

Cancer Association of South Africa (CANSA)



Fact Sheet on Cervical Dysplasia

Introduction

Dysplasia is an ambiguous term used in pathology to refer to an abnormality of development or an epithelial anomaly of growth and differentiation (epithelial dysplasia).

[Picture Credit: Cervical Dysplasia]

Epithelial dysplasia consists of an expansion of immature cells, with a corresponding decrease in the number and location of mature cells. Dysplasia is often indicative of an early neoplastic (cancerous) process.

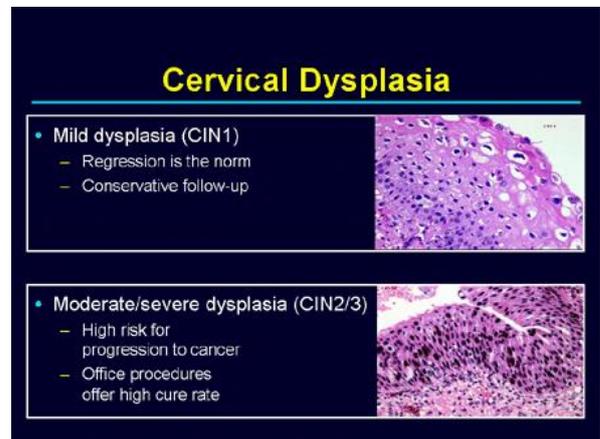
Dysplasia, in which cell maturation and differentiation are delayed, can be contrasted with metaplasia, in which cells of one mature differentiated type are replaced by cells of another mature, differentiated type.

Cervical Dysplasia

Cervical dysplasia is not cancer. The term indicates that abnormal cells are found on the surface of the cervix.

Cervical dysplasia can range from mild to severe, depending on the appearance of the abnormal cells. Dysplasia could go away on its own or, sometimes, it could develop into cancer. Another term for cervical dysplasia is cervical intraepithelial neoplasia.

[Picture Credit: Cervical Dysplasia 2]



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After an abnormality is detected on a Pap smear, the doctor may recommend more tests, including:

- A Human Papilloma Virus (HPV) test
- Colposcopy.

HPV Testing Compared to Routine Cytology in Cervical Screening

The National Screening Committee recommended that HPV testing should replace cytology in primary cervical screening.

Gilham, C., Sargent, A., Kitchener, H.C. & Peto, J. 2019.

BACKGROUND: The National Screening Committee (NSC) based its recommendation that human papillomavirus (HPV) testing should replace cytology in primary cervical screening largely on the 2009 follow-up results of the ARTISTIC trial (A Randomised Trial In Screening To Improve Cytology). The NSC must now decide on screening intervals and triage policy. Options include extending the screening interval up to 10 years for human papillomavirus-negative (HPV-) women, delaying recall for human papillomavirus-positive (HPV+) women with normal cytology (as their infections are usually transient), and basing triage on full HPV typing.

METHODS: In ARTISTIC, 24,510 women were recruited who were attending routine cervical cytology in Greater Manchester in 2001-3. The women were randomly allocated between revealing and concealing their HPV test results and were recalled every 3 years. After 2009, the women returned to routine cytological screening with recall every 3 years for those aged < 50 years, and every 5 years for those aged 50-64 years. We have followed the cohort to 2015 through national cancer registration for CIN3 (cervical intraepithelial neoplasia grade 3) and cancer, and through linkage to the cervical screening call-recall system to obtain lifetime cytology records.

