

# Cancer Association of South Africa (CANSA)



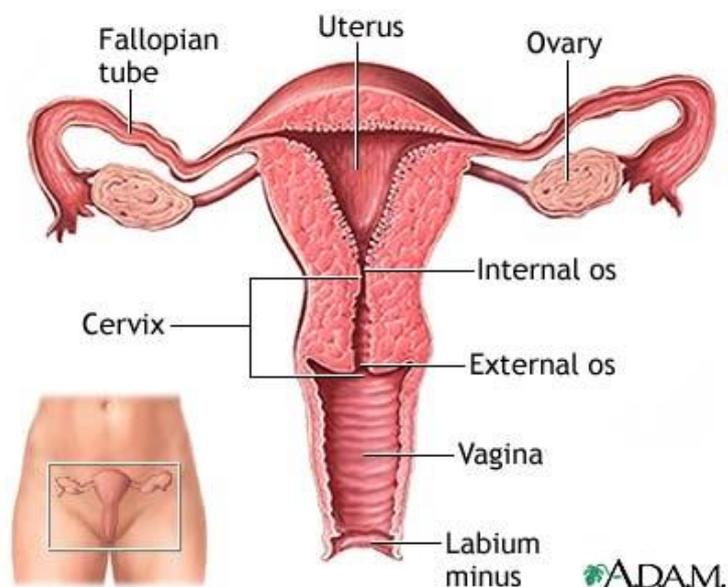
## Fact Sheet on Cancer of the Uterus

### 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.

### Tumour Grade and Tumour Stage

Tumour grade and stage are terms used to describe the severity of a tumour, while tumour grade describes the appearance of cancerous cells in the tissue by examining them under a microscope.

Tumour stage encompasses:

- The location of the tumour.
- The size and/or extent of the original tumour.
- Whether cancer cells have spread to lymph nodes or anywhere else in the body.
- The number of tumours present.

Doctors use tumour grade, cancer stage, and a patient's age and general health to decide the course of treatment for the patient and determine prognosis. Prognosis describes all factors including the disease course, cure rate, chances of survival, and risk of recurrence of cancer.

#### What are the cancer stages?

Different systems of cancer staging are used to describe the types of cancer. Below is a common method in which stages are ranged from 0 to IV.

- Stage 0: The tumour is confined to its place of origin (in situ) and has not spread to nearby tissue.
- Stage I: The tumour is located only in the original organ, is small, and has not spread.
- Stage II: The size of the tumour is large but has not spread.
- Stage III: The tumour has become larger and may have spread to surrounding tissues and/or lymph nodes.
- Stage IV: The tumour has spread to other distant organs of the body, which is known as the metastasis stage.

#### TNM staging

Another common staging method used for cancer is the TNM system, which stands for tumour, node (which means spread of the tumour to lymph nodes), and metastasis. When a patient's cancer is staged using the TNM system, a number will be present along with the letter. This number signifies the extent of the disease in each category - tumour, node, and metastases.

Another system of cancer staging divides cancer into five stages, which include:

- In situ: Abnormal cells are present but have not spread to nearby tissue.
- Localized: Cancer is located only in the original organ and shows no sign of its spread.
- Regional: Cancer has spread to nearby lymph nodes, tissues, or organs.
- Distant: Cancer has spread to distant parts of the body.
- Unknown: The stage cannot be figured out due to a lack of enough information.

#### What are the cancer grades?

Cancer grades are based on examination of the suspected tissue sample under a microscope. This involves surgically removing a piece of the suspected cancerous tissue and sending it to the lab for analysis. The entire procedure is known as a biopsy.

A doctor who specializes in diagnostic tests (pathologist) examines the cells of the tissue and determines whether they are harmless (benign or noncancerous) or harmful (malignant or cancerous). They describe the microscopic appearance of the cells and assign a numerical "grade" to most cancers.

Generally, a lower grade indicates slow-growing cancer and a higher grade indicates fast-growing cancer.

