Introduction
The ovaries form part of the female reproductive organs that house the ova and are also responsible for the production of sex hormones. The ovaries are paired organs located on either side of the uterus within the broad ligament below the uterine (fallopian) tubes. Each ovary is within the ovarian fossa, a space that is bound by the external iliac vessels, obliterated umbilical artery, and the ureter. The ovaries are responsible for housing and releasing ova, or eggs, necessary for reproduction. At birth, a female has approximately 1-2 million ova, but only about 300 of these eggs will ever become mature and be released for the purpose of fertilisation.

Ovarian Cancer
Ovarian cancer is cancer of the cells of one or both ovaries.

benign and borderline mucinous ovarian tumors, and compare these to tumors from other potential extra-ovarian sites of origin. Here we show that MOC is distinct from tumors from other sites and supports a progressive model of evolution from borderline precursors to high-grade invasive MOC. Key drivers of progression identified are TP53 mutation and copy number aberrations, including a notable amplicon on 9p13. High copy number aberration burden is associated with worse prognosis in MOC. Our data conclusively demonstrate that MOC arise from benign and borderline precursors at the ovary and are not extra-ovarian metastases.”

Incidence of Ovarian Cancer in South Africa
According to the National Cancer Registry (2014) the following number of ovarian cancer cases was histologically diagnosed in South Africa during 2014:

<table>
<thead>
<tr>
<th>Group - Females 2014</th>
<th>No of Cases</th>
<th>Lifetime Risk</th>
<th>Percentage of All Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>All females</td>
<td>518</td>
<td>1:387</td>
<td>1,37%</td>
</tr>
<tr>
<td>Asian females</td>
<td>22</td>
<td>1:248</td>
<td>3,36%</td>
</tr>
<tr>
<td>Black females</td>
<td>194</td>
<td>1:777</td>
<td>1,20%</td>
</tr>
<tr>
<td>Coloured females</td>
<td>42</td>
<td>1:457</td>
<td>1,02%</td>
</tr>
<tr>
<td>White females</td>
<td>260</td>
<td>1:134</td>
<td>1,58%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Group - Females 2014</th>
<th>0 – 19 Years</th>
<th>20 – 29 Years</th>
<th>30 – 39 Years</th>
<th>40 – 49 Years</th>
<th>50 – 59 Years</th>
<th>60 – 69 Years</th>
<th>70 – 79 Years</th>
<th>80+ Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All females</td>
<td>4</td>
<td>18</td>
<td>23</td>
<td>73</td>
<td>111</td>
<td>161</td>
<td>93</td>
<td>30</td>
</tr>
<tr>
<td>Asian females</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>8</td>
<td>7</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Black females</td>
<td>3</td>
<td>15</td>
<td>17</td>
<td>28</td>
<td>39</td>
<td>48</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td>Coloured females</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>7</td>
<td>15</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>White females</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>33</td>
<td>56</td>
<td>86</td>
<td>64</td>
<td>18</td>
</tr>
</tbody>
</table>

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.

Causes of Ovarian Cancer
It is not clear what causes ovarian cancer. In general, cancer begins when healthy cells acquire a genetic mutation that turns normal cells into abnormal cells. Healthy cells grow and multiply at a set rate, eventually dying at a set time. Cancer cells grow and multiply out of control, and they do not die. The accumulating abnormal cells form a mass (tumour).

Risk Factors for Ovarian Cancer
The risk for developing ovarian cancer appears to be affected by several factors:

- The more children a woman has and the earlier in life she gives birth, the lower her risk for ovarian cancer.
• Certain genes defects (BRCA1 and BRCA2) are responsible for a small number of ovarian cancer cases. Women with a personal history of breast cancer or a family history of breast or ovarian cancer have an increased risk for ovarian cancer
• Women who take oestrogen replacement only (not with progesterone) for 5 years or more seem to have a higher risk of ovarian cancer
• Birth control pills decrease the risk of ovarian cancer.
• Being infertile or having fertility treatment
• Using a coil (intra-uterine device (IUD)
• Older women are at highest risk for developing ovarian cancer. Most deaths from ovarian cancer occur in women age 55 and older
• Research suggests that the risk of ovarian cancer is slightly higher for women who:
  • have medical conditions such as endometriosis
    ▪ smoke tobacco products
    ▪ are obese
    ▪ are tall

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 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


“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.”


