OPEN

ASCCP Clinical Consensus: Screening Recommendations for Clear Cell Adenocarcinomas in People Exposed to DES In Utero

Jenna Z. Marcus, MD,[1] Erin Nelson, MD,[2] Mitchell Linder, MD,[3] and David P. Chelmow, MD[4]

Objectives: The cohort of diethylstilbestrol (DES)-exposed people is aging, and a substantial fraction have already passed the age of 65, when unexposed average-risk people may exit cervical cancer screening provided they have had adequate prior screening. Current guidelines exclude individuals with a history of in utero exposure to DES. This clinical consensus includes a systematic review of relevant studies and provides updated guidance for surveillance of the aging DES-exposed cohort.

Methods: A literature search was performed to find all relevant DES and clear cell adenocarcinoma (CCA) papers that addressed key clinical questions. Study quality was assessed and recommendations were rated on strength (A–E) and quality of evidence (I–III) using the system described for previous American Society of Colposcopy and Cervical Pathology consensus guidelines.

Results: DES-exposed patients were 40 times more likely (standardized incidence ratio = 40.9; 95% CI, 13.1–126.2) to develop cervical and vaginal CCAs compared with unexposed individuals, with most cases diagnosed in individuals between the ages of 15 and 31. DES exposure in utero significantly increases the risk of CCA compared with nonexposed people, but the absolute risk of CCA is low. While CCA does seem to occur in older exposed patients, cases were rare and calculated incidence rates were extremely low, with the largest in any of the cohorts at 2.86 per million women-years.

Conclusions: The American Society of Colposcopy and Cervical Pathology recommends people with prenatal exposure to DES receive annual screening for CCA with cytology until the age of 65 and discontinue screening beyond the age of 65 provided they otherwise meet criteria for cessation of screening.

Key Words: DES, cervical clear cell adenocarcinoma, vaginal clear cell adenocarcinoma, CCA, screening in DES-exposed individuals

(*J Low Genit Tract Dis* 2024;28: 351–355)

Diethylstilbestrol (DES) is an orally active nonsteroidal estrogen administered for a wide range of obstetric and gynecological conditions in the United States from 1938 to 1971. When used to manage adverse obstetric outcomes such as preterm delivery and threatened abortion, the drug was administered during the first trimester and often continued throughout pregnancy.[1] In 1971, DES exposure was linked to the development of clear cell adenocarcinomas (CCAs) of the cervix and vagina in patients who had been antenatally exposed. At this time the Food and Drug Administration issued a bulletin advising that the use of DES in pregnant women be discontinued.[2] An estimated 5–10 million people were exposed to DES during their pregnancy or in utero during this timeframe.[3] The term "DES daughters" was coined for individuals with a cervix who had been exposed to DES in utero.

Some of these patients who had been exposed in utero presented in their midteens and 20s with prolonged vaginal bleeding and were found to have CCA tumors of the cervix or vagina.[4] While most cases of cervical and vaginal CCA in DES-exposed people occur at an early age, older individuals seem to remain at elevated risk for development of cancer.[5,6] DES exposure has also been linked to other cancers, cervical dysplasia, and reproductive tract abnormalities.[7–10] During organogenesis, DES crosses the placenta and has been proposed to cause both embryologic disruption of normal genitourinary development and genomic instability leading to induced carcinogenesis.[11,12]

The cohort of DES-exposed people is aging, and a substantial fraction have already passed the age of 65, when unexposed average-risk people may exit cervical cancer screening provided they have had adequate prior screening. Current cervical cancer screening guidelines by the United States Preventive Services Task force, endorsed by the American College of Obstetricians and Gynecologists (ACOG), the American Society of Colposcopy and Cervical Pathology (ASCCP), and the Society of Gynecologic Oncology, recommend against screening for cervical cancer in people older than 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer. These guidelines specifically exclude individuals with a history of in utero exposure to DES.[13–15] Screening recommendations for individuals exposed in utero to DES were included in an ACOG Practice Bulletin that was withdrawn when ACOG endorsed the most recent United States Preventive Services Task force screening guidelines.[16]

This ASCCP clinical consensus includes a systematic review of relevant studies and provides updated guidance for surveillance of the aging DES-exposed cohort.