RESULTS: The analysis comprised 24,496 women at round 1 and 13,591 women at round 2 (which was 30-48 months later). Follow-up via local histology laboratories and national cancer registration identified 505 cases of cervical intraepithelial neoplasia grade 3 or cervical cancer (CIN3+) (including 22 invasive cervical cancers). The cumulative CIN3+ risk 10 years after a negative HPV test [0.31%, 95% confidence interval (CI) 0.18% to 0.49%, in the revealed arm] was similar to that 3 years after negative cytology (0.30%, 95% CI 0.23% to 0.41%, in the concealed arm) and fell sharply with age, from 1.1% (95% CI 0.7% to 1.8%) in those women aged < 25 years to 0.08% (95% CI 0.03% to 0.20%) in those women aged > 50 years. The 10-year cumulative CIN3+ risk following a new HPV infection at round 2 was 3.4% (95% CI 2.1% to 5.4%). The highest risks were associated with type-specific persistent infections that, overall, resulted in a 10-year cumulative CIN3+ risk of 20.4% (95% CI 15.6% to 26.4%).

CONCLUSIONS: We found a similar level of protection 10 years after a negative HPV test and 3 years after negative cytology. These data support a considerably longer screening interval after a negative HPV test than after a negative cytology test. About three-quarters of women with HPV infection and normal cytology clear their infections within about 3 years. Their risk of CIN3+ within this time frame is low (1.5%), suggesting that the current policy of annual repeat testing and referral after 2 years may be unnecessarily cautious. Approximately 40% of women who remained HPV+ had cleared their initial infection and acquired a new HPV type. The cumulative CIN3+ risks in women with type-specific persistent infections are about six times higher than in women with new infections. Triage strategies based on HPV persistence would, therefore, reduce unnecessary referral of women with new (and largely transient) infections. HPV assays that identify HPV types 31, 33, 45, 52 and 58 in addition to 16 and 18 could be useful in triage as well as in primary HPV testing. Similar results in recent routine

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HPV screening suggest that our results are generalisable despite changes in cytology and HPV assay methods. We are continuing to follow the ARTISTIC cohort into the new era of primary HPV screening. Future work will focus on the implications of more sensitive HPV testing for primary HPV screening policy and triage of HPV-positive women. Our results suggest that a more sensitive test is needed to detect occult CIN3 at high risk of progression to cancer, but this would substantially increase the overall HPV detection rate. Tests such as DNA (deoxyribonucleic acid) methylation for distinguishing HPV infection from neoplasia will be evaluated on stored samples and on further samples now being collected from women in the cohort who are still being screened.

FUNDING: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 23, No. 28. See the NIHR Journals Library website for further project information.

PLAIN-LANGUAGE-SUMMARY: Human papillomavirus (HPV) causes cervical cancer. The latest scientific evidence shows that screening for HPV is better than screening for abnormal cytology with a 'smear' test, so HPV testing is being rolled out nationally. The main disadvantage is that more women will test positive and be referred for further tests. Most infections are harmless and clear without treatment, and balance must be achieved so that women who progress to CIN3 (pre-cancer) are identified but that unnecessary referral and anxiety for women is minimised. A Randomised Trial In Screening To Improve Cytology (ARTISTIC) recruited 24,510 women attending for cervical screening in Greater Manchester in 2001–3. Cervical samples taken at recruitment and again at screening 3 and 6 years later were tested for HPV. The women then returned to routine screening. We have followed them through national screening records and cancer registration until the end of 2015. By comparing the HPV results taken at entry with those collected 3 years later, we can categorise HPV infections into new and persistent. We have found that the CIN3 risk in women with persistent infections is about six times higher than in women with new infections, which in turn is about 30 times higher than in women with no infection. About three-quarters of women with HPV infection but no abnormal cells clear their infections within 3 years. Their risk of pre-cancer within 3 years is low (1.5%) and so intensive follow-up is unnecessary. Moreover, 40% of those who remain human papillomavirus positive (HPV+) have cleared their initial infection and acquired a new infection, meaning that they are also at much lower risk of disease than those with a persistent infection. The current practice in the national pilot study of annual repeat testing and referral of anyone who is still HPV+ after 2 years may, therefore, be too conservative. We have also shown that the CIN3 risk after 10 years in women testing negative for HPV is similar to the risk after about 3 years in women testing negative for cytology. This means that screening intervals could be extended for women testing negative for HPV.

