

Management of women exposed to DES in utero – evidence summary

PICO: For women who were exposed to diethylstilbestrol (DES) in utero what is the safety and effectiveness of screening using strategies other than those currently used for these women compared to current practice?

Summary of findings

The 2023 review added two more comparative studies conducted in the USA and the Netherlands to the two studies included in the 2016 review. These two studies generally provided results based on additional data from the two previously identified studies and the findings were broadly consistent. For instance, a 2011 case-control study (4653 exposed and 1927 unexposed) from the 2016 review conducted in the USA reported that women exposed to DES had a two-fold risk of CIN2/CIN2+ as compared with those not exposed and the risk was significant (cumulative risk for CIN2/CIN2+: 6.9% vs 3.4%, Hazard Ratio (HR): 2.28, 95% CI: 1.59-3.27). This was consistent with the findings of the later study (2016, the USA) that used a prospective cohort design with additional data. Based on 4,062 women exposed to DES in utero and 1,837 unexposed daughters who were followed from 1982 to 2013 for pathology-confirmed diagnosis of CIN2+, this study reported that women exposed to DES compared to unexposed daughters had nearly two-fold significantly increased risk of squamous CIN2+ (cervix, vagina, vulva) (HR: 1.98, 95% CI: 1.33-2.94). This study also reported an increased risk of invasive cervical or vulvar cancer (cervical squamous cell cancers, vulvar cancers and cervical adenocarcinomas) among women exposed to DES compared to the unexposed cohort, however, the risk was not significant (HR:1.38, 95% CI: 0.41-4.73). In both of these studies, study women underwent five annual examinations. Furthermore, a prospective cohort study (2010) conducted in the Netherlands included in the 2016 review reported no additional risk for squamous cell cancer of the vagina and cervix in a cohort of 12,091 women exposed to DES compared to the general population (Standardised Incidence Ratio (SIR): 0.64, 95%CI: 0.31-1.17). A further study (2017, 11,894 women with self-reported DES exposure followed from 2000-2008) conducted in the Netherlands by the same team with additional data reported approximately three-fold significantly increased risk of CIN1 (SIR: 2.8, 95% CI: 2.3-3.4) but no excess risk of CIN2+ (SIR: 1.1, 95% CI: 0.95-1.4) among women exposed to DES compared to the screened general population.

Detailed findings

Systematic reviews were undertaken in 2015 and 2023 and did not find any RCTs comparing different screening protocols for women exposed to DES in utero. Therefore, on the advice of the Working Party evidence reviews in 2015 and 2023 were undertaken to address the following question:

For women who were exposed to DES in utero what are the **relative risks** of cervical and vaginal carcinomas or dysplasia (any or moderate/ severe) when compared with women who were not exposed or the general population?

Evidence review for 2016 guidelines

Results: Two studies were identified that reported on the relative risks of cervical or vaginal cancers or dysplasia. These studies are summarized in Table 1.

Table 1: *Studies investigating the risk of cervical or vaginal cancers or high-grade abnormalities for women exposed to DES in utero compared to un-exposed women or the general population identified in 2015 literature searches.*

Study	Country	Study design	Population	Findings
Hoover 2011	USA	Case control	<p>Women in the DES Adenosis cohort, and daughters of women in the Dieckmann cohort, and the Women's Health Study cohort with long term follow-up.</p> <p>4653 women exposed in utero (medical records) and 1927 unexposed controls.</p> <p>Followed up until CIN2+ or clear cell carcinoma? Women in DES Adenosis (DESAD) cohort women underwent 5 annual examinations and subsequently completed periodic questionnaires specific to the DESAD cohort assessing clinical and lifestyle information. Clinical follow-up of DES-exposed women in other two cohorts NR Excluded women who had undergone a hysterectomy NR</p>	Cumulative risk for CIN2/CIN2+ in women exposed to DES as compared with those not exposed was 6.9% vs 3.4% and the hazard ratio was 2.28 (95%CI 1.59-3.27).
Verloop 2010	Netherlands	Prospective cohort	<p>Data from 12,091 Dutch women exposed to DES in utero (self-reported) were analysed. Women were recruited in 1992 and followed up until 2008.</p> <p>Followed up until cancer diagnosis or death Clinical follow-up of DES-exposed women NR Excluded women who had undergone a hysterectomy NR</p>	Cancer incidence was obtained through linkage with the nationwide population-based Cancer Registry. Based on data from the whole cohort, the risk of squamous cell cancer of the vagina and cervix was non-significantly decreased compared to the general population [SIR=0.64 (95%CI 0.31- 1.17)].

