Cancer Association of South Africa (CANSA)

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Fact Sheet
on Clear-Cell
Adenosarcoma
of the Vagina

Introduction

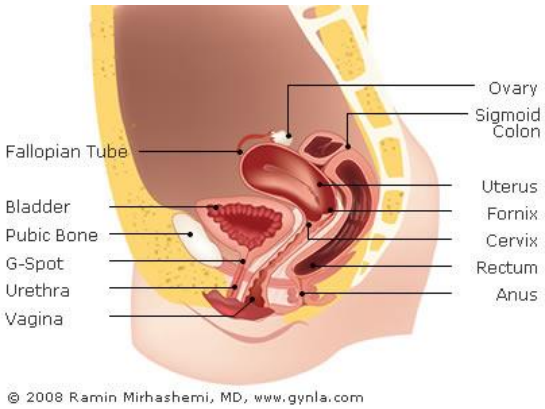
Clear-cell adenocarcinoma (CCA) of the vagina (or cervix) is a rare cancer often linked to the drug diethylstilbestrol (DES), which was prescribed in the mistaken belief that it prevented miscarriage and ensured a healthy pregnancy.

[Picture Credit: Diethylstilbestrol]

This synthetic oestrogen was given to millions of pregnant women, primarily from 1938-1971 but not limited to those years. Internationally, DES use continued until the early 1980s. DES was given if a woman had a previous miscarriage, diabetes, or a problem-pregnancy with bleeding, threatened miscarriage or premature labour. Up until the mid to late 1950s some women were given DES shots. After that, DES was primarily prescribed in pill form. DES also was included in some prenatal vitamins. In the late 1960s through 1971 a cluster of young women, from their teens into their twenties, was mysteriously diagnosed with CCA, a cancer not generally found in women until after menopause. (Wikipedia).

Clear-Cell Adenosarcoma (CCA) of the Vagina

Clear-Cell Adenosarcoma (CCA) of the vagina is one of the most common subtype of vaginal adenocarcinoma associated with diethystilbestrol (DES) exposure in young females. CCA of the vagina can also occur in postmenopausal women without exposure to DES. It is a rare vaginal cancer, accounting for 5% to 10% of primary vaginal malignancies (PathologyOutlines.com).



[Picture Credit: Female Anatomy]

The relative risk of CCA of the Vagina in DES

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

Daughters (the daughter of a woman who received diethylstilbestrol (DES) during pregnancy) is 40.7 compared to the general population. It is said that about 1 to 1.5 in 1 000 DES Daughters will develop clear cell adenocarcinoma of the vagina and/or cervix. The peak incidence of CCA in DES Daughters occurs in the late teens and early 20s. However, cases associated with in utero exposure to DES have been reported in women in their 30s and 40s. In the absence of DES exposure, CCA occurs in the postmenopausal years. Most women enrolled in studies of DES Daughters are only now entering menopause. Therefore, it is possible that there could be a higher risk of CCA among elderly DES Daughters.
(Center for Disease Control and Prevention).

Incidence of Clear-Cell Adenosarcoma of the Vagina
According to the National Cancer Registry (2012) the following number of cancer of the vagina cases was histologically diagnosed in South Africa during 2012:

Group - Females 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	162	1:1 281	0,43%
Asian females	4	1:1 628	0,37%
Black females	122	1:1 227	0,74%
Coloured females	15	1:1 371	0,36%
White females	21	1:1 517	0,13%

The frequency of histologically diagnosed cases of cancer of the vagina in South Africa for 2012 was as follows (National Cancer Registry, 2012):

Group - Females 2012	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	1	2	20	24	38	29	27	7
Asian females	0	0	1	0	0	1	1	1
Black females	0	2	19	26	29	16	22	3
Coloured females	1	0	0	5	3	3	2	1
White females	0	0	0	3	6	8	2	2

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.

Risk Factors for Clear-Cell Adenosarcoma of the Vagina
Age and being exposed to the drug DES (diethylstilbestrol) before birth affect a woman's risk of vaginal cancer.

Anything that increases one's risk of getting a disease is called a risk factor. Having a risk factor does not mean that one will get cancer; not having risk factors does not mean that one will not get cancer. Talk with a doctor if you think you may be at risk. Risk factors for vaginal cancer include the following:

- Being aged 60 or older.
- Being exposed to DES while in the mother's womb. In the 1950s, the drug DES was given to some pregnant women to prevent miscarriage (premature birth of a foetus that cannot survive). Women who were exposed to DES before birth have an increased risk of vaginal cancer. Some of these women develop a rare form of vaginal cancer called clear cell adenocarcinoma.
- Having human papilloma virus (HPV) infection.