Colposcopy

Colposcopy is a medical diagnostic procedure to examine an illuminated, magnified view of the cervix and the tissues of the vagina and vulva. It is done using a colposcope, which provides an enlarged view of the areas, allowing the colposcopist (the person doing the examination) to visually distinguish normal from abnormal appearing tissue and take directed biopsies (small tissue samples) for further pathological examination. The main goal of colposcopy is to prevent cervical cancer by detecting precancerous lesions early and treating them.

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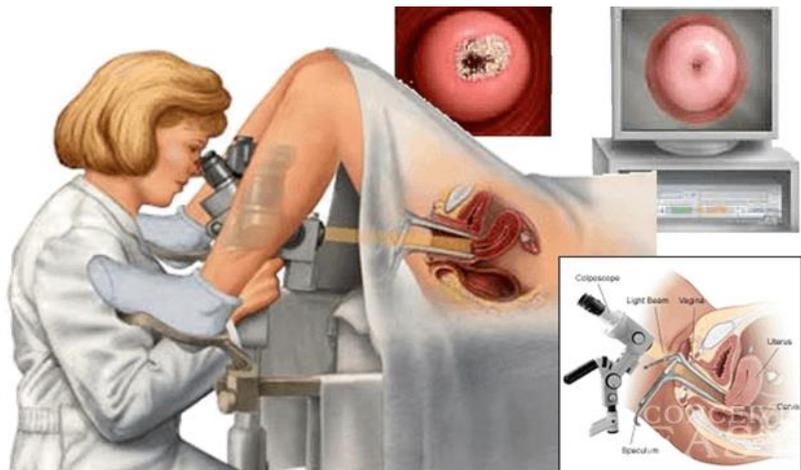
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[Picture Credit: Colposcope]

Causes of Cervical Dysplasia

In many women with cervical dysplasia, Human Papilloma Virus (HPV) is found in cervical cells. HPV infection is common in women and men, and most often affects sexually active women under age 20.



Bergergren, L., Lillsunde-Larsson, G., Helenius, G. & Karisson, M.G. 2019.

AIM: Many cervical cancers occurs among women over 65 and prevalence of HPV genotypes in this age cohort is sparingly studied. One aim of this study was to study the prevalence and distribution of HPV genotypes in women 55-59 years, with normal cytology when exiting the screening program. Secondly, HPV clearance as well as the value of HPV genotyping and/or liquid based cytology as triage tests for identifying histological dysplasia among women with persistent HPV was studied.

METHODS: Women that exited the screening program with normal cytology, between the years 2012-2014, in Örebro County, Sweden, were invited to this study. A total of 2946 samples were analyzed with a broad-spectrum assay to detect both hrHPV and lrHPV in order to investigate the distribution of genotypes. In the consent group, women with a positive hrHPV test were offered a follow-up test and a cone biopsy for histological confirmation, and a follow up sample 6 months post cone.

RESULTS: The overall prevalence of hrHPV was 7.4% and 59% of them remained hrHPV positive in a follow-up test after 12 months. A total of 99 women had a cone biopsy done, where 19% showed histological dysplasia. HPV 53 was the most common genotype, and among women with histology confirmed LSIL or HSIL, HPV 31 was most common. A positive hrHPV result showed a PPV of 25% for LSIL+ and 12.5% for HSIL+. Using detection of HPV 16/18 genotypes as a triage test for hrHPV positive tests, indicated FNR for histological LSIL+ and HSIL+ of 94% and 87.5% respectively, whilst triage based on cervical cytology had a FNR of 69% for LSIL+ and 37.5% for HSIL+.

CONCLUSION: The most common hrHPV genotypes among women 55-59 years of age were non HPV16/18 genotypes, and in this population, these genotypes represented most of the histological verified HSIL lesions. This result does not support the proposition of a HPV 16/18 triaging test after a positive hrHPV test as a marker of histological HSIL+ cervical lesions in women over 55 years of age. Similarly, cytological triage after a positive hrHPV showed no additional benefit in this population. Specific triaging tests should be validated to follow post-menopausal women with a positive hrHPV test.