METHODS

The search was organized around the following key clinical questions:

- *What is the frequency of clear cell carcinoma in DES-exposed individuals compared to an age-based unexposed cohort?*
- *What is the frequency of CCA in DES-exposed individuals over the age of 65?*
- *What is the evidence for the effectiveness of screening for CCA or squamous cell cervical cancer precursors for people below the age of 65?*

[1]Northwestern University, Feinberg School of Medicine, Chicago, IL; [2]University of Texas School of Medicine at San Antonio, San Antonio, TX; [3]University of Rochester Medical Center, Rochester NY; and [4]Virginia Commonwealth University, Richmond, VA

Correspondence to: Jenna Z. Marcus, MD, Division of GYN Oncology, Northwestern University, Feinberg School of Medicine, 250 E. Superior Street Suite 420, Chicago, IL 60611. E-mail: jenna.marcus@nm.org

Source of financial support: None.

Dr. Marcus is on the speaker's bureau for GlaxoSmithKlein and Seagen (Pfizer), both are unrelated to this work. The other authors have declared they have no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jlgtd.com).

DOI: 10.1097/LGT.0000000000000842

- *What is the evidence for the effectiveness of screening for CCA in DES-exposed individuals over the age of 65?*
- *What are the harms of screening in DES-exposed individuals over the age of 65?*
- *What is the evidence for screening in DES-exposed individuals who have undergone hysterectomy with removal of the cervix?*

Given the anticipated paucity of studies, a single literature search (Appendix 1, http://links.lww.com/LGT/A368) was performed to find all relevant DES and CCA papers. Only published manuscripts in English were included. Animal studies were excluded. Eight hundred thirty-six articles were identified. Published studies pertaining to key clinical questions were included if they met the following inclusion criteria:

1. Study design: randomized clinical trials, prospective or retrospective cohort studies, and case–control studies were prioritized. If these were not available, case reports, descriptive studies, and case series were considered. Professional society guidance documents were also included in this search.
2. Participants: individuals exposed to DES in utero between the years of 1938–1971 and contemporaneous controls who were not exposed to DES and received cervical cancer screening that was per the usual standard of care for the time.

We excluded survey studies, unpublished meeting abstracts, editorials, and personal correspondence. In instances where serially published manuscripts existed, the most recent publication was used to answer the key clinical questions. Each study identified in the literature search was screened by 2 reviewers in 2 stages, with abstract review followed by full-text review of selected articles. Each study was reviewed for inclusion and exclusion criteria, study type, and quality. Study quality was assessed employing quality of evidence levels (I–III) used for previous ASCCP consensus guidelines (see Table 1).[17] The references of each included paper were also reviewed to identify other relevant studies not identified in the primary search. Discordance was resolved by discussion, and if a resolution could not be reached, a third reviewer made the determination. Each co-author was assigned 2 of the 6 clinical questions from the list noted under "study selection" and reviewed the manuscripts that met the inclusion criteria.

For each clinical question, the quality of evidence was determined by examining all included studies pertaining to that clinical question. In the absence of adequate-quality studies, lower-quality studies were included if deemed helpful, acknowledging these would contribute limited evidence and therefore some recommendations would be largely based on expert consensus.

The group met at the start of the project and upon completion of the literature review to discuss the evidence summary for each of the clinical questions. Recommendations were drafted, circulated to the group, and serially revised. The recommendations were rated on strength (A–E) and quality of evidence (I–III) using the system described for previous ASCCP consensus guidelines (see Table 1).[17] The group reached consensus on the recommendations, which were forwarded to the ASCCP board for review and approval, which occurred on April 9, 2024.

TABLE 1. Rating the Recommendations

Strength of recommendation

A. Good evidence for efficacy and substantial clinical benefit support recommendation for use.

B. Moderate evidence for efficacy or only limited clinical benefit supports recommendation for use.

C. Evidence for efficacy is insufficient to support a recommendation for or against use, but recommendations may be made on other grounds.

D. Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use.

E. Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use.

Quality of evidence

I. Evidence from at least one randomized, controlled trial.

II. Evidence from at least one clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies, or dramatic results from uncontrolled experiments.

