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Integrative Medicine for Female Patients with Gynecologic Cancer

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Abstract

Background: Integrative oncology provides a broad spectrum of complementary medicine therapies, many of which can augment the effects of supportive and palliative care for patients with gynecologic cancer.

Methods: The present review will focus on the findings of the research on the role of integrative medicine, within the challenges they face during treatment of gynecological cancer.

Results and conclusion: Integrative oncology focuses primarily on alleviating patients' suffering by reducing the adverse effects of chemotherapy and radiation, improving quality of life and function. At the same time, integrative oncology provides guidance on the safe and effective use of herbal and other dietary supplements during cancer treatment. This is a dynamic process requiring collaboration between conventional gynecologic oncologists and integrative physicians and practitioners, in an evolving process of care.

Keywords: integrative oncology, gynecologic oncology, ovarian cancer, endometrial cancer, cervical cancer, chemotherapy

Introduction

Cervical, endometrial, and ovarian cancer are the fourth, fifth, and seventh most prevalent types of cancer in the female population worldwide, respectively.[1] In 2012, cervical cancer was associated with 266,000 deaths worldwide, with ovarian cancer having the highest mortality rates due to difficulties faced in early diagnosis.[2] The most frequently-reported concerns among 1300 U.S. patients with ovarian cancer included disease recurrence; death; ''getting cancer under control'' or being ''cancer free''; and managing the side effects of the oncology treatment.[3] In this study, 32% of respondents reported using complementary and alternative medicine (CAM), mainly osteopathy, acupuncture, herbal and dietary supplements, dietary changes and massage.

Integrative oncology provides a broad spectrum of complementary medicine therapies, which can augment supportive and palliative care, including among patients with gynecologic cancer. Integrative oncology focuses primarily on reducing symptoms resulting from chemotherapy and radiation treatments, improving quality of life (QoL) and function. Integrative oncology also provides guidance on the safe and effective use of herbal and dietary supplements during cancer treatment. As many as 40% of European patients and 66% in the United States and Thailand report using at least one CAM-related modality.[4–6] Herbal and supplement use is usually dependent on geocultural factors, with Mediterranean and Middle Eastern patients using these products as part of the traditional medical culture.[7] Herbal medicine use is also prevalent in central Europe, where herbs such as mistletoe (*Viscum album*) are being used by as many as 67% of German patients with gynecologic cancer, as part of Anthroposophic medicine.[8] Oncology patients who use CAM often expect these treatments to improve well-being, boost the ''immune system,'' and even increase survival.[9] CAM use is also perceived as part of supportive care, improving QoL and relieving chemotherapy-induced symptoms.[10]

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The use of CAM in the oncology setting often takes place without the knowledge or input of the conventional healthcare professionals (HCPs) treating the patient. A U.S. study found that <25% of gynecology cancer patients using CAM reported having received any information about this practice from their physician, nurse, or other conventional HCP.[9] In a study of Canadian and United Kingdom patients undergoing chemotherapy for ovarian cancer, 89% considered it important that their oncologist be aware of their use of CAM, although in the Canadian cohort, only 50% had informed their physician of this practice.[11] In a U.S. study of ovarian cancer patients and survivors, the involvement of conventional HCPs in making decisions about CAM use and lifestyle changes was associated with greater vitality and better role-emotional health during survivorship.[12]

Many conventional oncology centers have established integrative oncology services as part of supportive and palliative care.[13] A survey of members of the Society of Gynecologic Oncologists and the Michigan Oncology Group found that gynecologic oncologists and nononcology female physicians were more likely to have a positive attitude toward CAM, and to believe that CAM should be part of conventional medical care.[14] In Israel, patients with gynecologic cancer expect their gynecologist–oncologist to refer them to an integrative oncology service, as well as participating in the design and implementation of the integrative treatment plan.[15] Patients also expect integrative physicians to provide guidance on the safe and effective use of nonconventional therapies, which can reduce the side effects of their oncology treatment while augmenting emotional and spiritual support for patients.[15]

