after age 50
- NCI-sponsored research will continue to monitor health risks for DES Sons, Daughters and third generation



Although no additional adverse effects of DES exposure are known, most DES Sons and Daughters currently are between the ages of 30 to 50 years. The baseline risk for many common reproductive tract malignancies does not begin until after age 50.

- 
- Further surveillance is needed as the cohort of DES Sons and Daughters ages
    - Breast cancer
    - Cancer of Müllerian-derived structures
      - Endometrial cancer
      - Fallopian tube cancer
      - Cancer of the prostatic utricle
    - Future risk for clear cell adenocarcinoma of the vagina and cervix



Further surveillance is needed as the cohort of DES Sons and Daughters ages. Of particular concern will be the potential for increased risk for cancer in estrogen-responsive tissues. These include cancers of the breast and of the Müllerian-derived structures such as the endometrium, fallopian tube, and prostatic utricle. In addition, CCA of the vagina usually develops in non-DES exposed women beyond the sixth decade of life. Whether DES Daughters may exhibit a similar increased risk later in life is unknown. Ongoing NCI studies will continue to monitor these and other health effects in DES Sons, Daughters and third generation.

- 
- All men and women born during 1938-1971 should attempt to ascertain their DES-exposure status
  - As time progresses, future ascertainment of exposure status will become more difficult



Our present understanding of the risks associated with DES exposure does not suggest that most exposed men and women should alter their usual routine of recommended health maintenance. Special monitoring routines for pregnant DES Daughters has been described earlier. Amplification and supplementation of gynecologic exams for DES Daughters also have been outlined. If future studies reveal additional health risks, these studies could lead to new management recommendations. Therefore, all men and women born during 1938–1971 should attempt to ascertain their DES-exposure status. As time progresses, medical records may be lost, and mothers of children exposed in utero will forget their pregnancy history or eventually die. Ascertainment of exposure status will therefore become more difficult over time.

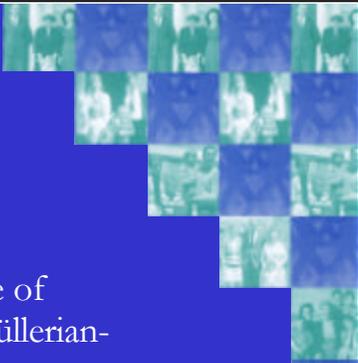
## Summary

- Women Prescribed DES While Pregnant
  - Modestly increased risk for breast cancer
    - A significantly increased risk (RR > 2) has been disproved
  - No evidence for other adverse effects at this time



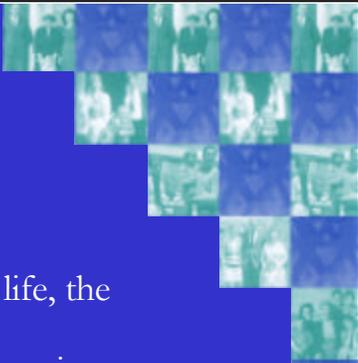
In summary, women prescribed DES while pregnant appear to have a modestly increased risk for breast cancer. These women should be encouraged to follow current recommendations for mammogram and breast self-exam, issued by the National Cancer Institute or the American Cancer Society.

No evidence exists of any other adverse effects from DES exposure at this time.

- 
- DES Daughters
    - Increased risk for a wide range of abnormalities involving the Müllerian-derived genital tract
      - Clear cell adenocarcinoma of the vagina and cervix
      - Genital malformations
      - Infertility
      - Adverse pregnancy outcomes
      - Possible increased risk of cervical dysplasia

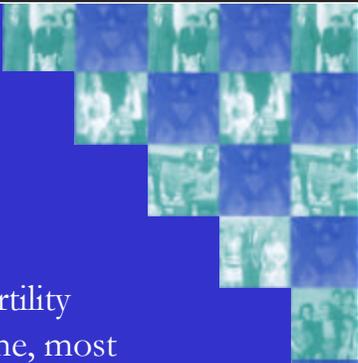


DES Daughters are at increased risk for a wide range of abnormalities involving the Müllerian-derived portion of the genital tract, including CCA of the vagina and cervix, genital malformations, infertility and adverse pregnancy outcomes. In addition, DES Daughters may be at increased risk for development of cervical dysplasia.

- 
- DES Daughters
    - In their 4th and 5th decade of life, the present risk of clear cell adenocarcinoma (CCA) of the vagina and cervix exists, but appears to be low
    - No other known increased risks of malignancy at this time
    - Further follow-up is needed



For DES Daughters in their fourth and fifth decades of life, the risk for CCA of the vagina and cervix exists, but appears to be low and still requires monitoring. No other increased risks of malignancy are known at this time. However, further follow-up is needed.



- DES Daughters

- Despite increased risks of infertility and adverse pregnancy outcome, most DES Daughters can become pregnant and carry a pregnancy to term
- Pregnancies in DES Daughters should be managed as high risk pregnancies

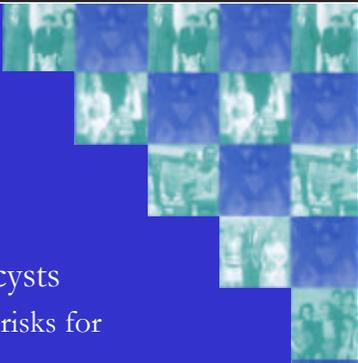


Despite the increased risks for infertility and adverse pregnancy outcome, most DES Daughters can become pregnant and can carry a pregnancy to term.