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The most commonly used grading system is as follows:

- Grade I: Cancer cells that look like normal cells but are not growing rapidly.
- Grade II: Cancer cells that don't look like normal cells with their growth being faster than normal cells.
- Grade III: Cancer cells that look abnormal and have the potential to grow rapidly or spread more aggressively.

Sometimes, the following system can be used:

- GX: Grade cannot be assessed (undetermined grade)
- G1: Well-differentiated (low grade)
- G2: Moderately differentiated (intermediate grade)
- G3: Poorly differentiated (high grade)
- G4: Undifferentiated (high grade)

### Incidence of Cancer of the Uterus in South Africa

According to the outdated National Cancer Registry (2017) with its known under-reporting, the following number of cases of cancer of the uterus was histologically diagnosed in South Africa during 2017:

Group - Females 2017	No of Cases	Lifetime Risk	Percentage of All Cancers
All females	1 570	1:128	3,77%
Asian females	87	1:83	6,68%
Black females	958	1:137	5,12%
Coloured females	159	1:133	3,50%
White females	366	1:100	2,13%

The frequency of histologically diagnosed cases of cancer of the uterus 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	2	4	27	110	301	542	448	136
Asian females	0	0	3	12	26	30	14	2
Black females	2	4	15	48	282	343	288	93
Coloured females	0	0	3	19	33	56	39	9
White females	0	0	6	31	79	110	107	32

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 6<sup>th</sup> most common cancer in women worldwide and the 14<sup>th</sup> 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
- 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 .

**Nasioudis, D., Wilson, E., Mastroyannis, S.A., Sisti, G., Haggerty, A.F., Ko, E.M. & Latif, N.A.** 2019.

**Background/aim:** We evaluated the incidence of uterine and breast cancer among women diagnosed with granulosa cell tumors (GCTs) of the ovary.

**Patients and methods:** The US Surveillance, Epidemiology, and End Results (SEER) database was accessed and patients diagnosed with a GCT and had a known follow-up between 1973-2014 were identified. Personal tumor history was extracted and patients with a previous or subsequent malignant breast or uterine tumor were identified. The expected incidence of breast and uterine cancer was calculated based on the U.S age-specific rate of breast and uterine cancer per 100,000 women. Standardized incidence ratio (SIR) with 95% confidence intervals (95% CI) were calculated for each tumor.

**Results:** A total of 1908 cases of GCT were identified. Seventy- nine (4.14%) and 53 (2.78%) patients were diagnosed with a malignant breast and uterine malignancy. The cumulative expected number of malignant breast and uterine tumors was 27 (1.41%) and 6 (0.31%), respectively. The calculated SIR for breast and uterine malignancies was 2.96 (95%CI=2.34, 3.68) and 8.83 (95%CI=6.61, 11.56), respectively.

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**Conclusion:** An increased incidence of breast and uterine malignancies among patients diagnosed with GCTs was observed.

**Clarke, M.A., Devesa, S.S., Harvy, S.V. & Wentzensen, N. 2019.**

**Purpose:** Uterine corpus cancer incidence rates have been projected to increase, a prediction often attributed to the obesity epidemic. However, correct estimation of these rates requires accounting for hysterectomy prevalence, which varies by race, ethnicity, and region. Here, we evaluated recent trends in hysterectomy-corrected rates by race and ethnicity and histologic subtype and estimated differences in relative survival by race and ethnicity, subtype, and stage.

**Methods:** We estimated hysterectomy prevalence from the Behavioral Risk Factor Surveillance System. Hysterectomy-corrected age-standardized uterine corpus cancer incidence rates from 2000 to 2015 were calculated from the SEER 18 registries. Incidence rates and trends were estimated separately by race and ethnicity, region, and histologic subtype. Five-year relative survival rates were estimated by race and ethnicity, histologic subtype, and stage.