The following review focuses primarily on the findings of clinical research adhering to an explanatory (randomized controlled trial) format, while acknowledging the importance of pragmatic (nonrandomized uncontrolled trial) or those assessing individualized treatment regimens. Pragmatic research has found a correlation between high adherence to a weekly patient-tailored integrative treatment program and improved QoL-related outcomes, including for patients with gynecologic cancer undergoing chemotherapy and/or palliative care. These studies have shown a greater improvement in the group of patients who were adherent to the complementary integrative medicine (CIM) regimen for a number of QoL-related outcomes, including cancer-related fatigue, gastrointestinal concerns (i.e., nausea and appetite), pain, anxiety and sleep-related problems, cognitive impairment, general well-being, as well as greater rates of adherence to the conventional chemotherapy dosing protocol.[16–20]

Role of Nutrition in Gynecologic Oncology

Many patients with gynecologic cancer consider nutritional advice as part of the integrative oncology consultation.[21] Conventional medicine recognizes the importance of diet on the risk for primary and recurrent disease, as well as for QoL-related outcomes during treatment. For example, a proinflammatory diet is associated with an increased risk for developing ovarian cancer,[22,23] as are high rates of consumption of total, saturated, and trans-fats[24] and intake of total sugars and glycemic load in African American women.[25] Researchers in Europe found an increased risk for epithelial ovarian cancer with a high (vs. low) intake of saturated fat.[26]

It has also been shown that drinking green (and not black) tea is associated with a reduced risk for developing endometrial cancer.[27] A study of African American female population showed that whole milk consumption and lactose intake were associated with an increased risk for ovarian cancer, while high dietary calcium intake was associated with a decreased risk.[28] A study published by the Australian Ovarian Cancer Study Group found that higher serum levels of Vitamin D (25-OH) in female patients with ovarian cancer at diagnosis were associated with increased survival rates.[29]

A Polish study explored changes in dietary habits among female patients undergoing chemotherapy for epithelial ovarian cancer and found that those undergoing second-line chemotherapy regimens were more likely to keep to a more ''healthy'' diet than those undergoing first-line treatment regimens. This ''healthy'' diet entailed cooking vegetables in water and increased use of rye bread, pasta, buttermilk, vegetable, fruit, oils, nuts, and juices.[30] A feasibility trial from the University of Texas MD Anderson Cancer Center showed an increase in level of phytonutrients among survivors of stage II–IV ovarian cancer adhering to either a low-fat diet, high-fiber diet, or a modified National Cancer Institute diet supplemented with a soy-based beverage and encapsulated fruit and vegetable juice concentrates.[31]

Herbal and Other Dietary Supplements

In many low-income societies throughout the world, the dietary supplements being used by oncology patients are herbal, and are taken within the context of traditional medicine practices.[32] While many herbal products have been shown to have anticancer properties, the research to date has been largely preclinical (*in vitro*), without clinical evidence of their effectiveness.

*Curcumin (*Curcuma longa*)*

Curcumin is the most widely researched medicinal herb and is the active ingredient of turmeric (*Curcuma longa*). *In vitro* studies of curcumin have shown significant effects on ovarian cancer cells, with enhanced induction of apoptotic cell death.[33] Curcumin can circumvent chemoresistance to chemotherapy agents such as cisplatin[34] and induce cytotoxic effects in paclitaxel-resistant cancer cells.[35] The herb inhibits the proliferation and apoptosis of endometrial carcinoma cells,[36] and it may improve paclitaxel-induced apoptosis of human papilloma virus-positive human cervical cancer cell lines.[37] However, curcumin can also inhibit the effects of chemotherapy agents such as vinblastine on cervical cancer cells.[38]

*Mistletoe (*Viscum album*)*

Mistletoe (*Viscum album*) is an important part of Anthroposophic medicine, with preparations administered via subcutaneous, intravenous, intraperitoneal, or intratumoral injections. Clinical studies have shown that mistletoe may improve patients' QoL during chemotherapy for ovarian cancer,[39] as well as potentially increasing survival time in patients with ovarian and cervical cancer.[40,41] *In vitro* research has shown that mistletoe exhibits anticancer activity in cisplatin-sensitive and -resistant ovarian cells; increases chemosensitivity to carboplatin in both cancer

cell lines; and increases sensitivity to cisplatin-resistant cells treated with carboplatin and paclitaxel.[42]