- 
- DES Daughters
    - Association between DES exposure in utero and development of cervical dysplasia is not well established
    - Further research is needed



Limited data exist on the relation between DES exposure in utero and subsequent development of cervical dysplasia. However, no data support altered Pap smear screening recommendations for DES Daughters. Further research in this area is needed.

- 
- DES Sons
    - Increased risk for epididymal cysts
      - Some studies indicate increased risks for other genital abnormalities
      - Most DES Sons have no discernible abnormalities
    - Research is ongoing on risks for testicular cancer
      - No demonstrated risks for other cancers



DES Sons have an increased risk for epididymal cysts. They may have increased risk for other genital abnormalities. Most DES Sons have no discernible abnormalities. Although questions remain unanswered about DES Sons' increased risk for testicular cancer, no evidence exists of increased risk for other types of cancer.

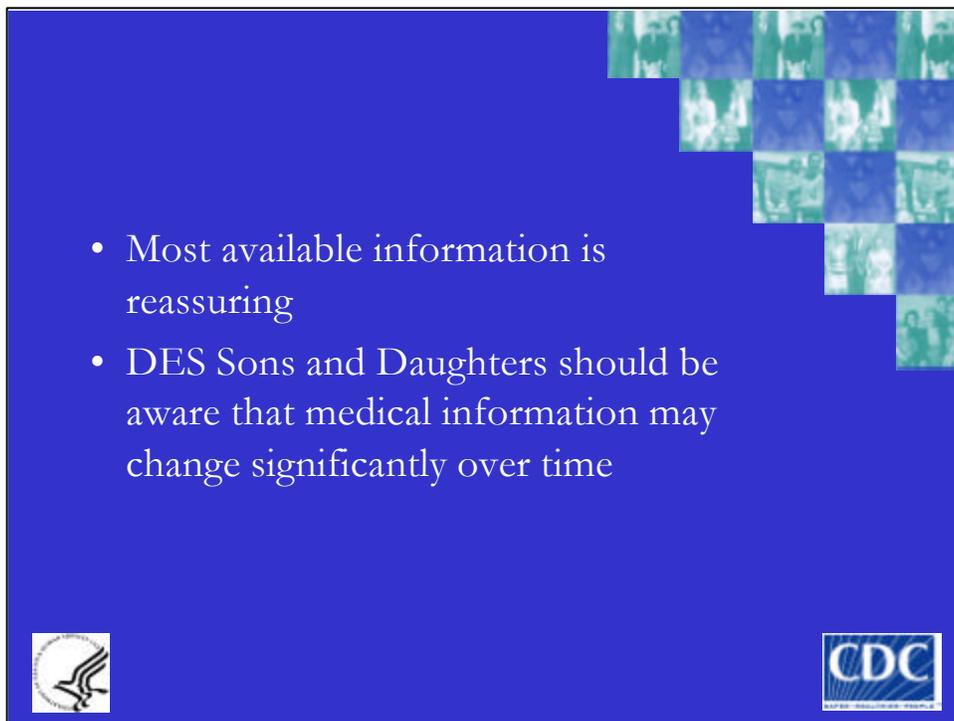


- DES Sons
  - No diminished fertility
  - No evidence of other adverse effects at this time
  - Counsel DES Sons to report any changes on or near testicles
    - American Cancer Society ([www.cancer.org](http://www.cancer.org)) instructions for examining testicles



Studies have shown that DES Sons do not experience increased risk for infertility. At this time, no evidence exists of other adverse effects.

Because of the unanswered questions about testicular cancer, DES Sons should be encouraged to report any suspicious changes (lumps or growths) on or near their testicles. The American Cancer Society includes clinical testicular examination in its recommendations for routine cancer-related exams. Because testicular cancer is a secondary risk for DES Sons with undescended and hypoplastic testes, and because questions remain about increased risks for testicular cancer among DES Sons, many Sons will be concerned about screening and self-examination. Physicians and DES Sons should discuss whether monthly self-examinations should be a part of the individual patients' health maintenance activities.



- Most available information is reassuring
- DES Sons and Daughters should be aware that medical information may change significantly over time



Most of the data should reassure men and women who are concerned about their exposure to DES. However, they should be aware that medical knowledge will change significantly as time progresses. Patients should routinely discuss their history of DES exposure with their health care providers every few years to determine whether alterations in their health promotion and disease prevention regimen are indicated.

## DES Resources

- CDC's DES Update
  - CDC Web site for health care providers ([www.cdc.gov/DES](http://www.cdc.gov/DES))
  - 1-888-232-6789
- NCI
  - [www.cancer.gov](http://www.cancer.gov)
  - 1-800-4CANCER
- Patient Support
  - DES Action USA ([www.desaction.org](http://www.desaction.org))
  - DES Cancer Network ([www.descancer.org](http://www.descancer.org))



Health care providers will find new resources and updates on DES research and treatment steps at CDC's DES Web site. Information for patients also can be found on the Web site. The NCI Web site also includes provider and patient information about DES. Organizations such as DES Action USA and the DES Cancer Network can provide additional support resources for your DES-exposed patients.

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# DES Update Current Information

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