**Results:** Hysterectomy-corrected incidence rates of uterine corpus cancer were similar among non-Hispanic whites and blacks and lower among Hispanics and Asians/Pacific Islanders. Endometrioid carcinoma rates were highest in non-Hispanic whites, whereas nonendometrioid carcinoma and sarcoma rates were highest in non-Hispanic blacks. Hysterectomy-corrected uterine corpus cancer incidence increased among non-Hispanic whites from 2003 to 2015 and among non-Hispanic blacks, Hispanics, and Asians/Pacific Islanders from 2000 to 2015. Overall incidence rates among non-Hispanic blacks surpassed those of non-Hispanic whites in 2007. Endometrioid carcinoma rates rose among non-Hispanic blacks, Hispanics, and Asians/Pacific Islanders but were stable among non-Hispanic whites; however, nonendometrioid carcinoma rates rose significantly among all women. Non-Hispanic blacks had the lowest survival rates, irrespective of stage at diagnosis or histologic subtype.

**Conclusion:** Among all women, rates of nonendometrioid subtypes have been rising rapidly. Our analysis shows profound racial differences and disparities indicated by higher rates of nonendometrioid subtypes and poorer survival among non-Hispanic black women.

**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.

**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,

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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.

<b>Gynaecological Cancer Symptoms</b>					
<b>Symptoms</b>	<b>Cervical Cancer</b>	<b>Ovarian Cancer</b>	<b>Uterine Cancer</b>	<b>Vaginal Cancer</b>	<b>Vulvar Cancer</b>
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:

- 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).

**Son, J., Carr, C., Yao, M., Radeva, M., Priyadarshini, A., Marquard, J., Michener, C.M. & AlHilli, M. 2020.**

**Objective:** Endometrial cancer in pre-menopausal patients aged  $\leq 40$  years is rare and poses both diagnostic and management challenges. The goal of this study was to investigate the clinical and pathologic factors associated with endometrial cancer in this group and their impact on survival.

**Methods:** Patients with endometrial cancer treated between January 2004 and August 2016 were retrospectively reviewed. Patients who underwent either primary surgical treatment or fertility-sparing therapy were included. Exclusion criteria were age  $>60$  years and patients who received neoadjuvant chemotherapy or primary radiation. Age at diagnosis was used to classify patients into two groups:  $\leq 40$  and 41-60 years. Clinical and pathologic variables were compared between the groups. Progression-free survival and overall survival were estimated using Cox proportional hazards.

**Results:** A total of 551 patients were evaluated, of which 103 (18.7%) patients were  $\leq 40$  years and 448 (81.3%) were 41-60 years. Age  $\leq 40$  years was associated with higher body mass index (38.8 vs 35.8 kg/m<sup>2</sup>,  $p=0.008$ ), non-invasive cancers (54.2% vs 32.6%,  $p<0.001$ ), lower uterine segment involvement (27.2% vs 22.5%,  $p<0.001$ ), and less lymphovascular space invasion (16.8% vs 29.1%,  $p=0.015$ ). The rate of synchronous ovarian cancer was 9.2% vs 0.7% in age 41-60 years ( $p<0.001$ ), and 19% of women with endometrial cancer aged  $\leq 40$  years underwent fertility-sparing therapy. Grade, stage, myometrial invasion, lymphovascular space invasion, and lymph node status were associated with survival, and fertility-sparing therapy adversely affected the recurrence rate of the age  $\leq 40$  years cohort. Among all patients aged  $\leq 60$  years, mismatch repair deficiency due to MLH1 methylation was associated with worse progression-free survival, 48.6% vs 83.3% (HR 1.98, 95% CI 1.06 to 3.17,  $p=0.032$ ), and overall survival, 56.5% vs 90.0% (HR 2.58, 95% CI 1.13 to 5.90,  $p=0.025$ ).

**Conclusions:** Patients aged  $\leq 40$  years with endometrial cancer have more favorable prognostic factors and higher rates of synchronous tumors. Fertility-sparing therapy was associated with higher recurrence rates. The prognostic value of MLH1 methylation in this population warrants further investigation.

