Research

Clinical Brief: Identifying Symptoms of Ovarian Cancer in Chiropractic and Complementary Health Care Settings

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Abstract

The purpose of this brief is to discuss the clinical presentation of ovarian cancer and to review risk factors, symptoms, and current diagnosis and treatment strategies. Here, we concisely review the incidence, risk factors, signs & symptoms, diagnosis and treatment of ovarian cancer. The diagnosis of ovarian cancer can be difficult in clinical practice. Since it may be encountered at various stages by all clinicians, chiropractors and other complementary health care providers should be aware of the clinical picture with which it might present to assist in earlier diagnosis of their patients.

Overview of ovarian cancers

Ovarian cancers are the fifth leading cause of cancer deaths in women in the United States, and represent the most lethal of all gynecologic cancers globally.1,2 Approximately 1 in 70 women in the United States will develop ovarian cancer in their lifetime3. Although mortality rates for many solid tumors have decreased in the past 5 decades, mortality rates among ovarian cancers has largely remained static. For instance, overall five-year survival of ovarian cancer patients is 44.2%, while 5-year survival in breast cancer has risen from 74.8% during the 1970s to 89.2% in 2009 (see Figure 1).4 Reasons for this lack of progress in disease treatment are multifactorial and include poor understanding of ovarian cancer pathogenesis, lack of sensitive and specific diagnostic exams and late stage at time of diagnosis. Symptoms of ovarian cancer are often ambiguous (leading to the disease being referred to as
a ‘silent killer’) and, as the average age at diagnosis is 63 years, are often mistaken for symptoms secondary to aging and to hormone changes during menopause. Subsequent misdiagnosis and/or delay in diagnosis allow treatment-free progression of the disease and patients are frequently diagnosed after the cancer has metastasized (61%).

Figure 1. Five-Year Survival Rates Among Breast and Ovarian Cancer Patients in the United States: 1975-2006.

Five-year survival among patients, defined as women surviving five years or longer at the time of data collection, in the United States was collected by the National Cancer Institute over 31 years (SEER Surveillance Data, NCI, 2010). Data are presented in 4-year clusters for ease of reading. Five-year survival in women with breast cancer has increased by 16%, improving to 90%, whereas five-year survival of women with ovarian cancer has increased by 8.6%, remaining below 50%.

Ovarian cancers, a collective group of cancers with four subtypes, are differentiated by their cellular phenotype: germ cell tumors, stromal tumors, primary peritoneal carcinomas and epithelial tumors. Epithelial ovarian carcinomas (EOCs) represent 90% of all ovarian cancer diagnosed in the United States,
and are further divided into five major histotypes: high-grade serous carcinoma, endometrioid carcinoma, clear-cell carcinoma, mucinous carcinoma, and low-grade serous carcinoma. Of these, high-grade serous carcinoma is the most deadly, representing 75% of EOCs and 90% of ovarian cancer deaths. As such, this discussion will focus on the risk factors, symptoms, and diagnosis of epithelial ovarian carcinomas.

### Risk Factors

Risk factors for development of the disease are often related reproduction; the primary theory of disease etiology suggests improper ovulatory wound healing gives rise to acquired genetic mutations and subsequent tumorigenesis (summarized in Table 1). Positive, protective risk factors include multiparity, breastfeeding, long term oral contraceptive use, and (potentially) long term use of depot medroxyprogesterone (birth control injection). Anecdotal evidence suggests progesterone is a protective hormone, and estrogen is a potential pro-tumorigenic factor. Additionally, surgical procedures involving the reproductive organs (hysterectomy, prophylactic oophorectomy for women with high risk, tubal ligation) have been shown to decrease the risk of ovarian cancer. Conversely, nulliparity, non-use of oral or injected contraceptives, and use of hormone replacement therapies increase risk of developing the disease.

