

Cancer Association of South Africa (CANSA)



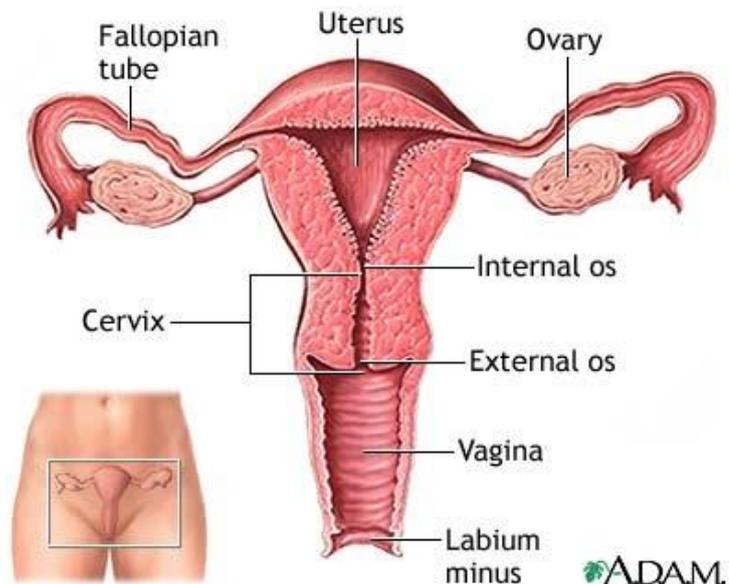
Fact Sheet on Cancer of the Uterus

Introduction

The uterus or womb is part of the female reproductive system.

[Picture Credit: Uterus]

In humans one end of the cervix opens into the vagina, while the other is connected to both fallopian tubes. During pregnancy, the foetus develops completely within the uterus. In English, the term *uterus* is used consistently within the medical and related professions, while the Germanic-derived term *womb* is more common in everyday usage.



Cancer of the Uterus

Cancer of the uterus will refer to endometrial cancer or uterine cancer unless indicated otherwise. Endometrial cancer is a disease in which malignant (cancer) cells form in the tissues of the endometrium, the lining inside the uterus. Cancer of the endometrium is different from cancer of the muscle of the uterus, which is called sarcoma of the uterus.

Cancer is a disease in which cells in the body grow and multiply out of control. Cancer is always named for the part of the body where it starts, even if it spreads to other body parts later. When cancer starts in the uterus, it is called uterine cancer or cancer of the uterus. When uterine cancer is found early, treatment is most effective.

Incidence of Cancer of the Uterus in South Africa

According to the outdated National Cancer Registry (2014) with its known under-reporting, the following number of cancer of the uterus cases was histologically diagnosed in South Africa during 2014:

Group - Females 2014	No of Cases	Lifetime Risk	Percentage of All Cancers
All females	1 256	1:195	3,32%
Asian females	88	1:69	7,43%
Black females	731	1:165	4,54%
Coloured females	118	1:127	2,89%
White females	319	1:114	1,94%

The frequency of histologically diagnosed cases of cancer of the uterus in South Africa for 2014 was as follows (National Cancer Registry, 2014):

Group - Females 2014	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	21	79	244	474	308	91
Asian females	0	0	1	8	27	33	15	2
Black females	1	2	10	42	113	275	192	55
Coloured females	0	0	3	3	24	54	25	8
White females	0	0	7	24	76	110	70	26

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.

The most common type of uterine cancer is endometrial cancer which is the 6th most common cancer in women worldwide and the 14th most common cancer among women overall.

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

- Annual number of cancer of the uterus cases 1 983
- Annual number of uterine cancer deaths 549

Causes and Risk Factors of Cancer of the Uterus

Although the exact cause of endometrial cancer is unknown, increased levels of oestrogen appear to play a role. Oestrogen helps stimulate the build-up of the lining of the uterus. Studies have shown that high levels of oestrogen result in excessive endometrial growth and cancer.

Most cases of endometrial cancer occur between the ages of 60 and 70 years, but a few cases may occur before age 40.