Risk Factors for Cervical Dysplasia

There are several risk factors for cervical dysplasia, some of them directly related to the risk of HPV:

- having an illness that suppresses the immune system or being on immunosuppressant drugs

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- having multiple sexual partners
- giving birth before the age of 16
- having sex before the age of 18
- smoking cigarettes
- having sex with an uncircumcised man
- Human papillomavirus (HPV) infection
- Genital warts
- History of one or more sexually transmitted diseases, such as genital herpes or HIV
- Having suppressed immune system, such as from HIV or chemotherapy to treat cancer
- Using birth control pills for longer than 5 years
- Being born to a mother who took diethylstilbestrol (DES) to become pregnant or to sustain pregnancy. This drug was used many years ago to promote pregnancy but it is no longer used for these purposes.
- Low levels of folate (vitamin B9) in red blood cells
- Dietary deficiencies in vitamin A, beta-carotene, selenium, vitamin E, and vitamin C (scientific data is not entirely conclusive at this time; see section on Nutrition and Dietary Supplements)

If one is sexually active, a condom is said to reduce the risk of getting HPV, but the virus can still live on the skin surrounding the genitals not covered by the condom.

Cohen, O., Schejter, E., Agizim, R., Schonman, R., Chodick, G., Fishman, A. & Hershko Klement, A. 2019.

BACKGROUND: Postcoital bleeding (PCB) is a common gynecological symptom that may cause concern among both patients and physicians. Current literature is inconclusive regarding management recommendations.

OBJECTIVE: To identify risk-factors for dysplasia/cancer among patients presenting post-coital bleeding (PCB).

METHODS: Using large health maintenance organization (HMO) database, all women reporting PCB in 2012-2015 were identified. PCB patient records in a single colposcopy center were reviewed. Age, marital status, ethnicity, gravidity, parity, BMI, smoking, PAP smear result (within 1 year of PCB presentation), colposcopy and biopsy results were recorded. Cases were matched by age and socio-economic enumeration area to controls accessing primary care clinics for routine care.

RESULTS: Yearly incidence of PCB ranged from 400 to 900 per 100,000 women; highest among patients aged 26-30 years. Among the sample of 411 PCB cases with colposcopy, 201 (48.9%) had directed biopsy. Biopsy results included 68 cervicitis (33.8%), 61 koilocytosis/CIN 1/condyloma (30.3%), 44 normal tissue (21.9%), 25 cervical polyp (12.4%), 2 CIN 2/3 (1%) and 1 carcinoma (0.5%). Positive predictive value for koilocytosis/CIN 1 or higher pathology was 15.6% (64/411) and 0.7% for CIN 2 or higher grade pathology (3/411). In conditional logistic regression, multiparity was a protective factor: OR 0.39 (95% CI 0.22-0.88, P = 0.02), while pathological PAP smear was a related risk-factor: OR 3.3 (95% CI 1.31-8.35, P = 0.01). When compared to controls, PCB patients were significantly (P = 0.04) more likely to present CIN 1 or higher grade pathology (OR 1.82, 95% CI 1.02-3.33).

CONCLUSIONS: Study results indicate that PCB may require colposcopy, especially for nulliparous women with an abnormal PAP smear.

Classification of Cervical Dysplasia

ASC-US

This abbreviation stands for atypical squamous cells of undetermined significance. The word "squamous" describes the thin, flat cells that lie on the surface of the cervix. One of two choices are added at the end of ASC: ASC-US, which means undetermined significance, or ASC-H, which means cannot exclude HSIL (see below).

LSIL

This abbreviation stands for low-grade squamous intraepithelial lesion. This means changes characteristic of mild dysplasia are observed in the cervical cells.

HSIL

This abbreviation stands for high-grade squamous intraepithelial lesion. And refers to the fact that cells with a severe degree of dysplasia are seen.