*Ginger (*Zingiber officinale*)*

Ginger (*Zingiber officinale*) has been shown anticancer activity, increasing carboplatin chemosensitivity in cisplatin-sensitive and -resistant ovarian cells.[36] Despite the evidence supporting the antiemetic effect of ginger, the clinical research to date has not shown any benefit with this herb in treating chemotherapy-induced nausea and vomiting in the gynecologic cancer setting.[43]

*Agaricus (*Agaricus blazei Murill Kyowa*)*

A Korean study examined the medicinal mushroom Agaricus (*Agaricus blazei Murill Kyowa*) in patients undergoing chemotherapy for various gynecologic cancers. The mushroom remedy was associated with improved QoL, including reduced hair loss (alopecia) and fatigue, with increased appetite and emotional stability.[44] However, *A. blazei* has also been linked to severe hepatic dysfunction in oncology patients.[45]

*Gingko (*Gingko biloba*)*

Ginkgo biloba and its extract components (quercetin, ginkgolides A and B) have been shown to induce antiproliferative and apoptosis-inducing effects in serous ovarian cancer cells, as well as sensitizing ovarian cancer cells to cisplatin.[46,47] However, *G. biloba* may negatively interact with the chemotherapy agent paclitaxel.[48]

*Ginseng (*Panax ginseng*)*

Ginseng is a popular herb among oncology patients, and its ginsenoside components have been shown to exhibit *in vitro* anticancer effects on ovarian cancer cells.[49] A randomized controlled clinical trial from Korea showed that the use of red ginseng (*Panax ginseng Meyer)* reduced symptoms of fatigue, nausea, and dyspnea in patients undergoing adjuvant chemotherapy for epithelial ovarian cancer.[50] Also, while a double-blind randomized controlled trial of female patients undergoing chemotherapy for ovarian cancer did not show a benefit of the herb for QoL-related outcomes, a significant reduction in the severity of neutropenia, lymphocytopenia, and cytokine activity was observed in patients treated with this herb following three cycles of chemotherapy.[51]

Selenium

Selenium is a popular nonherbal nutritional supplement among oncology patients.[52] A population-based, case–control study of 11 geographical areas in the United States found that African American women taking selenium supplements had a nearly 30% lower risk for developing ovarian cancer.[53] A daily dose of 200-mcg Selenium supplementation for a 3-month period was associated with a significant increase in white blood cell counts and decrease in hair loss, flatulence, abdominal pain, weakness, malaise, and loss of appetite in a cohort of patients with ovarian cancer undergoing chemotherapy.[47] Supplementation with 500 mcg of selenium in patients with cervical and uterine cancers showed significant reduction in radiation-induced diarrhea.[54] Also, while a follow-up study did not find any benefit of selenium supplementation on QoL-related outcomes following radiation therapy, it was shown not to have any negative impact on 10-year disease-free survival rates.[55]

Probiotics

The use of live probiotics, such as lactobacillus acidophilus and bifidobacterium bifidum, has been shown to reduce the incidence of radiation-induced diarrhea and the need for antidiarrheal medication in patients undergoing treatment with cisplatin and pelvic radiotherapy for locally advanced cervical cancer.[56] While a yogurt containing Lactobacillus casei DN-114 was not found to reduce the incidence of radiation-induced diarrhea in patients with cervical or endometrial cancer, it significantly improved stool consistency (as measured on the Bristol scale).[57] Finally, the use of a high-potency probiotic preparation (VSL#3) was as also shown in a placebo-controlled trial of patients with lower gastrointestinal tract (sigmoid, rectal) and cervical cancer to reduce the incidence of postoperative radiation-induced diarrhea.[58]