III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Terminology used for recommendations

Recommended. Good data to support use when only one option is available

Preferred. Option is the best (or one of the best) when there are multiple options

Acceptable. One of multiple options when there is either data indicating that another approach is superior or when there are no data to favor any single option

Not recommended. Weak evidence against use and marginal risk for adverse consequences

Unacceptable. Good evidence against use

KEY CLINICAL QUESTIONS AND RECOMMENDATIONS

- What is the frequency of clear cell carcinoma for DES-exposed individuals compared with an age-based unexposed cohort?

Primary clear cell adenocarcinomas of the vagina comprise approximately 5%–10% of all histologic subtypes of vaginal cancer, with the majority found in patients exposed to DES in utero.[18] In 2020, there were an estimated 1272 cases (0.6 case per 100,000 women) of all histologic types of vaginal cancer diagnosed in the United States. Squamous cell carcinomas were the most common. Higher rates occur in non-Hispanic Black individuals (0.8 case per 100,000).[19,20] Our literature search did not find accurate estimates of CCA in unexposed people, likely due to its rarity. Several large cohort studies followed patients exposed to DES in utero for the development of DES exposure–related cancers and chronic health conditions. The 2 largest nationwide cohorts were established in the 1970s and are as follows:

- The National Cancer Institute DES Combined Cohort Follow-up Study, comprised of 5 cohorts: Diethylstilbestrol Adenosis Project Cohort, Women's Health Study Cohort, Mayo Clinic Cohort, Diekmann Cohort, and Horne Cohort
- The DES-net Cohort (registry of the Netherlands DES Center)

The Registry for Research on Hormonal Transplacental Carcinogenesis was established in 1971 and is one of the largest registries of patients with cervical, vaginal, or combined cervical and vaginal CCA.[21] These large prospective cohorts established the link between in utero DES exposure and the development of CCA.[6,9,22,23]

A combined follow-up study that included patients from the Diethylstilbestrol Adenosis Project Cohort, Dieckmann, and Horne cohorts assessed cancer risk of those exposed to DES in utero. There were 3 observed cases of CCA among the 4536 DES-exposed patients as compared with no cases in the 1544

patients without a history of DES exposure. Based on case observation applied to a standardized incidence ratio (SIR), DES-exposed patients were 40 times more likely (SIR = 40.9; 95% CI, 13.1–126.2) to develop cervical and vaginal CCAs compared with unexposed individuals.[24] In a similar study, the DES-net cohort of 12,091 patients was evaluated for cancer risk utilizing a questionnaire to ascertain risk factors and obtaining permission to verify DES exposure. While the SIR was increased across all patients registered in the cohort (SIR = 24.34; 95% CI, 8.89–52.74), the SIR estimates were the highest (SIR = 109.9; 95% CI, 12.3–396.79) in the 881 patients where DES exposure confirmation was available.[6] A review of the 720 cases in the CCA registry at the University of Chicago revealed a cumulative risk of confirmed DES-associated CCA of approximately 1 in 750. When including subjects with unclear exposure who developed CCA, the cumulative risk increased to 1 in 520, which is likely higher than historically estimated given the limitations of patient recall, the variety of DES preparations available, and lack of adequate documentation.[5,25] Approximately 80% of cervical and vaginal CCA were diagnosed in DES-exposed patients between the ages of 15 and 31, with a median age of 20 years old and the highest frequency at 19 years of age, 0.13 per 1000.[5] The studies generally agree that DES exposure in utero significantly increases the risk of CCA compared with nonexposed people, but that the absolute risk is low.

- What is the frequency of CCA in DES-exposed individuals over the age of 65?