### 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

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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.

**Gómez-Raposo, C., Merino Salvador, M., Aguayo Zamora, C. & Casado Saenz, E. 2020.**

“The role of adjuvant chemotherapy (CT) is controversial in endometrial carcinoma (EC). Surgery alone is usually curative for women who are at a low risk of disease recurrence. The treatment of EC following surgical staging is based on the risk of relapse, which is defined by the cancer stage at diagnosis, histology of the tumor and other prognostic factors such as grade differentiation, the presence of substantial lymphovascular invasion (LVSI), or depth of myometrial invasion (MI). External beam radiotherapy (EBRT) and/or vaginal brachytherapy (VBT) improved local control and are used as adjuvant treatment for early-stage disease. The role of adjuvant CT is controversial in early-stage EC, and there is no uniform approach to the treatment of women with stage III EC or early-staged non-endometrioid EC. Available evidence did not support the indication of adjuvant CT in stage I-II endometrioid EC. In those cases at higher risk of relapse, defined as grade 3 tumors with substantial (no focal) LVSI, specifically with deep MI or cervical involvement, could be considered. Adjuvant CT should be administered to stage III EC patients. When RT is indicated (extensive lymph node involvement or deep MI), sequential treatment with RT or "sandwich" regimen may be considered rather than concurrent CRT. The patients with stage IA MI or IB USC may be offered adjuvant CT alone or in combination with VBT, whereas in stage II uterine serous carcinoma patients adding EBRT may be reasonable. Management approach for patients with stage IA without MI USC who underwent a comprehensive surgery remains controversial, and surveillance alone or CT plus VBT is an appropriate option. Early-stage clear-cell carcinoma patients might not benefit for adjuvant

CT, but stage III patients might benefit from the combination of CT and EBRT. Stage I-III uterine carcinosarcoma patients might be offered adjuvant CT followed by RT or as a "sandwich" régime."

**Tamura, K., Hasegawa, K., Katsumata, N., Matsumoto, K. Mukai, H., Takahashi, S., Nomura, H. & Minami, H. 2019.**

Nivolumab is a human monoclonal antibody against the immune checkpoint receptor programmed death-1, inhibiting binding to programmed death-ligand 1 or 2 (PD-L1 or PD-L2). This phase 2 study evaluated the efficacy and safety of nivolumab in patients with advanced/recurrent uterine cervical cancer, uterine corpus cancer, or soft tissue sarcoma (STS). Patients received nivolumab 240 mg at 2-week intervals. Primary endpoint was objective response rate; secondary endpoints included overall survival, progression-free survival, and safety. PD-L1 expression and microsatellite-instability (MSI) status were analyzed as potential efficacy biomarkers. Objective response rate was 25%, 23%, and 0% in patients with cervical cancer (n = 20), corpus cancer (n = 22), and STS (n = 21), respectively. The lower 80% confidence intervals of objective response rates in patients with cervical or corpus cancer exceeded the threshold rate (5%); the primary endpoint was met in cervical and corpus cancer, but not in STS. Median progression-free survival was 5.6, 3.4, and 1.4 months, and 6-month overall survival was 84%, 73%, and 86% in cervical cancer, corpus cancer, and STS, respectively. The objective response rate was higher in patients with cervical cancer with PD-L1-positive (n = 5/15; 33%) versus PD-L1-negative (n = 0/5; 0%) tumors. The two patients with corpus cancer classified as MSI-high responded; the six patients classified as microsatellite stable did not respond. Overall, nivolumab showed acceptable toxicity in all cohorts, with evidence of clinical activity in uterine cervical or corpus cancer, but not in STS. PD-L1 expression in cervical cancer and MSI-high in corpus cancer may predict clinical activity of nivolumab in these cancers.

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/](http://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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**Tumour Grade and Tumour Stage**

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**Uterus**

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

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