Lifestyle Changes

Lifestyle-related factors such as weight gain and physical inactivity are considered to have significant implications for the development of gynecologic cancer. Increased physical activity is correlated with a lower incidence of endometrial cancer,[59] and obesity has been associated with more frequent and severe chemotherapy-related toxicities, although this association is complex. In a study exploring the association between body composition and toxicities from a liposomal doxorubicin (Doxil)/trabectedin (Yondelis) regimen in patients with advanced relapsing ovarian cancer, an association between chemotherapy-related toxicities and a lower ratio of fat mass/lean body mass in individuals with excess body weight was identified.[60] A randomized clinical trial examining a number of weight-loss interventions in survivors of endometrial cancer found that the use of telemedicine with Wi-Fi scales and text messaging resulted in greater weight loss and improved QoL.[61]

Physical activity is also an important lifestyle factor affecting QoL during chemotherapy, and is a feasible intervention for patients with ovarian cancer.[62] In a systematic review and meta-analysis, physical activity was found to improve QoL-related outcomes such as fatigue in survivors of endometrial and ovarian cancer.[63] Physical exercise was also shown to be a modifiable lifestyle factor associated with post-traumatic growth in gynecologic cancer survivors.[64] A randomized controlled trial in China demonstrated that a nurse-delivered home-based exercise and cognitive behavioral therapy program for patients with ovarian cancer undergoing chemotherapy resulted in a reduction in cancer-related fatigue and depression and improved quality of sleep.[65]

Decreased sexual function is an oft-neglected lifestyle-related concern, and can significantly impact QoL in patients with gynecologic cancer. In a controlled study conducted in Norway, survivors of epithelial ovarian cancer who were sexually active exhibited lower levels of fatigue and better QoL when compared with patients who were sexually inactive.[66] In another study, patients treated for ovarian cancer underwent a brief behavioral intervention, which included education on sexual health, rehabilitation training, relaxation, and cognitive behavioral therapy. The group showed

Table 1. Impact of Nutritional and Lifestyle Changes in Gynecologic Oncology

Intervention	*Effects*	*Refs.*
I. Nutritional		
i. Drink green tea	↓ Risk for endometrial cancer	27
ii. Low milk/high-calcium diet	↓ Risk for ovarian cancer	28
iii. High-vitamin D diet	↑ Survival with ovarian cancer	29
II. Dietary supplements		
1. Herbal supplements		
i. Curcumin (*Curcuma longa*)	Preclinical research:	
	* Apoptosis of ovarian cancer cells	33
	* ↓ Chemoresistance (cisplatin, paclitaxel)	34–37
	* ↓ Cytotoxic effects of vinblastine	38
ii. Mistletoe (*Viscum album*)	Preclinical research:	
	* Cytotoxic to ovarian cancer cells	
	* ↑ Chemosensitivity to carboplatin	
	* ↑ Chemosensitivity to cisplatin-resistant cells	42
	Clinical research:	
	* Improve QoL in patients with ovarian Ca.	39
	* Possibly increase survival (ovarian, cervical)	40,41
iii. Ginger (*Zingiber officinales*)	Preclinical research:	
	* Anticancer activity	
	* ↑ Chemosensitivity to carboplatin	42
	Clinical research:	
	* Antiemetic activity—unproven	43
iv. Agaricus (*Agaricus blazei Murill kyowa*)	Clinical research:	
	* Improved QoL	44
	* Cases of hepatic dysfunction	45
v. Gingko (*Gingko biloba*)	Preclinical research:	
	*↑ Antiproliferative	
	*↑ Apoptosis in ovarian cancer cells	
	*↑ Chemosensitization (to cisplatin)	46,47
	* Negative interaction with paclitaxel	48
vi. Ginseng (*Panax ginseng*)	Preclinical research:	
	* Anticancer effects on ovarian ca. cells	49
	Clinical:	
	* ↓ Fatigue, nausea, dyspnea	50
	* ↓ Neutropenia, lympocytopenia, cytokines	51
2. Nonherbal supplements		
i. Selenium	Clinical research:	
	* Reduced risk for developing ovarian ca.	53
	* ↑ WBC count	
	* ↑ QoL-related outcomes	52
	* ↓ Radiation-induced diarrhea	54
ii. Probiotics	Clinical research:	
	* ↓ Radiation-induced diarrhea	56,58
	* Improved stool consistency	57
III. Lifestyle changes		
i. Physical exercise	Clinical research:	
	↓ Incidence of endometrial cancer	59,64
	↓ Fatigue, depression, disturbed sleep	65
ii. Weight loss	Clinical research:	60,61
	↑ Frequency/severity of adverse effects of tx	
iii. Sexual activity	Clinical research:	
	↑ QoL, ↓ fatigue	66
IV. Additional CIM modalities		
Acupuncture	Clinical research:	
	* Preventing CINV	69
	*↓ Nausea, constipation	70
	* ↓ Incidence of neutropenia	73
Massage/touch therapies	Clinical research:	
	*↓ Express feelings of hopelessness	74
	* ↓ Physical complaints	76
Mind–body therapies	Clinical research:	77–79
	* ↓ Anxiety, depression	
	* ↑ Psychologic and QoL-related indices	
Yoga	Clinical research:	
	* ↓ Anxiety, depression, fatigue	81