- Having a history of abnormal cells in the cervix or cervical cancer.
- Having a history of abnormal cells in the uterus or cancer of the uterus.
- Having had a hysterectomy for health problems that affect the uterus.

(WebMD; NCBI).

Clinical Presentation of Clear-Cell Adenosarcoma of the Vagina

Vaginal carcinoma often presents as either an ulcerative or exophytic lesion, with the exophytic or fungating lesion being more common. The vaginal skin can be undermined by the growing cancer, producing thickening and rigidity of the vagina. This phenomenon is more commonly associated with clear-cell carcinoma. Early infiltration of the submucosa is a frequently observed feature, and local tissue reaction and induration tend to give the impression of significant extension, even in small tumours. More than half of vaginal carcinomas occur in the posterior wall of the upper third of the vagina. The second most common site is the anterior wall of the lower third of the vagina.

The prognosis is better for patients in whom the tumour occupies the upper third of the vagina, because the pattern of spread is similar to that of cervical carcinoma. Lower vaginal tumours have a tendency to spread by the pelvic and inguinal lymphatics, making management more complicated. The incidence of clinically positive nodes at initial diagnosis ranges from 5.3 to 20%, depending on the anatomic location of the lesion. Involvement of inguinal nodes is more common if the lesion involves the lower third of the vagina. Therefore, the site of the carcinoma and the disease stage must be considered to optimize patient management.

Abnormal vaginal bleeding is a presenting symptom in 50–75% of patients with primary vaginal tumours. It most commonly occurs as random bleeding or postcoital spotting; however, antepartum bleeding has been described. Vaginal discharge is frequent. Less common presenting symptoms are dysuria or pelvic pain.
(The Global Library of Women's Medicine).

Tests that Examine the Vagina and other Organs in the Pelvis are Used to Detect (find) and Diagnose Vaginal Cancer

The following tests and procedures may be used:

Physical examination and history: an examination of the body to check general signs of health, including checking for signs of disease, such as lumps or anything else that seems unusual. A history of the patient's health habits and past illnesses and treatments will also be taken.

Pelvic examination: an examination of the vagina, cervix, uterus, fallopian tubes, ovaries, and rectum. The doctor inserts one or two lubricated, gloved fingers of one hand into the vagina and places the other hand over the lower abdomen to feel the size, shape, and position of the uterus and ovaries. A speculum is also inserted into the vagina and the doctor looks at the vagina and cervix for signs of disease. A Pap test or Pap smear of the cervix is usually done. The doctor also inserts a lubricated, gloved finger into the rectum to feel for lumps or abnormal areas.

Pap smear: A procedure to collect cells from the surface of the cervix and vagina. A piece of cotton, a brush, or a small wooden stick is used to gently scrape cells from the cervix and

vagina. The cells are viewed under a microscope to find out if they are abnormal. This procedure is also called a Pap test.

Biopsy: The removal of cells or tissues from the vagina and cervix so they can be viewed under a microscope by a pathologist to check for signs of cancer. A biopsy may be done during a colposcopy.
Colposcopy: A procedure in which a colposcope (a lighted, magnifying instrument) is used to check the vagina and cervix for abnormal areas. Tissue samples may be taken using a curette (spoon-shaped instrument) and checked under a microscope for signs of disease.

FIGO Staging of Vaginal Cancer
The FIGO system of staging is mostly used in staging cancer of the vagina:

FIGO stage	**Disease extent**
O	Carcinoma *in situ*
I	Carcinoma limited to vaginal wall
II	Carcinoma extending into sub-vaginal tissues, not extending to pelvic wall
III	Extension to pelvic wall
IV	Extension beyond the true pelvis or involvement of the mucosa of bladder or rectum. Bullous oedema alone does not allow a case to be allocated as stage IV
IVa	Invasion of the bladder or rectal mucosa, or extension beyond the true pelvis
IVb	Distant spread

(Source: Beller U, Sideri M, Maisonneuve P et al. Carcinoma of the vagina, J Epidemiol Biostat 2001;6:141)

Treatment of Clear-Cell Adenosarcoma of the Vagina
Approximately 5% of primary vaginal malignancies are adenocarcinomas. Whenever this diagnosis is considered, it is necessary to rule out metastatic lesions from the bowel, uterus, or ovary. The most common variant is the clear-cell adenocarcinoma, which can occur spontaneously and in women with *in utero* exposure to DES. Primary non-DES-related adenocarcinoma of the vagina is rare and occurs predominately in postmenopausal women.