The following may increase the risk of endometrial cancer:

- diabetes
- oestrogen replacement therapy without the use of progesterone
- history of endometrial polyps

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- infertility (inability to become pregnant)
- infrequent periods
- Tamoxifen, a drug used for breast cancer treatment
- never being pregnant
- obesity
- polycystic ovarian syndrome (PCOS)
- starting menstruation at an early age (before age 12)
- starting menopause after age 50
- Women who have had radiation to her pelvic area.
- Women with a family history of uterine cancer.
- White women are at higher risk than other ethnic groups.
- Women with diabetes have an increased risk of uterine cancer, which is often associated with obesity .

Saso, S, Liouis, L.S., Doctor, F., Hamen, A.H., Chatterjee, J., Yazbek, J., Bora, S., Abdalla, H., Ghaem-Maghami, S. & Thum, M.Y. 2015.

An ongoing debate over the last two decades has focused on whether fertility treatment in women may lead to an increased risk of developing uterine cancer over a period of time. Uterine cancer (including mainly endometrial carcinoma and the less common uterine sarcoma) is the commonest reproductive tract cancer and the fourth commonest cancer in women. The risk for the development of uterine and in particular endometrial cancer posed by infertility and an unopposed oestrogen state is widely recognised. The present analysis aimed to perceive whether standard fertility drugs were also a risk to future uterine cancer development. The treatment does increase the concentrations of unopposed oestrogen for a short periods of time but if successful leads to fertility. This meta-analysis points to a non-deleterious effect of fertility drugs towards the development of uterine cancer, a conclusion strongly supported by our sub-group analysis.”

Torres, D., Myers, J.A., Eshraghi, L.W., Riley, E.D., Soliman, P.T. & Milam, M.R. 2015.

“This study compares breast cancer survivors without a secondary diagnosis of uterine cancer (BC) to breast cancer survivors with a diagnosis of uterine cancer (BUC) to determine clinical characteristics that increase the odds of developing uterine cancer. Hypertension, gallbladder disease, and thyroid disease in breast cancer survivors increase the odds of developing uterine cancer. Breast cancer survivors also express significant interest in potential serum tests to assess the risk of developing uterine cancer.”

Lee, Y..C., Milne, R.L., Lheureux, S., Friedlander, M., McLachlan, S.A., Martin, K.L., Bernardini, M.Q., Smith, C., Picken, S., Nesci, S., Hopper, J.L., Phillips, K.A. & Kathleen Cuninghame Foundation Consortium for Research into Familial Breast Cancer kConFab). 2017.

BACKGROUND: Whether BRCA1 and BRCA2 mutation carriers have a clinically relevant elevated risk of uterine cancer has implications for risk-reducing surgery.

AIM: This multicentre, prospective cohort study assessed uterine cancer risk for mutation carriers compared with the general population.

METHODS: Eligible mutation carriers were enrolled in the Kathleen Cuninghame Foundation Consortium for Research into Familial Breast Cancer (kConFab) cohort study, had a uterus present and no history of uterine cancer at cohort entry. Epidemiological, lifestyle and clinical data were collected at cohort entry and updated three-yearly. Cancer events were verified using pathology reports. Follow-up was censored at death or last contact. Relative risk of uterine cancer was estimated using the standardised incidence ratio (SIR), with the expected number of cases determined using population-based data for Australia.

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RESULTS: Of 1,111 mutation carriers in kConFab, 283 were excluded due to prior hysterectomy (N = 278), prior uterine cancer (N = 2) or being non-residents (N = 3). After a median follow-up of 9.0 years, five incident uterine cancers were reported in the 828 eligible women (419 had prior breast cancer and 160 had prior tamoxifen use), compared to 2.04 expected (SIR = 2.45; 95% confidence interval [CI]: 0.80-5.72; P = 0.11). In 438 BRCA1 mutation carriers and 390 BRCA2 mutation carriers, three and two incident cases of uterine cancer were reported, respectively, compared to 1.04 expected (SIR = 2.87; 95% CI: 0.59-8.43; P = 0.18) and 0.99 expected (SIR = 2.01; 95% CI: 0.24-7.30; P = 0.52), respectively. All cases were endometrioid subtype, International Federation of Gynaecology and Obstetrics stage I-II disease. No serous uterine cancers were reported.