CIM, complementary integrative medicine; CINV, chemotherapy-induced nausea and vomiting; QoL, quality of life; WBC, white blood cell.

significant improvement in overall sexual functioning and reduced psychologic distress, and the effects of the intervention were maintained for a period of 6 months.[67] Finally, a study of survivors of endometrial cancer found that an increase of 1 h/week of physical activity was associated with a 6.5% increase in the likelihood of improved sexual interest.[68]

Acupuncture

Despite the large body of research published on the clinical benefits of acupuncture in oncology patients with breast cancer, little has been published on the use of this modality for gynecologic cancer. The studies, which have been published, support the use of acupuncture in the prevention and treatment of chemotherapy-related gastrointestinal complaints, primarily nausea and vomiting. A crossover study from Thailand showed that acupuncture was as effective as ondansetron in preventing immediate-onset emesis (within 24 h) following a carboplatin–paclitaxel regimen for ovarian cancer (<24 h), and superior to the drug in preventing delayed emesis (at days 4–5).[69] The acupuncture-treated group also reported significantly less adverse effects such as insomnia and constipation and better physical, social, and overall scores for wellbeing.[67] In a randomized controlled trial from China, wrist-ankle acupuncture with ginger moxibustion was shown to be superior to tropisetron hydrochloride and dexamethasone in preventing emesis and constipation in patients with gynecologic cancer.[70]

Self-treatment with acupressure may also be of benefit in gynecologic cancer patients. In a study conducted in China, self-administered acupressure was shown to reduce urinary retention in patients undergoing radical hysterectomy for cervical cancer.[71] Another study from China showed that early postoperative treatment with electroacupuncture resulted in a reduced residual urine volume and promoted bladder function recovery in patients with cervical cancer.[72] In addition to its clinical benefits, acupuncture treatment is associated with a reduced incidence in chemotherapy-induced neutropenia in patients with gynecologic cancer.[73]

Massage/Touch Therapies

A survey conducted at the Dana-Farber Cancer Institute in Boston found that patients with ovarian cancer who were being treated with massage therapy were less likely to express feelings of hopelessness.[74] In a randomized clinical trial, Judson et al. explored the impact of an integrative medicine intervention, which included hypnosis, therapeutic massage, and healing touch on patients recently diagnosed with ovarian cancer.[75] While the intervention was not found to lead to any additional benefit regarding QoL-related outcomes, it resulted in higher levels of the immune modulators CD4, CD8, and NK cells, although this was not of statistical significance. Finally, a study of Japanese massage (Anma therapy) treatment on a cohort of patients with gynecologic cancer found a reduction in subjective physical complaints, while at the same time reducing urinary epinephrine levels following the intervention.[76]

Mind–Body Therapies

Much of the clinical research published on the use of mind–body medicine in the gynecologic oncology setting has been focused on relaxation techniques, with only a few examining other modalities such as meditation, *Qigong*, and *t'ai chi*. An Australian study found a physician-administered relaxation and counseling intervention to be effective in