<table>
<thead>
<tr>
<th>Table 1. Positive and Negative Risk Factors in Ovarian Cancer</th>
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<tbody>
<tr>
<td><strong>Decreased Risk</strong></td>
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<tr>
<td><strong>Reproductive</strong></td>
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<tr>
<td>Multiparity</td>
</tr>
<tr>
<td>Breastfeeding</td>
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<tr>
<td><strong>Hormonal</strong></td>
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<tr>
<td>Long term depot medroxyprogesterone use</td>
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<td>Long term oral contraceptive use</td>
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<tr>
<td><strong>Surgical</strong></td>
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<tr>
<td>Hysterectomy</td>
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<tr>
<td>Prophylactic oophorectomy</td>
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<td>Tubal ligation</td>
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**Lifestyle**
Obesity

Low circulating vitamin D (25[OH]D)

Perineal use of talcum powder*

*Literature reviewing perineal use of talcum powder as a risk factor in ovarian cancer both supports and refutes its risk.

Perhaps the most commonly discussed negative risk factors for ovarian cancer are those of hereditary nature. Women with a personal history of breast cancer demonstrate an increased risk of developing ovarian cancer, as do women who have a first-degree relative (mother, sister, daughter), maternal or paternal second-degree (aunt, niece, grandmother, granddaughter, first cousin) or maternal or paternal third-degree (great grandmother, great aunt) who has been diagnosed with either breast or ovarian cancer. Mutations in BRCA1 (breast cancer 1, early onset) and BRCA2 (breast cancer 2, early onset) have been shown to increase risk of developing both breast and ovarian cancer. Female members of families that exhibit HNPCC/Lynch Syndrome, an autosomal dominant condition characterized by early-onset (45 years) colorectal cancer, are also at increased risk for developing ovarian cancer and should be monitored closely for symptoms.

With the exception of a few studies, the evidence for correlation between lifestyle and risk of ovarian cancer is largely anecdotal. There are weak associations between ovarian cancer and low circulating vitamin D (25[OH]D) or perineal use of talcum powder. Current literature does not support strong correlation between obesity (as measured by BMI) and risk of ovarian cancer; however, a systematic review published in 2007 suggests that pooled data support the hypothesis that an inverse association exists between physical activity level and risk of ovarian cancer. Further, vigorous-intensity physical activity decreases risk of ovarian cancer-related mortality by 26% (HR = 0.76; CI: 0.56–0.98). It is also interesting to note that in mouse models of serous ovarian cancer, obesity (mice on high fat diets) increases tumor aggressiveness compared with controls (mice on low fat diets).

Symptoms

Major hurdles in the early diagnosis of epithelial ovarian cancer include vagueness of symptoms, and high likelihood of patients overlooking the symptoms as common and/or not pathologic. The most commons reported symptoms of women diagnosed with ovarian cancer include abdominal pain, back pain, bloating, feeling of fullness (without having eaten), vaginal bleeding and gastrointestinal distress. Often, these symptoms are dismissed by not only patients, but also by primary care physicians as attributed to menopause and/or aging. Of particular interest is the symptom of lower back pain, which may lead a patient to seek chiropractic care. In a recent study seeking to validate the M. D. Anderson Symptom Inventory in 113 ovarian cancer patients, more than half (52.0%) of women diagnosed with ovarian cancer reported lower back pain as an early and persistent symptom prior to their diagnosis. A second study, investigating pre-diagnosis symptoms in young patients (ages 15-35) also found 52% of patients reported back pain as a symptom as early as 2 years prior to diagnosis. Considering these data, it is imperative that chiropractors consider the possibility of patients presenting with back pain actually demonstrating symptoms of ovarian cancer.
Diagnosis and treatment

Diagnosis of ovarian cancer is typically pursued based on the cumulative results of physical examination and transvaginal ultrasonography, and is achieved through exploratory laparotomy and histologic confirmation to rule out other causes of ovarian cysts\(^3\). During exploratory laparotomy, surgical staging (see Table 2)\(^5\) and debulking of the tumor are also performed; taking these steps during initial surgery can inform the oncologist on further treatment strategies and improve survival rates for patients with small (< 1 cm) primary tumor burden.\(^3\)