CONCLUSIONS: Our findings are consistent with those from most other reports and do not support routine risk-reducing hysterectomy for BRCA1 and BRCA2 mutation carriers.

Caution Expressed Around Consumption of Foods High in Phytoestrogens by Individuals Diagnosed with a Hormone-Sensitive Cancer

The Cancer Association of South Africa (CANSA) has noted:

- A statement by Memorial Sloan Kettering Cancer Center saying that "... because compounds isolated from rooibos leaves demonstrated estrogenic activity, patients with hormone-sensitive cancers should use caution before taking rooibos." (Memorial Sloan Kettering Cancer Center).
- That phytoestrogens were successfully isolated from rooibos leaves by scientists from the School of Pharmaceutical Sciences, University of Shizuoka, Japan (Shimamura, *et al.*, 2006).
- That according to Deng, et al., (2010), "... there are important safety concerns associated with dietary supplements and foods rich in phytoestrogens, especially for breast cancer patients with hormone-sensitive disease. Based on current evidence, we propose recommendations for advising breast cancer patients, ..."
- That, according to Nelles, Hu & Prins (2011), "Early work on the hormonal basis of prostate cancer focused on the role of androgens, but more recently estrogens have been implicated as potential agents in the development and progression of prostate cancer."
- That, according to Reger, *et al.*, (2016), "Experimental studies suggest that phytoestrogen intake alters cancer and cardiovascular risk. Some urinary phytoestrogens were associated with cardiovascular and all-cause mortality in a representative sample of 5 179 participants. This is one of the first studies that used urinary phytoestrogens as biomarkers of their dietary intake to evaluate the effect of these bioactive compounds on the risk of death from cancer and cardiovascular disease."

CANSA, therefore, wishes to advise individuals diagnosed with the following hormone-sensitive cancers, namely: Breast Cancer, Ovarian Cancer, Endometrial Cancer, and Prostate Cancer, to:

- use caution before taking Rooibos tea and to discuss the issue around Rooibos tea consumption with their treating Oncologist prior to consuming Rooibos tea

- also use caution before taking the following high phytoestrogen-containing foods: all soy foods (including soybeans, tofu, miso, and tempeh); legumes (especially lentils, peanuts and chickpeas) and flaxseed-containing foods. Patients are advised to discuss consumption of the listed high phytoestrogen-containing foods with their treating Oncologist prior to consuming them.

Research on Foods High in Phytoestrogens and Breast Cancer

Deng, G., Davatgarzadeh, A., Yeung, S. & Cassileth, B. 2010. Phytoestrogens: science, evidence, and advice for breast cancer patients. *Soc Integr Oncol.* 2010 Winter;8(1):20-30.

“There are important safety concerns associated with dietary supplements and foods rich in phytoestrogens, especially for breast cancer patients with hormone-sensitive disease. However, no consensus has been reached concerning specific dietary items that should be avoided, and safe levels of potentially problematic foods have yet to be determined. Excellent qualitative reviews of phytoestrogens and breast cancer have been published. These list agents that contain phytoestrogens and offer general cautions. Quantitative reviews, however, are needed but not yet available. Here we review quantitative data on phytoestrogens, their interaction with estrogen receptors, their bioavailability and pharmacokinetics, and their effects on breast cancer cells and animal models. We also note foods and botanicals with substances that interact with estrogen receptors and discuss the phytoestrogens they contain. Based on current evidence, we propose recommendations for advising breast cancer patients, which may also serve as a basis for the development of clinical practice guidelines.”

Shimamura, N., Miyase, T., Umehara, K., Warashina, T. & Fuji, S. 2006. Phytoestrogens from *Aspalathus linearis*. *Biol Pharm Bull.* 2006 Jun;29(6):1271-4.

“From the leaves of *Aspalathus linearis*, 24 known compounds and a new one, aspalalinin (25), were isolated. The structures of the compounds were determined mainly based on spectral evidence. The absolute configuration of aspalalinin was presented on the basis of X-ray analysis. Each isolate was assessed for its estrogenic activity by an estrogen ELISA assay. Compounds 12, 15, and 24 showed the estrogenic activity.”