Table 2. Potential Impact of Integrative Medicine in Gynecologic Oncology

Outcomes	*Integrative medicine interventions*
Nutritional/lifestyle changes	
I. Epidemiologic research	
↓ Risk for gynecologic cancer	Drinking green tea,[27] low dairy/high calcium diet,[28] Selenium supplementation,[53] Physical activity[59,64]
↑ Survival (ovarian cancer)	High-vitamin D diet,[29] Mistletoe[40,41]
II. Preclinical research	
↑ Anticancer cytotoxic/apoptotic effects	Curcumin,[33–35] Mistletoe,[42] Ginger,[42] Gingko,[46,47] Ginseng,[49]
↓ Chemoresistance/↑ chemosensitivity	Curcumin[33–35] Mistletoe,[42] Ginger,[42] Gingko,[46,47]
↓ Cytotoxic effects of chemotherapy	Curcumin (Vinblastine)[38] Gingko (Paclitaxel),[48]
III. Clinical research	
1. QoL-related outcomes:	Mistletoe,[39] Agaricus,[44] Ginseng (fatigue, nausea),[50] Selenium,[52]
i. General, fatigue	Physical activity,[65] Avoidance of obesity,[60,61] Sexual Activity,[66]
ii. Radiation-induced diarrhea	Massage/Touch therapies,[76] Yoga[81] Selenium,[54] Probiotics[56–58]
2. Laboratory-related outcomes	Ginseng (neutropenia, lymphopenia),[51] Selenium (white cell count)[52]
3. Negative effects	Agaricus (hepatotoxicity)[45]
Integrative medicine modalities	
1. Clinical outcomes	
i. Chemotherapy-induced nausea/vomiting	Acupuncture[70,71]
ii. Constipation	Acupuncture[70]
iii. Fatigue	Yoga[81]
iv. Anxiety and depression	Massage/touch therapies,[74] Mind-body techniques[77–79]
2. Laboratory outcomes	
↓ Neutropenia	Acupuncture[73]

preventing and reducing anxiety and moderate depression subscales in postoperative patients recently diagnosed with gynecologic cancer. A follow-up study by the same group showed a further benefit with training in relaxation and guided imagery techniques, with improved psychologic and QoL-related indices for gynecologic and breast cancer patients undergoing brachytherapy.[77,78] A study comparing a single psycho-oncologic therapy intervention with a single relaxation intervention in hospitalized patients with gynecologic cancer considered at risk for developing anxiety and depression found that both interventions reduced anxiety, although the psycho-oncologic treatment was slightly more effective in preventing depression.[79] The use of healing touch in patients undergoing chemoradiation for cervical cancer resulted in a greater decrease in depressed mood when compared with those receiving relaxation training or usual care.[80] Finally, in a study of patients with ovarian and breast cancer, the majority of which were undergoing active cancer treatment, participation in a weekly restorative yoga class combining physical posture, breathing and deep relaxation led to improved QoL-related outcomes, including depression, state anxiety, and fatigue.[81]

Summary

The findings of the research to date, both preclinical and clinical, support the use of integrative medicine as part of supportive care in the gynecologic oncology setting. The findings of the research on the impact of nutritional and lifestyle changes in gynecologic oncology are summarized in Table 1; on the potential impact of integrative medicine therapies in this setting in Table 2.

The findings of the research on the impact of integrative medicine in the gynecologic oncology setting indicate an improvement in QoL during active oncology treatment (chemotherapy, radiation therapy), with a potential role, for additional gynecologic cancer treatment settings, such as perisurgical care; primary and secondary prevention; advanced palliative care; end-of-life treatment; and rehabilitation during survivorship. However, the available research to date is limited and can provide only preliminary recommendations to patients and healthcare providers for dosage and frequency of those integrative practices, which are potentially beneficial in gynecologic oncology. There is therefore a need to establish a working group which would set out to establish evidence-based clinical practice guidelines for integrative therapies in this patient population. These recommendations would be on the lines of those published recently for patients with breast cancer by the Society of Integrative Oncology and endorsed by the American Association of Clinical Oncology.[82,83]

Author Disclosure Statement

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