Abbreviations: CI = confidence interval; CIN = cervical intraepithelial neoplasia; DES = diethylstilbestrol; NR = not reported; SIR = standardised incidence rate

Evidence review for 2023 guidelines update

Searches: EMBASE and Medline databases were searched on 17 March 2023 by combining terms for diethylstilbestrol and cervix or vagina. The search was limited to English language articles published from 2015 onwards. Full details of the search strategy are included in the Appendices.

Results: Two comparative studies were identified that reported on cervical or vaginal cancers or dysplasia; both provided additional data for the two previously identified cohorts. These studies are summarised in Table 2.

Table 2: *Studies investigating the risk of cervical or vaginal cancers or high-grade abnormalities for women exposed to DES in utero compared to un-exposed women identified in 2023 literature searches.*

Study	Country	Study design	Population	Findings
Troisi 2016	USA	Prospective cohort	<p>NCI Combined DES Cohorts Follow-Up Study: Women in the DES Adenosis cohort, and daughters of women in the Dieckmann cohort, Horne cohort, and Women's Health Study cohort.</p> <p>4062 women exposed to DES in utero (medical records) and 1837 unexposed daughters were followed from 1982-2013 for pathology-confirmed diagnosis of CIN2+ Median follow-up: 25 years exposed vs 18 years unexposed</p> <p>Followed up until CIN2+ diagnosis or death Women in DES Adenosis (DESAD) cohort women underwent 5 annual examinations and subsequently completed periodic questionnaires specific to the DESAD cohort assessing clinical and lifestyle information. Clinical follow-up of DES-exposed women in other three cohorts NR Excluded women who had undergone a hysterectomy prior to 1982</p>	<p>145 DES-exposed vs 33 unexposed daughters were diagnosed with squamous CIN2+ (cervix, vagina, vulva). Cumulative incidence of squamous CIN2+ in DES-exposed vs unexposed daughters was 5.3% (95% CI 4.1-6.5) vs 2.6% (95% CI 1.5-3.7), respectively, with a birth-year and cohort adjusted HR 1.98 (95% CI 1.33-2.94).</p> <p>11 DES-exposed vs 4 unexposed daughters were diagnosed with invasive cervical or vulvar cancer; 7 cervical squamous cell cancers, 2 vulvar cancers and 2 cervical adenocarcinomas were diagnosed in the DES-exposed population and 4 cervical squamous cancers were diagnosed in the non-exposed population with a HR of 1.38 (95% CI 0.41-4.73) (unclear if adjusted).</p> <p>7 DES-exposed vs 1 unexposed daughters were diagnosed with "glandular CIN2+" (cervix).</p>
Verloop 2017	Netherlands	Retrospective cohort study with prospective follow-up	<p>DES-net study: DES-daughters identified through the Netherlands DES Center registry.</p> <p>11,894 women with DES exposure in utero (self-reported) followed from 2000-2008 for diagnosis of pathology-confirmed CIN2+ and compared to incident CIN2+ in the screened general population (excluding prevalent screens).</p> <p>Followed up until CIN diagnosis or death Clinical follow-up of DES-exposed women NR Excluded women who had undergone a hysterectomy NR</p>	<p>The risk of CIN1 was increased compared to the screened general population [SIR = 2.8 (95% CI 2.3-3.4)]. The risk of CIN2+ was not increased compared to the screened general population [SIR = 1.1 (95% CI 0.95-1.4)].</p> <p>Excludes clear cell adenocarcinoma as a cancer outcome was excluded and prevalent lesions detected on first screen for exposed and general population were not included.</p>

Abbreviations: CI= confidence interval; CIN = cervical intraepithelial neoplasia; DES = diethylstilbestrol; HR = hazard ratio; NCI = National Cancer Institute; NR = not reported; SIR = standardised incidence rate

Updated evidence summary for 2023 guidelines update

Table 3: Studies investigating the risk of cervical or vaginal cancers or high-grade abnormalities for women exposed to DES in utero compared to un-exposed women identified in 2015 and in 2023 (grey background) literature searches.