“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.”

Ovarian Cancer and Use of Talc

There have been several lawsuits in the United States of America against the manufacturer of a popular brand of baby powder which contains talc. Retrospective research was conducted by Cramer, et al. (2016). They concluded that multiple studies of ovarian cancer and genital talc use have led only to consensus about possible carcinogenicity. Risks for epithelial ovarian cancer from genital talc use vary by histologic subtype, menopausal status at diagnosis, hormone therapy use, weight, and smoking. These observations suggest that oestrogen and/or prolactin may play a role via macrophage activity and inflammatory response to talc.


Over the past four decades, there has been increasing concern that perineal use of talc powder, a commonly used personal care product, might be associated with an increased risk of ovarian cancer.

OBJECTIVES: To critically review all available human epidemiological data on the relationship between perineal use of talc powder and ovarian cancer, with consideration of other relevant experimental evidence.

METHODOLOGY: We identified 30 human studies for qualitative assessment of evidence, including 27 that were retained for further quantitative analysis.

RESULTS: A positive association between perineal use of talc powder and ovarian cancer was found [OR: 1.28 (95% CI: 1.20 - 1.37)]. A significant risk was noted in Hispanics and Whites, in women applying talc to underwear, in pre-menopausal women and in post-menopausal women receiving hormonal therapy. A negative association was noted with tubal ligation.
CONCLUSION: Perineal use of talc powder is a possible cause of human ovarian cancer.

Protective Factors for Ovarian Cancer
There’s currently nothing that can be done to prevent ovarian cancer. However, there are some things that are thought to protect against ovarian cancer. These are called protective factors. Women with protective factors may still develop ovarian cancer.

Getting enough vitamin D may reduce your risk of developing a number of cancers, including ovarian cancer – although more research needs to be done to be certain.

Research has shown that the following may be associated with a reduced risk of certain types of ovarian cancer:
- removal of the uterus (womb)
- removal of the ovaries
- having the fallopian tubes tied
- having the fallopian tubes removed
- having been pregnant
- using oral contraceptives

Prophylactic Oophorectomy
Prophylactic oophorectomy may significantly reduce one’s odds of developing breast cancer and ovarian cancer if one is at high risk. One should weigh the pros and cons of this cancer-prevention option in collaboration with an oncology geneticist and a medical practitioner.

Who can consider prophylactic oophorectomy?
Prophylactic oophorectomy is usually reserved for women with a significantly increased risk of breast cancer and ovarian cancer due to an inherited mutation in the BRCA1 or BRCA2 gene - two genes linked to breast cancer, ovarian cancer and other cancers. Women who have inherited mutations and have completed childbearing are the best candidates for this surgery.

Prophylactic oophorectomy may also be recommended if one has a strong family history of breast cancer and ovarian cancer but no known genetic alteration. It might also be recommended if one has a strong likelihood of carrying the gene mutation based on one’s family history but choose not to proceed with genetic testing.

Women who are at risk, could consider this procedure as follows:
- Having a BRCA1 gene mutation: age 35 to 40
- Having a BRCA2 gene mutation: age 45 and older

Types of Ovarian Cancer
The type of cell where the cancer begins determines the type of ovarian cancer you have. Ovarian cancer types include:
• Cancer that begins in the cells on the outside of the ovaries. Called epithelial tumours, these cancers begin in the thin layer of tissue that covers the outside of the ovaries. Most ovarian cancers are epithelial tumours
• Cancer that begins in the egg-producing cells. Called germ cell tumours, these ovarian cancers tend to occur in younger women
• Cancer that begins in the hormone-producing cells. These cancers, called stromal tumours, begin in the ovarian tissue that produces the hormones oestrogen, progesterone and testosterone
• The type of ovarian cancer you have helps determine your prognosis and treatment options

