Management of women exposed to DES in utero

For women who were exposed to diethylstilboestrol (DES) in utero and their daughters what is the safety and effectiveness of screening using strategies other than those recommended for the general population compared to those recommended for the general population?

No studies were found comparing screening protocols for DES exposed women and their daughters with those commonly recommended for all women of the same age. Therefore, on the advice of the Working Party , three separate literature searches were conducted in EMBASE and PUBMED.

1. Studies detecting the presence of HPV infections in Clear Cell Carcinoma (CCC) of the vagina or cervix, irrespective of DES exposure to determine whether CCCs are HPV positive or negative.

Search terms: clear cell carcinoma, cervix, vagina, HPV, human papillomavirus. There was no date or language limit as this search was most likely not conducted for previous guidelines.

Table 1: studies investigating the presence of HPV DNA in clear cell carcinomas of the vagina or cervix.

Author	Country	Study	Subjects	Findings
Holl et al, 2015	Multiple	Retrospective	29 individual CCC tissues as part of collection of 614 cervical glandular neoplasias from 17 European countries	Processing of paraffin blocks and DNA extraction and detection were performed centrally in the Netherlands. Of the 29 cases of CCC 27.6% (8 cases) were HPV positive: 3 cases were HPV16+, 2 were HPV18+, 2 cases had multiple HPV DNA detected and 1 case had an unknown HPV type.
Pirog et al, 2014	Multiple,	Retrospective	30 cases of CCC as part of collection of 760 cervical adenocarcinomas from 38 countries worldwide	Paraffin blocks were processed under strict conditions to avoid cross contamination. HPV detection and typing of high and low risk HPVs were conducted centrally for all samples. HPV prevalence was found in 20% (6 cases) of clear cell adenocarcinomas. 4/30 cases were HPV16+ve and 2/30 cases were HPV18+.
Guo et al, 2014	China	Case report	14 year old female with stage II CCC	Female admitted with 3 week metrorrhagia. She had no sexual history or DES exposure in utero. U/S detected enlargement of cervix and a nodule, which was confirmed as clear cell carcinoma after biopsy. Genomic DNA was isolated from paraffin embedded specimen (9y after excision) and HPV18 was confirmed by PCR. 2 PCR methods used.

Table 1: continuation

Author	Country	Study	Subjects	Findings
Ueno et al, 2013	Japan	Retrospective review	13 patients with CCC of the cervix	Cervical tissue samples were collected from patients and tested for high risk HPV DNA by PCR. High risk HPV DNA was not detected in any of the 13 cases.
Pawlowski et al, 2013	Poland	Case report	2 women with clear cell adenocarcinoma of the cervix	2 women developed clear cell adenocarcinoma of the cervix despite yearly pap smear screening. HPV18 DNA was detected in post-surgical tissues in both patients.
Watanabe et al, 2012	Japan	Case report	1 woman with Herlyn-Werner-Wunderlich syndrome and primary clear cell carcinoma of the upper vagina	53 year old woman presented with vaginal pain and atypical genital bleeding diagnosed with syndrome at the age of 12. There was no history of DES exposure in utero. Radical hysterectomy was performed. HPV was not detected either in the tumour or on the visible sides of the cervix and vagina.
Kocken et al, 2011	Netherlands	Retrospective	28 women with cervical clear cell adenocarcinoma of which 15 were exposed to DES.	Tissue from paraffin embedded samples from 28 women were tested for hrHPV by 2 PCR methods. 4 DES exposed cases tested HPV16 +ve by both PCR methods and 1 DES case was HPV18+ve from 1 PCR method. 3 nonDES exposed cases also tested +ve by both PCR methods: one for HPV16, one for HPV18 and one for HPV45. 5 nonDES exposed cases were HPV+ve from 1 PCR method; 2 with HPV16, 1 with HPV51, 1 with HPV31 and 1 with HPVX. Authors stated that HPV positivity detected by only 1 method most likely reflects non-transforming transient HPV infections.
Park et al, 2011	Japan and US (NY and Boston)	Retrospective study	9 cases of CCC as part of a collection of 26 unusual subtypes of endocervical adenocarcinoma	Paraffin sections used for HPV DNA amplification. 5 cases of usual cervical adenocarcinoma drawn from the same populations, were included in the study as controls. HPV DNA was not detected in any of the CCC cases but was detected in 4/5 control cases.
Houghton et al, 2010	N.Ireland	Retrospective study	4 cases of CCC as part of a collection of 63 cases of adenocarcinomas and unusual variants	Tissue sections from paraffin-embedded tissue blocks were used to extract DNA and perform PCR HPV amplification. All CCC cases were HPV negative.
Nofech-Mozes et al, 2010	Canada	Retrospective	3 cases of CCC as part of a collection of 13 cases of serous, small cell and CC carcinomas	None of the cases had a history of DES exposure. PCR amplification carried out on de-paraffinised sections of tissue. 2/3 CCC were found to be positive for high-risk HPV. HPV types were not specified.

Table 1: continuation.