Study	Country	Study design	Population	Findings
Hoover 2011 & Troisi 2016	USA	Case control	<p>Women in the DES Adenosis cohort, and daughters of women in the Dieckmann cohort, and the Women's Health Study cohort with long term follow-up.</p> <p>4653 women exposed in utero (medical records) and 1927 unexposed controls.</p> <p>Followed up until CIN2+ or clear cell carcinoma? Women in DES Adenosis (DESAD) cohort women underwent 5 annual examinations and subsequently completed periodic questionnaires specific to the DESAD cohort assessing clinical and lifestyle information. Clinical follow-up of DES-exposed women in other two cohorts NR Excluded women who had undergone a hysterectomy NR</p>	Cumulative risk for CIN2/CIN2+ in women exposed to DES as compared with those not exposed was 6.9% vs 3.4% and the HR was 2.28 (95%CI 1.59-3.27).
	USA	Prospective Cohort	<p>NCI Combined DES Cohorts Follow-Up Study: Women in the DES Adenosis cohort, and daughters of women in the Dieckmann cohort, Horne cohort, and Women's Health Study cohort.</p> <p>4062 women exposed to DES in utero (medical records) and 1837 unexposed daughters were followed from 1982-2013 for pathology-confirmed diagnosis of CIN2+ Median follow-up: 25 years exposed vs 18 years unexposed</p> <p>Followed up until CIN2+ diagnosis or death Women in DES Adenosis (DESAD) cohort women underwent 5 annual examinations and subsequently completed periodic questionnaires specific to the DESAD cohort assessing clinical and lifestyle information. Clinical follow-up of DES-exposed women in other three cohorts NR Excluded women who had undergone a hysterectomy prior to 1982</p>	<p>145 DES-exposed vs 33 unexposed daughters were diagnosed with squamous CIN2+ (cervix, vagina, vulva). Cumulative incidence of squamous CIN2+ in DES-exposed vs unexposed daughters was 5.3% (95% CI 4.1-6.5) vs 2.6% (95% CI 1.5-3.7), respectively, with a birth-year and cohort adjusted HR 1.98 (95% CI 1.33-2.94).</p> <p>11 DES-exposed vs 4 unexposed daughters were diagnosed with invasive cervical or vulvar cancer; 7 cervical squamous cell cancers, 2 vulvar cancers and 2 cervical adenocarcinomas were diagnosed in the DES-exposed population and 4 cervical squamous cancers were diagnosed in the non-exposed population with a HR of 1.38 (95% CI 0.41-4.73) (unclear if adjusted).</p> <p>7 DES-exposed vs 1 unexposed daughters were diagnosed with "glandular CIN2+" (cervix).</p>
Verloop 2010 & 2017	Netherlands	Prospective cohort	<p>Data from 12,091 women exposed to DES in utero (self-reported) were analysed. Women were recruited in 1992 and followed up until 2008</p> <p>Followed up until cancer diagnosis or death Clinical follow-up of DES-exposed women NR</p>	Cancer incidence was obtained through linkage with the nationwide population-based Cancer Registry. Based on data from the whole cohort, the risk of squamous cell cancer of the vagina and cervix was non-significantly decreased compared to the general population [SIR=0.64 (95%CI 0.31- 1.17)].