CIN 1

Refers to the presence of dysplasia confined to the basal third of the cervical lining, or epithelium (formerly called mild dysplasia). This is considered to be a low-grade lesion.

CIN 2

Is considered to be a high-grade lesion. It refers to dysplastic cellular changes confined to the basal two-thirds of the lining tissue (formerly called moderate dysplasia).

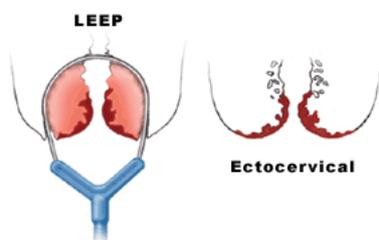
CIN 3

Is also a high grade lesion. It refers to precancerous changes in the cells encompassing greater than two-thirds of the cervical lining thickness, including full-thickness lesions that were formerly referred to as severe dysplasia and carcinoma in situ.

Treatment of Cervical Dysplasia

Treatment of Cervical Dysplasia may include:

Surgical Treatments - The two most common methods of removing cervical lesions are by procedures called a **LEEP** or **Cold Knife Cone**.



[Picture Credit: LEEP]

Cold Knife Conisation is performed in the operating room, using a scalpel. The patient will be sedated using anaesthesia. She will lie on a table and place her feet in stirrups to position the pelvis for

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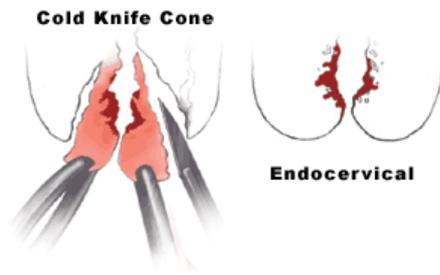
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examination. An instrument called a speculum will be inserted into the vagina to hold the vaginal walls open so the physician can view the inside of the vaginal walls and the cervix.



[Picture Credit: Cold Knife Cone]

Hysterectomy is the surgical removal of the uterus. Hysterectomy may be used if dysplasia recurs after any of the other treatment procedures.

Mutombo, A.B., Simoens, C., Tozin, R., Bogers, J., Van Geertruyden, J.P. & Jacquemyn, Y. 2019.

BACKGROUND: Cervical cancer is a major public health issue in the world, especially in developing countries. It can be prevented through vaccination against HPV (primary prevention) and through screening and treatment of cervical intraepithelial neoplasia (CIN) (secondary prevention). Surgical methods for treatment of CIN are linked to complications such as bleeding and adverse pregnancy outcomes. Furthermore, these methods are not generally available in resource-poor settings. Therefore, topical agents for local application on the cervix have been used since decades to overpass complications and limitations of the surgical methods.

AIMS: Review of the literature on the efficacy of commercially available biological agents used for topical treatment of cervical intraepithelial neoplasia (CIN).

METHODS: A systematic search through PubMed and the Cochrane database was performed up to December 2017, using the medical subheadings (MeSH) for topical agent, treatment, and cervical intraepithelial neoplasia. Appropriate inclusion/exclusion criteria have been used for the selection of eligible clinical studies. Clinical studies containing a minimum of 20 women, aged 18-50 with a diagnosis of CIN 1-3, and at least a 4 weeks follow-up after the end of the topical treatment were included.

RESULTS: The initial electronic database search resulted in a total of 849 articles. After screening titles and abstracts, 62 articles were selected as potential studies. Of these, six articles were included in the review after reading the full text: two were on 5-FluoroUracil, two on trans retinoic acid, one on Imiquimod, and one on Cidofovir. The reported regression/remission rates for CIN differed among studies. In CIN2 patients, the overall remission rate ranged between 43 and 93% for the active agents.

CONCLUSION: Among the topical agents studied, 5-FluoroUracil showed good remission rates above 80%. Varying results seen in this review is due to the differences in quality of the design between studies. Large-scale and less biased studies are needed to elucidate the true efficacy and safety of topical agents in the treatment of CIN.