Author	Country	Study	Subjects	Findings
Liebrich et al, 2009	Germany	Prospective Cohort	2 cases of CCC from 178 prospectively recruited patients diagnosed with primary cervical cancer	Cervical samples from patients were tested for HPV infection using hybrid capture 2. Sufficient material was only available for 1 case of CCC. PCR showed this case to be HPV-ve.
Tan et al, 2008	China	Retrospective	4 patients with primary CCC of the cervix	None of the 4 cases were positive for HPV DNA. Article in Chinese. Limited information.
Hadzisejdc et al, 2007	Croatia	Retrospective	5 Cases of CCC in a collection of 102 of primary cervical adenocarcinoma	DNA extracted from formalin-fixed tissues. Detection of HPV DNA performed using E6 and E7 primers. All 5 cases of CCC were HPV +ve, 2 for HPV18, 1 for HPV33, 1 untyped HPV and 1 had HPV16/18/33.
Stewart et al, 2006	US	Case report	Case of 19 year old woman with clear cell endocervical adenocarcinoma	Woman presented to outpatient seeking treatment for suspected Candida infection. No prior exposure to DES, no family history of gynae cancer. Sexually active for 1 year, with 1 partner. Biopsy confirmed CC endocervical adenocarcinoma. In situ hybridization method used to detect HPV DNA but cell and tissue samples were negative.
Pirog et al, 2000	US and Poland	Retrospective study	4 cases of CCC as part of a collection of 73 invasive adenocarcinomas	Tissue from formalin-fixed paraffin embedded tissue was used for DNA extraction and HPV DNA amplification. All 4 cases of CCC were negative for HPV16,18, 45.
Waggoner et al, 1995	US	Retrospective study	14 cases of CC adenocarcinoma of vagina or cervix	9/14 cases had a history of intrauterine DES exposure. 7 tumours were from the vagina and 7 from the cervix. Paraffin-embedded tissue specimens were used to extract DNA and run PCR amplification. 3 tumours were HPV31 +ve (2 cases had DES exposure), 8 tumours were HPV DNA –ve and 3 had insufficient intact DNA. 3 patients developed metastatic disease and in all cases the primary tumour and sites of metastasis were HPV-ve.
Tenti et al, 1996	Italy	Retrospective review	10 cases of CCC from 138 cases of primary, infiltrating cervical adenocarcinoma	Sections from paraffin embedded tissue blocks used for DNA extraction. PCR was conducted and HPV detected by Southern blotting. 7/10 cases were HPV DNA +ve; 1 case for HPV16, 5 for HPV18 and 1 for both HPV16 and 18.
Duggan et al, 1995	Canada	Retrospective	1 case of CCC in a collection of 77 cases of cervical adenocarinomas	DNA extracted from paraffin block. PCR amplification performed with confirmation of the products by dot blot hybridization. The case was positive for HPV16 only.

Table 1: continuation.

Author	Country	Study	Subjects	Findings
Milde-Langosh et al, 1993	Germany	Retrospective	1 patient with CCC among 25 pts with primary cervical adenocarcinomas	Paraffin embedded tumour tissue used for DNA extraction and PCR. The one case of CCC was negative for HPV DNA.

Abbreviations: CCC clear cell carcinoma, HPV+ve: HPV positive, HPV-ve: HPV negative, PCR: polymerase chain reaction.

Summary: A total of 19 studies have reported testing of CCC samples for the presence of HPV DNA. A total of 48 cases of CCC in 10 studies tested HPV positive out of a total of 158 samples of CCC tested in all studies.

2. Risk of squamous cell carcinoma

Search terms: DES, diethylstilbestrol, squamous cell carcinoma, cervix, vagina, cervical intraepithelial neoplasia 3, CIN3, high grade. The search was conducted from 2004 onwards and articles limited to the English language.

Table 2: Studies investigating the risk of cervical and vaginal squamous cell carcinoma in women exposed in utero to DES compared with the general population

Author	Country	Study type	Subjects	Findings
Hoover et al, 2015	US	Case control	Data from 3 studies initiated in 1970s with long term FU of 4653 women exposed in utero and 1927 unexposed controls	Cumulative risk for CIN2/CIN2+ in women exposed to DES as compared with those not exposed was 6.9% vs 3.4% and hazard ratio 2.28 (95%CI 1.59-3.27).
Verloop et al, 2010	Netherlands	Prospective cohort	Data from 12,091 Dutch women exposed to DESin utero were analysed. Women were recruited in 1992 and followed up until 2008.	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: CCA: clear cell adenocarcinoma; DES: diethylstilbestrol; FU: follow-up; RR: relative risk; SIR: standardised incidence rate.

3. What are the risks of clear cell carcinomas of the cervix or vagina and cervical and vaginal dysplasia, including CIN3+ and VAIN 3+, in daughters and granddaughters of women who took DES compared to the daughters of unexposed women?

Search terms: DES, diethylstilbestrol, clear cell carcinoma, cancer risk, cervical intraepithelial neoplasia, cervical dysplasia, vaginal intraepithelial neoplasia, vaginal dysplasia, vagina, cervix. The search was conducted from 2004 onwards.

Table 3: Studies investigating the risk of cervical cancer or high grade abnormalities in daughters of women exposed to DES in utero compared to un-exposed women.

Author	Country	Study type	Subjects	Findings
Titus-Ernstoff et al, 2008	US	Prospective cohort follow-up study	Data obtained from the DES Combined Cohort Follow-up study. Analysis based on 463 daughters of women exposed to DES and 330 daughters of unexposed women.	None of the daughters was affected by vaginal or cervical adenocarcinoma. Adjusted for birth year and study centre, the relative risk of any cervical dysplasia (mild/moderate/severe) in women in relation to their mothers' prenatal DES exposure was 1.45 (95% CI 0.69 –3.1; 22 cases in exposed group and 16 cases in exposed group). The risk for moderate/severe cervical dysplasia only and mother's DES exposure was 0.93 (0.29 –2.94) based on 7 cases in the exposed group and 9 cases in the unexposed group. There were two cases of vulvar dysplasia, both in exposed women. After adjustment for birth year and study centre, the RR was 1.6 (0.78 –3.4) for the combined cervical and vulvar diagnoses (24 exposed, 16 unexposed). The authors state that due to the small number of cases in the population of daughters, statistical power is inadequate to rule out adverse outcomes with certainty.

Abbreviations: CIN: cervical intraepithelial neoplasia, VAIN: vaginal intraepithelial neoplasia.

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