Symptoms of Ovarian Cancer
Many ovarian cancer symptoms mimic those of less life-threatening conditions such as irritable bowel syndrome. These symptoms may include:

• Bloating
• Pelvic or abdominal pain
• Urinary urgency or frequency
• Difficulty eating or feeling full quickly

Further Late Stage Symptoms of Ovarian Cancer
• Spread of the cancer to other organs
• Loss of organ function
• Fluid in the abdomen (ascites)
• Blockage of the intestines

Early Detection of Ovarian Cancer
Early detection of ovarian cancer saves women’s lives. No screening test exists that can test all women for ovarian cancer. The Pap test does not test for ovarian cancer; it screens for cervical cancer.

Diagnosis of Ovarian Cancer
In someone showing the symptoms mentioned above, the doctor may order one or more of the following tests:

Ultrasound - Ultrasound (ultrasonography) is the use of sound waves to create an image on a video screen. Sound waves are released from a small probe placed in the woman's vagina or on the surface of her abdomen. The sound waves create echoes as they enter the ovaries and other organs. The same probe detects the echoes that bounce back, and a computer translates the pattern of echoes into a picture.
Computed Tomography - The CT scan is an x-ray procedure that produces detailed cross-sectional images of your body. Instead of taking one picture, like a conventional x-ray, a CT scanner takes many pictures as it rotates around you. A computer then combines these pictures into an image of a slice of your body. The machine will take pictures of multiple slices of the part of your body that is being studied.

Barium Enema X-ray - This is a test to see whether the cancer has invaded the colon (large intestine) or rectum (it is also used to look for colorectal cancer). After taking laxatives the day before, the radiology technician puts barium sulphate, a chalky substance, into the rectum and colon. Because barium is impermeable to x-rays (impossible for x-rays to go through), it outlines the colon and rectum on x-rays of the abdomen.

Magnetic Resonance Imaging - MRI scans use radio waves and strong magnets instead of X-rays. The energy from the radio waves is absorbed and then released in a pattern formed by the type of tissue and by certain diseases. A computer translates the pattern of radio waves given off by the tissues into a very detailed image of parts of the body.

Chest X-ray - This procedure may be done to determine whether ovarian cancer has spread (metastasised) to the lungs.

Positron Emission Tomography (PET scan) - In this test, radioactive glucose (sugar) is given to look for the cancer. Because cancers use glucose (sugar) at a higher rate than normal tissues, the radioactivity will tend to concentrate in the cancer. A scanner can spot the radioactive deposits.

Staging of Ovarian Cancer
Staging of ovarian cancer is done as it assists the oncologist in deciding treatment.

Where Ovarian Cancer May Spread to in the Body
Should ovarian cancer spread (metastasise) in the body, it would most probably spread as indicated below:

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Main Sites of Metastasis (Spread)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>Bone, liver, lung</td>
</tr>
<tr>
<td>Breast</td>
<td>Bone, brain, liver, lung</td>
</tr>
<tr>
<td>Colon</td>
<td>Liver, lung</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Liver, lung, peritoneum (lining of abdomen)</td>
</tr>
<tr>
<td>Kidney</td>
<td>Adrenal gland, bone, brain, liver, lung</td>
</tr>
<tr>
<td>Lung</td>
<td>Adrenal gland, bone, brain, liver, other lung</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Bone, brain, liver, lung, skin, muscle</td>
</tr>
<tr>
<td>Ovary</td>
<td>Liver, lung, peritoneum (lining of abdomen)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Liver lung, peritoneum (lining of abdomen)</td>
</tr>
<tr>
<td>Prostate</td>
<td>Adrenal gland, bone, liver, lung</td>
</tr>
<tr>
<td>Stomach</td>
<td>Liver, lung, peritoneum (lining of abdomen), ovaries</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Bone, liver, lung</td>
</tr>
<tr>
<td>Uterus</td>
<td>Bone, liver, lung, peritoneum (lining of abdomen), vagina</td>
</tr>
<tr>
<td>Non-melanoma skin cancer</td>
<td>Very rare: lymph nodes, lung, bone (if in head/neck region)</td>
</tr>
</tbody>
</table>
Treatment of Ovarian Cancer

Treatment for ovarian cancer usually involves a combination of surgery and chemotherapy. Less often, treatment may include radiotherapy. The type of treatment women receive depends on the type and stage of their ovarian cancer and their general health. Treatment is best managed by a gynaecological oncologist.