DES was used extensively in the late 1940s and early 1950s to maintain high-risk pregnancies, such as those in women with a past history of abortion, diabetes, or multiple gestation. Approximately 5% of all pregnant women in the United States during the late 1940s and early 1950s used DES. In 1953, Dieckmann and colleagues reported that DES offered no improvement in foetal outcome, and its use gradually decreased until it was discontinued by the Food and Drug Administration in 1971. In the same year, Herbst and associates reported seven young women (aged 15–22 years) who presented to Vincent

Memorial Hospital (Boston, MA, USA) between 1966 and 1969 with a diagnosis of clear-cell carcinoma or endometrioid-type adenocarcinoma with intrauterine exposure to DES. The Registry for Hormonal Transplacental Carcinogenesis and the Registry for Research on Hormonal Transplacental Carcinogenesis were established to correlate clinical and pathologic data on these unusual cancers.

Many DES-exposed women have unusual vaginal epithelial changes such as adenosis. Vaginal adenosis is a condition in which müllerian-type glandular epithelium is present after vaginal development is complete. It most commonly involves the anterior wall and upper third of the vagina, and the classical gross appearance is that of red, velvety, grape-like clusters. The process may involve the surface epithelium or glands in the superficial stroma. Microscopically, the glandular epithelium can be composed of any of the müllerian epithelial cell types, but cervical-type mucus cells are most common. The glands within the lamina propria may be lined by tuboendometrial-type epithelium, which exists in approximately 25% of cases and is more common in the lower vagina. Robboy and associates suggested that atypical vaginal adenosis and atypical cervical ectropion of the tuboendometrial type are precursors of adenocarcinoma.

Most DES-associated tumours have occurred in women between 17 and 21 years (median age 19 years). Clear-cell carcinoma develops in 0.1% of exposed women. The DES-associated clear-cell cervical adenocarcinomas have a predilection for the ectocervix. Most vaginal carcinomas arise on the anterior wall, usually in the upper third, corresponding to the most common site of adenosis. The tumours vary greatly in size (range 1–30 cm). Most of the tumours are exophytic and superficially invasive. The larger tumours are polypoid and nodular, and the smaller tumours appear flat or ulcerated with a granular or indurated surface. Small tumours can be easily missed on colposcopic examination if confined to the lamina propria and if covered by intact, normal epithelium. These small tumours are usually asymptomatic and are detected only by palpation and directed biopsies as part of a thorough examination for a DES-exposed patient. Microscopically, they exhibit three basic histologic patterns: tubulocystic (most common); papillary; and solid. The tumour cells are cuboidal or columnar with clear cytoplasm and a distinct cell membrane, or they are the hobnail-type with large, atypical, protruding nuclei rimmed by a small amount of cytoplasm. Glycogen is also found to be abundant.

Treatment can involve surgical intervention and radiation therapy. For stage I clear-cell adenocarcinoma in the typical young patient, surgery may be considered to preserve ovarian function. Surgery for vaginal clear-cell adenocarcinoma requires a radical hysterectomy and vaginectomy with reconstruction. The vaginectomy is performed only to the level required to obtain an adequate margin. Local excision appears inferior to radical surgery. The role of chemotherapy has not been determined.

The overall recurrence rate for clear-cell carcinoma approaches 21%, with the lungs, supraclavicular lymph nodes, and pelvis being the most common areas. Such cancers appear to have recurrence patterns different from those of squamous cell carcinomas, with a greater tendency to develop metastases in these distant sites. Although most recur within 3 years, late relapse of more than 19 years has been reported. Recurrent disease can be treated with radiation, surgery, or chemotherapy if widely metastatic. For central recurrences after surgery, pelvic radiation with external and interstitial therapy has been used. Pelvic exenteration appears to be more successful for patients with clear-cell carcinoma than for those with squamous cell carcinoma.
(The Global Library of Women's Medicine).

About Clinical Trials
Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials
Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer.

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted
Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.
Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different “phase” in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or “trial arms”: (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers

can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

Use of Placebos

The use of placebos as comparison or “control” interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.

- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

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