Some studies report a second peak of CCA in older patients. In one series of DES-exposed people with documentation of exposure, the estimated cumulative risk of CCA by age 50 was 1.33 per 1000 (95% CI, 1.19–1.48). When all people with CCA were included regardless of documentation of exposure, the estimated cumulative risk increased to 1.93 per 1000 (95% CI, 1.75–2.10).[5] Updated data from the Netherlands registry describe a bimodal age distribution with mean ages of CCA development at 26 and 71 years old; however, incidence rates were not calculated. Data from the Dutch cohort also describe a "second peak" that occurred in 34 patients between the ages of 44 and 88 and was entirely comprised of those born before 1947, before DES was prescribed. The development of CCA in non-DES exposed older patients may be a result of cumulative risk from exogenous carcinogen exposure or genetic susceptibility.[26]

One of the most recent updates to the US cohort, which utilized data from the National Program of Cancer Registries, the Surveillance, Epidemiology and End Results (SEER), and the United States Cancer Statistics databases, compared SIRs among birth cohorts. Age-specific incidence rates for CCA were generally higher for the DES-era birth cohort than for the comparison cohort (see Table 2). An increased incidence of CCA was seen in the DES-era birth cohort (patients born between 1947 and 1971 when DES was prescribed in the US, without official documentation and instead presumed exposure) at ages 60–64 (1.50 per 1,000,000 women-years) and 65–69 (2.86 per 1,000,000 women-years) and generally increased with age.[27] A recent retrospective review of over 500 patients with confirmed DES exposure discovered 10 human papillomavirus (HPV)-negative cervical/vaginal cancers, with 1 diagnosed in a patient older than 50 (0.2%). Of those cases, 2 were found to be CCA (patient ages of 17 and 37 years at time of diagnosis). Notably, greater than 90% of patients in the study were over 65 and no patients were diagnosed with a cervical/vaginal cancer after age 65.[28]

While CCA does seem to occur in older exposed patients, cases were rare and calculated incidence rates were extremely low, with the largest in any of the cohorts at 2.86 per million women-years.

TABLE 2. Annual Age-Specific Incidence Rates of Clear Cell Adenocarcinoma Based on Age and Diethylstilbestrol Exposure[27]

Age at diagnosis (years)	Comparison cohort[a] (SEER-9)	DES-era cohort[b] (SEER-9)	DES-era cohort[b] (USCS)
50–54	0.63	1.15	1.25
55–59	1.28	1.48	1.23
60–64	0.86	1.50	1.56
65–69	1.86	2.86	2.62

Rates are per 1,000,000 women-years.

[a]Comparison cohort included patients born before 1947.

[b]DES-era birth cohort included patients born between 1947 and 1971.

USCS indicates United States Cancer Statistics database.

- What is the evidence for the effectiveness of screening for CCA or squamous cell cervical cancer precursors in DES-exposed people below the age of 65?

The rationale for screening exposed people was the belief that cytology and physical examination were likely to accurately detect CCA and early detection would improve patient outcomes. We found very little data on the accuracy of screening. Screening for CCA was routinely performed in younger patients by obtaining cytology of the vagina and cervix (without a standard method of collecting; either circumferentially sampling the cervix and vagina or individual collections of the cervix and all 4 walls of the vagina) with or without colposcopy from the 1970s to 1990s.[29–35] Descriptive data from the Netherlands registry calculated the sensitivity of cytology to detect CCA in antenatally DES-exposed patients. The sensitivity of cervical cytology was 89% for cervical CCA and 64% for vaginal CCA. When vaginal cytology was performed independently, the sensitivity increased to 100% for the detection of vaginal CCA.[35] While the sensitivity of cytology seems promising, the study only evaluated known cases of CCA. We found no studies reporting specificity or constructed in a way that could calculate predictive values. We found no studies assessing improvement in patient outcome with screening.

- What is the evidence for the effectiveness of screening for CCA in patients over the age of 65?

Our search found no studies that evaluated the effectiveness of screening beyond the age of 65. The current clinical practice of continuing to screen DES-exposed individuals beyond age 65 is based on expert opinion largely extrapolated from prior practice. We found no specific evidence to support either continued screening or the discontinuation of screening in patients over the age of 65.

- What is the evidence for harms of screening in patients over the age of 65?

We found no evidence in our search addressing screening harms in postmenopausal DES-exposed patients. Historical recommendations for DES-exposed individuals included annual visits and more frequent examinations with colposcopy and directed biopsies, which have been associated with increased distress and anxiety in nonexposed populations.[36,37] We found no data regarding specificity or predictive values of screening in

patients over the age of 65, making it impossible to estimate harms of false-positive testing specific to this population. However, when extrapolating from a non–DES-exposed average-risk population, cervical cancer screening may have a poor positive predictive value and have increased risks of harm and injury during the workup of abnormal results.[38,39]

- What is the evidence for screening DES-exposed individuals who have undergone hysterectomy with removal of the cervix?