Study	Country	Study design	Population	Findings
			Excluded women who had undergone a hysterectomy NR	
		Retrospective cohort study with prospective follow - up	DES-net study: DES-daughters identified through the Netherlands DES Center registry. 11,894 women with self-reported DES exposure in utero followed from 2000-2008 for diagnosis of pathology-confirmed CIN2+ and compared to incident CIN2+ in the screened general population (excluding prevalent screens). Followed up until CIN diagnosis or death Clinical follow-up of DES-exposed women NR Excluded women who had undergone a hysterectomy NR	The risk of CIN1 was increased compared to the screened general population [SIR = 2.8 (95% CI 2.3-3.4)]. The risk of CIN2+ was not increased compared to the screened general population [SIR = 1.1 (95% CI 0.95-1.4)]. Excludes clear cell adenocarcinoma as a cancer outcome was excluded and prevalent lesions detected on first screen for exposed and general population were not included.

Abbreviations: CI = confidence interval; CIN = cervical intraepithelial neoplasia; DES = diethylstilbestrol; HR = hazard ratio; NR = not reported; SIR = standardised incidence rate

Existing guidelines

Current (2017) Australian guidelines

Women exposed to DES in utero should be offered an annual co-test and colposcopic examination of both the cervix and vagina indefinitely.

Women exposed to DES in utero who have a screen-detected abnormality should be managed by an experienced colposcopist.

Other existing potentially relevant consensus-based guidelines

Guideline	Organisation	Recommendation
Cervical Cancer Screening Guidelines	University of Michigan Rogel Cancer Center	Women who are at high risk for cervical cancer may need to be screened more often. Women at high risk might include those with HIV infection, organ transplant, or exposure to the drug DES. They should talk with their doctor or nurse.
Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society (Fontham 2020)	The American Cancer Society	Screening recommendations for the general population do not apply to individuals with in utero exposure to diethylstilbestrol.
2021 Update cervical cancer screening guidelines	American College of Obstetricians and Gynecologists	Screening recommendations for the general population do not apply to individuals with in utero exposure to diethylstilbestrol.

Guideline	Organisation	Recommendation
Screening for cervical cancer US Preventative Task force Recommendation Statement (Curry 2018)	US Preventative Task Force	Screening recommendations for the general population do not apply to individuals with in utero exposure to diethylstilbestrol, they should receive individualized follow up.

References

American College of Obstetricians and Gynecologists. Updated Cervical Cancer Screening Guidelines 2021 <https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2021/04/updated-cervical-cancer-screening-guidelines> Accessed March 2023.

Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, Davidson KW, et al. Screening for cervical cancer: US Preventive Services Task Force recommendation statement. *Jama*. 2018;320(7):674-86

Fontham ET, Wolf AM, Church TR, Etzioni R, Flowers CR, Herzig A, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. *CA: a cancer journal for clinicians*. 2020;70(5):321-46.

Hoover RN, Hyer M, Pfeiffer RM, Adam E, Bond B, Cheville AL, et al. Adverse health outcomes in women exposed in utero to diethylstilbestrol. *N Engl J Med*. 2011 Oct 6;365(14):1304-14.

Troisi R, Hatch EE, Palmer JR, Titus L, Robboy SJ, Strohsnitter WC, et al. Prenatal diethylstilbestrol exposure and high-grade squamous cell neoplasia of the lower genital tract. *American Journal of Obstetrics and Gynecology*. 2016;215(3):e1-322.

University of Michigan Rogel Cancer Center. Cervical Cancer Screening Guidelines. <https://www.rogelcancercenter.org/cancer-prevention/cervical> Accessed March 2023

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Verloop J, van Leeuwen FE, Helmerhorst TJM, de Kok IMCM, van Erp EJM, van Boven HH, et al. Risk of cervical intra-epithelial neoplasia and invasive cancer of the cervix in DES daughters. *Gynecologic Oncology*. 2017;144(2):305-11.

APPENDICES

Appendix A: Medline and Embase database (via Ovid platform) search strategy

#	Searches
1	DES.tw.
2	Diethylstilbestrol.tw.
3	Diethylstilboestrol.tw.
4	1 or 2 or 3
5	Cervi*.tw.
6	Vagina*.tw.
7	5 or 6
8	4 and 7
9	limit 8 to english language
10	limit 9 to human
11	limit 10 to yr="2015 -Current"
12	limit 11 to conference abstract [Limit not valid in Ovid MEDLINE(R); records were retained]
13	limit 12 to medline
14	12 not 13
15	11 not 14

16

remove duplicates from 15