Patisaul, H. & Jefferson, W. 2010. The pros and cons of phytoestrogens. *Front Neuroendocrinol.* Author manuscript; available in PMC 2011 Apr 12.

Phytoestrogens are plant derived compounds found in a wide variety of foods, most notably soy. A litany of health benefits including a lowered risk of osteoporosis, heart disease, breast cancer, and menopausal symptoms, are frequently attributed to phytoestrogens but many are also considered endocrine disruptors, indicating that they have the potential to cause adverse health effects as well. Consequently, the question of whether or not phytoestrogens are beneficial or harmful to human health remains unresolved. The answer is likely complex and may depend on age, health status, and even the presence or absence of specific gut microflora. Clarity on this issue is needed because global consumption is rapidly increasing. Phytoestrogens are present in numerous dietary supplements and widely marketed as a natural alternative to estrogen replacement therapy. Soy infant formula now constitutes up to a third of the US market, and soy protein is now added to many processed foods. As weak estrogen agonists/antagonists with molecular and cellular properties similar to synthetic endocrine disruptors such as Bisphenol A (BPA), the phytoestrogens provide a useful model to comprehensively investigate the biological impact of endocrine disruptors in

general. This review weighs the evidence for and against the purported health benefits and adverse effects of phytoestrogens.

Rodriguez-Garcia, C., Sánchez-Quesada, C., Toledo, E., Delgado-Rodriguez, M. & Gaforio, J.J. 2019. "Dietary guidelines universally advise adherence to plant-based diets. Plant-based foods confer considerable health benefits, partly attributable to their abundant micronutrient (e.g., polyphenol) content. Interest in polyphenols is largely focused on the contribution of their antioxidant activity to the prevention of various disorders, including cardiovascular disease and cancer. Polyphenols are classified into groups, such as stilbenes, flavonoids, phenolic acids, lignans and others. Lignans, which possess a steroid-like chemical structure and are defined as phytoestrogens, are of particular interest to researchers. Traditionally, health benefits attributed to lignans have included a lowered risk of heart disease, menopausal symptoms, osteoporosis and breast cancer. However, the intake of naturally lignan-rich foods varies with the type of diet. Consequently, based on the latest humans' findings and gathered information on lignan-rich foods collected from Phenol Explorer database this review focuses on the potential health benefits attributable to the consumption of different diets containing naturally lignan-rich foods. Current evidence highlight the bioactive properties of lignans as human health-promoting molecules. Thus, dietary intake of lignan-rich foods could be a useful way to bolster the prevention of chronic illness, such as certain types of cancers and cardiovascular disease."

Lowering the Risk of Cancer of the Uterus

Different factors contribute to different types of cancer. Researchers continue to investigate what factors increase risk for uterine cancer, including ways to reduce the risk. Although there is no proven way to completely prevent uterine cancer, one may be able to lower one's risk.

Research has shown that certain factors can lower the risk of uterine cancer:

- Taking birth control pills. Birth control pills have a combination of oestrogen and progesterone that are taken cyclically to produce a monthly menstrual period, which reduces the risk of an overgrowth of the uterine lining, especially when taken over a long period of time.
- Using a progestin-secreting intrauterine device (IUD), which is a form of birth control.
- Considering the risk of uterine cancer before starting hormone replacement therapy (HRT), especially oestrogen replacement therapy alone. Using a combination of oestrogen and progesterone for HRT may help lower risk.
- Maintaining a healthy weight.

Signs and Symptoms of Cancer of the Uterus

Endometrial Cancer may cause abnormal vaginal discharge or bleeding. Abnormal bleeding is mostly associated with high volumes or when it happens, such as after someone has gone through menopause, between periods, or any other bleeding that is longer or heavier than is normal. It may also cause other symptoms, such as pain or a feeling of pressure in the pelvis.