### Table 2. Stages of Ovarian Cancer (International Federation of Gynecology and Obstetrics, FIGO*)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>I – Tumor confined to ovaries or fallopian tubes</td>
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<tr>
<td>IA - Tumor confined to one ovary (capsule intact) or fallopian tube. No tumor on surface. No malignant cells in the ascites or peritoneal washings</td>
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<tr>
<td>IB – Tumor limited to both ovaries (capsules intact) or fallopian tubes</td>
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<tr>
<td>IC – Tumor limited to one or both ovaries or fallopian tubes, with any of the following</td>
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<td>IC1 – Surgical spill intraoperatively</td>
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<tr>
<td>IC2 – Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface</td>
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<tr>
<td>IC3 – Malignant cells present in the ascites or peritoneal washings</td>
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<tr>
<td>II – Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer</td>
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<td>IIA – Extension and/or implants on the uterus and/or fallopian tubes and/or ovaries</td>
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<tr>
<td>IIB – Extension to other pelvic intraperitoneal tissues</td>
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<tr>
<td>III – Tumor involves one or both ovaries, or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes</td>
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<tr>
<td>IIIA – Metastasis to the retroperitoneal lymph nodes with or without microscopic peritoneal involvement beyond the pelvis</td>
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III A1 – Positive retroperitoneal lymph nodes only (cytologically or histologically proven)

III A1(i) – Metastasis = 10 mm in greatest dimension (note this is tumor dimension and note lymph node dimension)

III A1(ii) – Metastasis > 10 mm in greatest dimension

III A2 – Microscopic extrapelvic (above pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes

III B – Macroscopic peritoneal metastases beyond the pelvic brim = 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes

III C – Macroscopic peritoneal metastases beyond the pelvic brim > 2 cm in greatest dimension, with or without metastases to the retroperitoneal nodes

*Includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ

IV – Distant metastases excluding peritoneal metastases

IVA – Pleural effusion with positive cytology

IVB – Metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of abdominal cavity†

* Published in Mutch DG, *Gynecol Oncol*, 2014
† *Parenchymal metastases are Stage IVB*

The current treatment for ovarian cancer includes surgical debulking, followed by 3-6 cycles of combination therapy of taxane-based (paclitaxel; Taxol®) and platinum-based (carboplatin; Paraplatin®, Paraplatin AQ®). Two exceptions exist to this standard course of care: patients with an ovarian cyst and iron-deficiency anemia due to occult gastrointestinal bleeding (may require additional evaluation) and patients with coexisting conditions that may preclude a safe surgical procedure (ovarian cancer confirmed with biopsy, patient treated chemotherapeutically to improve suitability for surgery). Further, a small subset of women with early stage disease exhibit a five-year survival of approximately 90%, and do not benefit further from postoperative adjuvant chemotherapy. It should be noted that in many patients who initially respond to a taxane/carboplatin combination treatment, recurrence and resistance are observed within 5 years of adjuvant therapy.
Novel, targeted therapeutics are in development and offer hope for improving progression-free survival in ovarian cancer patients. These include the angiogenesis inhibitor bevacizumab (targets VEGF-A), the PARP inhibitors olaparib (targets PARP in patients with BRCA1/2 mutations), and the Ras/MEK/ERK pathway inhibitor selumetinib (targets MEK1/2 in patients with low-grade serous EOC). There are also clinical trials planned to investigate the effects of inhibitors of proposed pathways of taxane/platinum resistance, including PI3K/Akt/mTOR pathways and the ErbB3 (EGF receptor) family. These and other compounds in earlier stages of development provide promising future directions for ovarian cancer therapeutics research.

Discussion

Early diagnosis of ovarian cancer poses significant challenges. Chiropractors encountering women with back pain, abdominal pain, bloating, feeling of fullness without having eaten, vaginal bleeding, and other gastrointestinal symptoms should consider a differential diagnosis of ovarian cancer, especially in patients who do not experience improvement or return with similar symptoms after a course of conservative care. Chiropractors and other complementary health care providers can play a role in early detection of ovarian cancer by remaining vigilant for typical or unusual symptoms. It is estimated that nearly 60% of 66 queried comprehensive cancer control programs in the United States, its territories and tribes implement complementary and alternative medicine practices. Chiropractors and other complementary health care providers should also be mindful of the possibility of relapse or the development of metastatic disease when encountering patients who have been diagnosed or are undergoing treatment for ovarian cancer.

Acknowledgements

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References


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