Our search found no studies relating to screening DES-exposed patients who have undergone hysterectomy. We found no evidence to support screening or the discontinuation of screening in this group.

ASCCP RECOMMENDATIONS REGARDING SCREENING FOR CERVICAL AND VAGINAL CLEAR CELL ADENOCARCINOMAS IN PEOPLE ANTENATALLY EXPOSED TO DES

- ASCCP recommends people with prenatal exposure to DES receive annual screening for CCA with cytology until the age of 65 and discontinue screening beyond the age of 65 provided they otherwise meet criteria for cessation of screening (preferred) (CIII). Annual screening for CCA with cytology may be continued after age 65 following shared decision making including a discussion regarding the absence of data for evidence of effectiveness of screening and the potential harms associated with screening postmenopausal patients with cytology (acceptable) (CIII). In patients who choose to continue screening beyond the age of 65, screening should cease when the patient's age and comorbidities preclude acting on screen-detected abnormalities (CIII).
- ASCCP recommends DES-exposed people who have been diagnosed with HPV-related disease be managed using the 2019 ASCCP Risk-Based Management Consensus Guidelines.[17]
- ASCCP recommends people with prenatal exposure to DES who have undergone hysterectomy with removal of their cervix and who otherwise have no indications for screening discontinue screening (preferred) (CIII). Annual vaginal cytology may be continued people with prenatal exposure to DES who have undergone hysterectomy with removal of their cervix and who otherwise have no indications for screening after shared decision making that includes discussion of the absence of supportive evidence and the potential harms of continued screening (acceptable) (CIII).

If screening is continued, it should include an annual pelvic examination with focused attention to the cervix, upper vagina, and vaginal sidewalls (see Table 3). Cytology should include separate collections of the cervix and the vaginal sidewalls. Biopsy is warranted for any visible lesions (see Table 4) of the cervix or vagina seen during routine examination, and colposcopy should be performed to identify any other lesions that would warrant biopsy.

TABLE 3. Examination Recommendations[7,10]

Examination recommendations
• Annual pelvic examination
◦ Visual inspection of the upper vagina and vaginal sidewalls
◦ Bimanual examination with palpation of the upper vagina and vaginal sidewalls
• Separate cervical and vaginal cytology of all 4 walls (can be performed circumferentially)
If abnormal findings are noted:
• Biopsy of visible suspicious lesions
• Colposcopic evaluation to identify any additional lesions

TABLE 4. Examination Findings[7,10]

• Reproductive tract abnormalities
◦ Vaginal adenosis—red, granular patches with or without exudate (nonstaining with Lugol's)
◦ Vaginal and cervical transverse ridges—partial or complete fibrous bands
• Clear cell adenocarcinomas
◦ Superficial lesions
◦ Varying size
◦ Papillary or nodular
◦ Typically involving upper or middle third of the vagina, but can involve lower third of vagina (vaginal CCA)

COMMENT

The workgroup recognizes that the recommendation to cease screening DES-exposed people over age 65 is a substantial change from a long-accepted standard of care. In making this recommendation, the workgroup considered several key issues. Our search found inadequate evidence for the accuracy of cytology screening in this population and no evidence for improved clinical outcomes in screened patients. Our review confirmed that while still potentially elevated in this age group, baseline risk of CCA is extremely low. Screening tests in general have extremely poor predictive values for rare diseases with low population prevalence, so the group was concerned that screening is at best of limited value. No studies found in our search examined harms of screening in this population. In average-risk people, adequately screened patients cease screening beyond age 65 because the harms of screening outweigh the small benefits. The workgroup felt the harms of screening in average-risk people are also likely present in DES-exposed people. With the limited evidence found in the review, it was difficult to conclusively balance benefits and harms, so the workgroup felt that continued screening is acceptable after shared decision making that includes discussion of the lack of evidence for effectiveness and the potential for false-positive tests and need for additional testing. Our updated literature search focused on CCA, but more broadly covered cervical and vaginal disease in DES-exposed patients. We found no convincing evidence that HPV behaves differently in these patients and do not recommend any additional screening for HPV-related disease beyond standard screening recommendations. The recommendation for DES-exposed patients who have undergone hysterectomy was extrapolated from the recommendations for patients who have a cervix, with risk further reduced through no longer having a cervix.