Surgery

Nearly all women who have ovarian cancer will require surgery. Sometimes, it is not possible to confirm the stage of the cancer until the surgery.

Chemotherapy

Chemotherapy involves using anti-cancer (cytotoxic) drugs to kill cancer cells. It is often given after surgery for ovarian cancer. In some cases, it can be given before surgery as it may help to shrink the tumour and make it easier to remove. This is called neo-adjuvant chemotherapy.

Radiotherapy

Radiotherapy uses high energy X-rays. Like chemotherapy, it works by targeting rapidly growing cancer cells. Radiotherapy is not often used to treat ovarian cancer. But occasionally, the multidisciplinary team may recommend it for ovarian cancer treatment under very specific circumstances, such as treating pain and bleeding from a localised tumour mass.


“The poly ADP ribose polymerase olaparib is currently approved in front line BRCA-associated epithelial ovarian cancer (EOC), platinum-sensitive recurrence agnostic to BRCA status and for gBRCA as treatment in the fourth line and beyond. Women who are diagnosed with advanced stage EOC face a formidable challenge in overcoming their disease and achieving long-term, disease-free survival. The qualifier here is disease free. EOC is largely exquisitely chemosensitive, especially in the treatment naive (first line) setting and the expectation is that the vast majority of women will complete front line platinum-based chemotherapy with a response. When unselected (not selected by BRCA) women are enrolled on clinical trials, the response rate among those who have measurable disease at the time of chemotherapy initiation is 48% for carboplatin/paclitaxel and 67% for carboplatin/paclitaxel plus bevacizumab. When one considers the addition of women who start chemotherapy without measurable disease, they will likely also end chemotherapy without measurable disease and the overall rate of no evidence of disease at conclusion of chemotherapy approaches 80%. Despite this, the majority of women will suffer relapse of their disease, typically within the first 3 years following completion of therapy. Once recurrent, the disease is highly treatable for many years but no longer considered curable. This review will cover indications for olaparib in ovarian cancer as well as ongoing combination trials and rationale for these combinations.”


“Human epididymis protein 4 (HE4) is well known to be a predictor of ovarian cancer clinically. HE4 is reported to play crucial roles in ovarian cancer progression and metastasis. The purpose of the present study was to explore its biological role and molecular mechanism in ovarian cancer. In our study, we found that expression levels of HE4 in tissues, serum and urine in ovarian cancer were..."
upregulated compared to healthy and benign groups. HE4 expression was elevated in ovarian cancer cells. Knockdown of HE4 dampened cell proliferation and Ki67 expression, as well as enhanced apoptosis, caspase-3 activity and cleaved-caspase-3 expression. In addition, HE4 downregulation repressed invasion and migration capabilities of ovarian cancer cells. Western blot analyses showed that knockdown of HE4 reduced the levels of matrix metalloproteinases (MMP-2 and MMP-9) and inhibited epithelial to mesenchymal transition (EMT) in ovarian cancer cells. In vivo animal experiments revealed that HE4 downregulation constrained the growth of xenograft tumor. Mechanism research showed that knockdown HE4 inhibited the activity of JAK/STAT3 pathway in vitro and in vivo. In conclusion, our findings reported that knockdown of HE4 suppresses aggressive cell growth and malignant progression of ovarian cancer by inhibiting the JAK/STAT3 pathway, which provides valuable insights to contribute to develop novel HE4-targeted therapies.”

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/

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Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]
September 2018
Ovarian Anatomy


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