Incidence of Cervical Cancer in South Africa

According to the outdated National Cancer Registry (2017), known for the under reporting of cancer statistics, the following number of cervical cancer cases was histologically diagnosed in South Africa during 2017:

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Group - Females 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	6 600	1:40	15,85%
Asian females	75	1:113	5,82%
Black females	5 641	1:33	30,29%
Coloured females	395	1:73	8,64%
White females	489	1:69	2,89%

The frequency of histologically diagnosed cases of cervical cancer in South Africa for 2017 was as follows (National Cancer Registry, 2017):

Group - Females 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	10	149	1 162	1 087	1 619	1 026	513	234
Asian females	0	2	13	19	22	15	3	1
Black females	9	129	985	1 609	1 355	895	445	214
Coloured females	1	9	72	108	115	51	32	7
White females	0	9	92	151	127	65	33	12

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

According to **Bruni, et al.**, (2019), the burden of cervical cancer for South Africa for 2018 is estimated as:

- Annual number of cervical cancer cases 12 983
- Annual number of cervical cancer deaths 5 595

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

Medical Disclaimer

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek

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Sources and References

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Bruni, L., Albero, G., Serrano, B., Mena, M., Gómez, D., Muñoz, J., Bosch, F.X. & de Sanjosé, S. 2019. ICO/IARC Information Centre on HPV and Cancer (*HPV Information Centre*). Human Papillomavirus and Related Diseases in South Africa. Summary Report 17 June 2019. [Date Accessed]

Cervical Dysplasia

http://www.medscape.org/viewarticle/508691_1

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<http://www.southbaytotalhealth.com/Cervical.htm>

Cohen, O., Schejter, E., Agizim, R., Schonman, R., Chodick, G., Fishman, A. & Hershko Klement, A. 2019. Postcoital bleeding is a predictor for cervical dysplasia. *PLoS One*. 2019 May 23;14(5):e0217396. doi: 10.1371/journal.pone.0217396. eCollection 2019.

Cold Knife Cone

https://www.hopkinsmedicine.org/kimmel_cancer_center/centers/cervical_dysplasia/diagnosis_and_treatment/treatment.html

Colposcope

<http://www.conceiveeasy.com/get-pregnant/can-a-colposcopy-interfere-with-my-fertility/>

Gilham, C., Sargent, A., Kitchener, H.C. & Peto, J. 2019. HPV testing compared with routine cytology in cervical screening: long-term follow-up of ARTISTIC RCT. *Health Technol Assess*. 2019 Jun;23(28):1-44. doi: 10.3310/hta23280.

Healthline

<http://www.healthline.com/health/cervical-dysplasia#RiskFactors3>

Health Communities

<http://www.healthcommunities.com/cervical-dysplasia/risk-factors.shtml>

Johns Hopkins Medicine

http://www.hopkinsmedicine.org/kimmel_cancer_center/centers/cervical_dysplasia/treatment.htm

LEEP

https://www.hopkinsmedicine.org/kimmel_cancer_center/centers/cervical_dysplasia/diagnosis_and_treatment/treatment.html

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Mayo Clinic

<http://www.mayoclinic.org/diseases-conditions/cervical-cancer/expert-answers/cervical-dysplasia/faq-20058142>

MedicineNet.com

http://www.medicinenet.com/cervical_dysplasia/page4.htm#how_is_cervical_dysplasia_classified

http://www.medicinenet.com/cervical_dysplasia/page7.htm

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National Cancer Institute

<http://www.cancer.gov/about-cancer/treatment/clinical-trials/what-are-trials>

University of Maryland Medical Center

<http://umm.edu/health/medical/altmed/condition/cervical-dysplasia>

WebMD

<http://www.webmd.com/cancer/cervical-cancer/cervical-dysplasia-symptoms-causes-treatments#1>

<http://www.webmd.com/cancer/cervical-cancer/cervical-dysplasia-symptoms-causes-treatments?page=2>

Wikipedia

<http://en.wikipedia.org/wiki/Colposcopy>

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