REFERENCES

1. Smith OW. Diethylstilbestrol in the prevention and treatment of complications of pregnancy. *Am J Obstet Gynecol* 1948;56:821–34.
2. Selected item from the FDA drug bulletin-november 1971: diethylstilbestrol contraindicated in pregnancy. *Calif Med* 1972;116:85–6.
3. Giusti RM, Iwamoto K, Hatch EE. Diethylstilbestrol revisited: a review of the long-term health effects. *Ann Intern Med* 1995;122:778–88.
4. Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. *N Engl J Med* 1971;284:878–81.

5. Huo D, Anderson D, Palmer JR, et al. Incidence rates and risks of diethylstilbestrol-related clear-cell adenocarcinoma of the vagina and cervix: Update after 40-year follow-up. *Gynecol Oncol* 2017;146:566–71.
6. Verloop J, van Leeuwen FE, Helmerhorst TJ, et al. Cancer risk in DES daughters. *Cancer Causes Control* 2010;21:999–1007.
7. Herbst AL, Kurman RJ, Scully RE. Vaginal and cervical abnormalities after exposure to stilbestrol in utero. *Obstet Gynecol* 1972;40:287–98.
8. Hatch EE, Herbst AL, Hoover RN, et al. Incidence of squamous neoplasia of the cervix and vagina in women exposed prenatally to diethylstilbestrol (United States). *Cancer Causes Control* 2001;12:837–45.
9. Hoover RN, Hyer M, Pfeiffer RM, et al. Adverse health outcomes in women exposed in utero to diethylstilbestrol. *N Engl J Med* 2011;365: 1304–14.
10. Scully RE, Robboy SJ, Herbst AL. Vaginal and cervical abnormalities, including clear-cell adenocarcinoma, related to prenatal exposure to stilbestrol. *Ann Clin Lab Sci* 1974;4:222–33.
11. Boyd J, Takahashi H, Waggoner SE, et al. Molecular genetic analysis of clear cell adenocarcinomas of the vagina and cervix associated and unassociated with diethylstilbestrol exposure in utero. *Cancer* 1996;77: 507–13.
12. Forsberg JG. Physiological mechanisms of diethylstilbestrol organotropic carcinogenesis. *Arch Toxicol Suppl* 1979;2:263–74.
13. Curry SJ, Krist AH, Owens DK, et al. Screening for cervical cancer: US Preventive Services Task Force Recommendation Statement. *JAMA* 2018; 320:674–86.
14. American College of Obstetrics and Gynecology (ACOG) Practice Advisory: Updated Cervical Cancer Screening Guidelines. Replaces Practice Bulletin 168, updated April 2021. Available at: https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2021/04/updated-cervical-cancer-screening-guidelines#. Accessed August 28, 2024.
15. Marcus JZ, Cason P, Downs LS Jr., et al. The ASCCP Cervical Cancer Screening Task Force Endorsement and Opinion on the American Cancer Society Updated Cervical Cancer Screening Guidelines. *J Low Genit Tract Dis* 2021;25:187–91.
16. Practice Bulletin No. 168: Cervical Cancer Screening and Prevention. *Obstet Gynecol* 2016;128:e111–30.
17. Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. *J Low Genit Tract Dis* 2020;24: 102–31.
18. Güzin K, Kayataş Eser S, Yiğit A, et al. Primary clear cell carcinoma of the vagina that is not related to in utero diethylstilbestrol use. *Gynecol Surg* 2006;3:281–4.
19. Center for Disease Control: Vaginal and vulvar cancers. Available at: https://www.cdc.gov/vaginal-vulvar-cancers/statistics/?CDC_AAref_Val=https://www.cdc.gov/cancer/vagvulv/statistics/index.htm#. Accessed August 28, 2024.
20. Chelmow D, Cejtin H, Conageski C, et al. Executive summary of the Lower Anogenital Tract Cancer Evidence Review Conference. *Obstet Gynecol* 2023;142:708–24.