Gynaecological Cancer Symptoms					
Symptoms	Cervical Cancer	Ovarian Cancer	Uterine Cancer	Vaginal Cancer	Vulvar Cancer
Abnormal vaginal bleeding or discharge	♦	♦	♦	♦	
Pelvic pain or pressure		♦	♦		♦
Abdominal or back pain		♦			
Bloating		♦			
Changes in bathroom habits		♦		♦	
Itching or burning of the vulva					♦
Changes in vulva colour or skin, such as a rash, sores, or warts					♦

Diagnosis of Cancer of the Uterus

If a doctor suspects that someone may have cancer of the uterus, he/she will most probably do a biopsy. The doctor will decide the best way to do the biopsy. Methods include:

Endometrial biopsy: A thin, flexible tube is inserted through the cervix and into the uterus. Using suction, a small amount of tissue is removed through the tube.

Dilation and curettage (D&C): If an endometrial biopsy does not provide enough tissue or if a uterine cancer diagnosis is not definite, a D&C may be done. The cervix is dilated (enlarged) with a series of increasingly larger metal rods. A tool called a curette then is used to take cells from the uterus lining.

Hysteroscopy: A thin, telescope-like device with a light (hysteroscope) is put into the uterus through the vagina. The doctor then looks at the uterus and the openings to the fallopian tubes. Small pieces of tissue can be removed. Hysteroscopy may be done with a D&C.

One or more of the following tests may be used to find out if you have uterine cancer and if it has spread. These tests also may be used to find out if treatment is working.

Surgery, which may include:

- hysterectomy: removal of the uterus
- bilateral salpingo-oophorectomy: removal of the uterus, ovaries and Fallopian tubes
- lymph node dissection: removal of lymph nodes in the pelvis and lower abdomen

Imaging tests, which may include:

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- ultrasound
- computed axial tomography scans (CT or CAT)
- magnetic resonance imaging scans (MRI)
- positron emission tomography scans (PET)
- chest X-ray
- transvaginal ultrasound examination

Blood tests, which may include:

- complete blood count (CBC) – also known as full blood count (FBC)
- CA 125: Uterine cancers sometimes release this substance into the blood.

CA 125 test measures levels of CA 125. High levels of CA 125 may indicate that the cancer has spread beyond the uterus or come back after treatment (MD Anderson Cancer Centre; National Cancer Institute).

Recurrent Uterine Cancer

Recurrent cancer is cancer that comes back after treatment. Uterine cancer may come back in the uterus, pelvis, lymph nodes of the abdomen, or another part of the body. Approximately 70% of recurrent uterine cancer happens within three years of initial treatment. Some symptoms of recurrent cancer are similar to those experienced when the disease was first diagnosed:

- vaginal bleeding or discharge
- pain in the pelvic area, abdomen, or back of the legs
- difficulty or pain when urinating
- weight loss
- chronic cough

Should the cancer of the uterus spread to other parts of the body, it will most probably spread as indicated below:

Cancer Type:	Main Sites of Metastasis (Spread)
Bladder	Bone, liver, lung
Breast	Bone, brain, liver, lung
Ovary	Liver, lung, peritoneum (lining of abdomen)
Pancreas	Liver lung, peritoneum (lining of abdomen)
Uterus	Bones, liver, lung, peritoneum (lining of abdomen), vagina

Treatment of Cancer of the Uterus

Uterine cancer is usually treated by one or a combination of treatments:

Surgery - surgery refers the removal of the tumour and surrounding tissue during an operation. It is typically the first treatment used for uterine cancer. A surgical oncologist is a doctor who specialises in treating cancer using surgery.

Radiation therapy - radiation therapy is the use of high-energy x-rays or other particles to kill cancer cells. A doctor who specializes in giving radiation therapy to treat cancer is called a radiation oncologist. A radiation therapy regimen (schedule) usually consists of a specific number of treatments given over a set period of time. The most common type of radiation treatment is called external-beam radiation therapy, which is radiation given from a machine outside the body.

Onstad, M., Ducie, J., Fellman, B.M., Abu-Rustum, N.R., Leitao, M., Mariani, A., Multinu, F., Lu, K.H. & Soliman, P. 2020.

BACKGROUND: Patients with grade 3, deeply invasive endometrioid adenocarcinoma are typically managed with primary surgery. The role and type of adjuvant therapy used is controversial. We sought to evaluate the role of adjuvant radiation and/or chemotherapy in women with deeply invasive grade 3 endometrioid tumors.