21. Herbst AL, Kurman RJ, Scully RE, et al. Clear-cell adenocarcinoma of the genital tract in young females. Registry report. *N Engl J Med* 1972;287: 1259–64.
22. Troisi R, Hatch EE, Titus-Ernstoff L, et al. Cancer risk in women prenatally exposed to diethylstilbestrol. *Int J Cancer* 2007;121:356–60.
23. Troisi R, Hatch EE, Titus L, et al. Prenatal diethylstilbestrol exposure and cancer risk in women. *Environ Mol Mutagen* 2019;60:395–403.
24. Hatch EE, Palmer JR, Titus-Ernstoff L, et al. Cancer risk in women exposed to diethylstilbestrol in utero. *JAMA* 1998;280:630–4.
25. O'Brien PC, Noller KL, Robboy SJ, et al. Vaginal epithelial changes in young women enrolled in the National Cooperative Diethylstilbestrol Adenosis (DESAD) project. *Obstet Gynecol* 1979;53:300–8.
26. Hanselaar A, van Loosbroek M, Schuurbiers O, et al. Clear cell adenocarcinoma of the vagina and cervix. An update of the central Netherlands registry showing twin age incidence peaks. *Cancer* 1997;79: 2229–36.
27. White MC, Weir HK, Soman AV, et al. Risk of clear-cell adenocarcinoma of the vagina and cervix among US women with potential exposure to diethylstilbestrol in utero. *Cancer Causes Control* 2022;33:1121–4.
28. Wamakima BW, McKinney S, Bookman L, et al. Postmenopausal vaginal and cervical cancer risk related to in utero diethylstilbestrol exposure. *J Low Genit Tract Dis* 2023;27:35–9.
29. Robboy SJ, Keh PC, Nickerson RJ, et al. Squamous cell dysplasia and carcinoma in situ of the cervix and vagina after prenatal exposure to diethylstilbestrol. *Obstet Gynecol* 1978;51:528–35.
30. Orr JW Jr., Shingleton HM, Gore H, et al. Cervical intraepithelial neoplasia associated with exposure to diethylstilbestrol in utero: a clinical and pathologic study. *Obstet Gynecol* 1981;58:75–82.
31. Robboy SJ, Szyfelbein WM, Goellner JR, et al. Dysplasia and cytologic findings in 4,589 young women enrolled in diethylstilbestrol-adenosis (DESAD) project. *Am J Obstet Gynecol* 1981;140:579–86.
32. Fowler WC Jr., Schmidt G, Edelman DA, et al. Risks of cervical intraepithelial neoplasia among DES-exposed women. *Obstet Gynecol* 1981;58:720–4.
33. Robboy SJ, Noller KL, O'Brien P, et al. Increased incidence of cervical and vaginal dysplasia in 3,980 diethylstilbestrol-exposed young women. Experience of the National Collaborative Diethylstilbestrol Adenosis Project. *JAMA* 1984;252:2979–83.
34. Welch WR, Robboy SJ, Kaufman RH, et al. Pathology of colposcopic findings in 2635 diethylstilbestrol-exposed young women. *Gynecol Oncol* 1985;21:277–86.
35. Hanselaar AG, Boss EA, Massuger LF, et al. Cytologic examination to detect clear cell adenocarcinoma of the vagina or cervix. *Gynecol Oncol* 1999;75:338–44.
36. Lerman C, Miller SM, Scarborough R, et al. Adverse psychologic consequences of positive cytologic cervical screening. *Am J Obstet Gynecol* 1991;165:658–62.
37. Marteau TM, Walker P, Giles J, et al. Anxieties in women undergoing colposcopy. *Br J Obstet Gynaecol* 1990;97:859–61.
38. Sawaya GF, Grady D, Kerlikowske K, et al. The positive predictive value of cervical smears in previously screened postmenopausal women: the Heart and Estrogen/progestin Replacement Study (HERS). *Ann Intern Med* 2000; 133:942–50.
39. Shen Q, Lu D, Andrae B, et al. Risk of injuries around diagnosis of cervical cancer and its precursor lesions: a nationwide cohort study in Sweden. *Cancer Epidemiol Biomarkers Prev* 2020;29:2230–4.