METHODS: A multi-center retrospective chart review was performed at three large medical institutions in the United States. Patients with grade 3 endometrioid adenocarcinoma invading >50% of the myometrium were included. Medical records were queried to evaluate whether lymph node assessment was performed, the status of the lymph nodes, adjuvant treatment strategy used, and dates of death or recurrence.

RESULTS: Between 1984 and 2013, 257 patients were identified with a median follow-up of 3.08 years. Most patients (84.7%) had evaluation of pelvic and/or para-aortic lymph nodes and 43% had positive lymph nodes. For node negative patients, there was no difference in overall survival (OS) between those who received adjuvant pelvic radiation +/- vaginal brachytherapy (n=52) vs brachytherapy alone (n=46) (5-year probabilities were 0.73 vs 0.70, P=0.729). Among patients with positive lymph nodes (n=92), the adjuvant treatment strategy utilized impacted OS, with women undergoing a combination of chemotherapy and external beam radiation having the best outcomes (P=0.003).

CONCLUSIONS: Among women with grade 3, deeply invasive endometrioid adenocarcinoma, vaginal cuff brachytherapy alone resulted in similar survival when compared with pelvic radiation in node negative patients. The combination of chemotherapy with external beam radiation was associated with improved OS for women with positive nodes.

Hata, M., Koike, I., Miyagi, E., Numazaki, R., Asai-Sato, M., Kaizu, H., Mukai, Y., Takano, S., Ito, E., Sugiura, M. & Inoue, T. 2017.

“The purpose of the research was to evaluate the safety and efficacy of radiation therapy for stage IVA uterine cervical cancer and to identify an optimal radiation regimen. Radiation therapy is safe and effective for treatment of stage IVA uterine cervical cancer. The reduced radiation dose per fraction may contribute to the prevention of vesicovaginal fistula formation.”

Brachytherapy (a form of radiation therapy where radioactive seeds are inserted) - for women with surgically staged 1A or 1B endometrial adenocarcinoma, use of vaginal brachytherapy (VB) is associated with a reduction in mortality.

Chemotherapy - chemotherapy is the use of drugs to kill cancer cells, usually by stopping the cancer cells' ability to grow and divide. Systemic chemotherapy is delivered through the bloodstream to

reach cancer cells throughout the body. Chemotherapy is given by a medical oncologist, a doctor who specializes in treating cancer with medication.

Hormone therapy - hormone therapy is used to slow the growth of uterine cancer cells. Hormone therapy for uterine cancer involves the sex hormone progesterone, given in a pill form.

Palliative/supportive care - cancer and its treatment often cause side effects. In addition to treatment to slow, stop, or eliminate the cancer, an important part of cancer care is relieving a person's symptoms and side effects. This approach is called palliative or supportive care, and it includes supporting the patient with his or her physical, emotional, and social needs.

Recurrent uterine cancer - remission is when cancer cannot be detected in the body and there are no symptoms. This may also be called 'no evidence of disease' or NED.

Metastatic Uterine Cancer

If cancer has spread to another location in the body, it is called metastatic cancer. Patients with this diagnosis are encouraged to talk with doctors who are experienced in treating this stage of cancer, as there may be different opinions regarding the best treatment plan.

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 appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

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Centers for Disease Control and Prevention

<http://www.cdc.gov/cancer/uterine/>
http://www.cdc.gov/cancer/uterine/basic_info/symptoms.htm

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Mayo Clinic

<http://www.mayoclinic.com/health/endometrial-cancer/DS00306/DSECTION=causes>

MD Anderson Cancer Centre

<http://www.mdanderson.org/patient-and-cancer-information/cancer-information/cancer-types/uterine-cancer/diagnosis/index.html>

National Cancer Institute

<http://www.cancer.gov/cancertopics/pdq/treatment/endometrial/Patient/page1>
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Uterus

<http://www.bing.com/images/search?q=images+uterus+and+ovaries&view=detail&id=2DE688CAF70A48679EDB8C3C4649DE0318FC6753&qpv=images+uterus+and+ovaries&FORM=IDFRIR>

World Cancer Research Fund

<https://www.wcrf.org/dietandcancer/cancer-trends/endometrial-cancer-statistics>