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Dietary and lifestyle modifications in the prevention of epithelial ovarian cancer recurrence

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DIETARY AND LIFESTYLE MODIFICATIONS IN THE PREVENTION OF EPITHELIAL OVARIAN CANCER RECURRENCE

by

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ABSTRACT

Background

Advanced stage epithelial ovarian cancer (EOC) presents with an extremely poor prognosis. While some patients respond well to standard treatments of chemotherapy and cytoreductive surgery, the recurrence rate is high and five-year survival is low. The importance of nutritional eating and a healthy lifestyle has been recognized as a protective factor against the development of many cancers. There may be a role for dietary and lifestyle interventions on reducing the recurrence of EOC, thereby prolonging survival.

Literature Review Findings

A review of the literature was performed, focusing on dietary and lifestyle patterns and their effects on the development and recurrence of epithelial ovarian cancers. In general, carotenoids, flavonoids, cruciferous vegetables, and flaxseed rich diets have all been proposed to reduce the risk of developing ovarian cancer. Conversely, red and processed meats, and foods with high glycemic index have been associated with an increased risk of ovarian cancer development. Additionally, obesity and high Body Mass Index (BMI) have been linked to increased cancer risk as well as increased mortality rates from cancer.

Proposed Methods

Given the broad spectrum of dietary and lifestyle recommendations for prevention of EOC, many providers are not aware of what information they can give to their patients regarding this topic. A Continuing Medical Education (CME) lecture summarizing the most up-to-date literature on the topic of lifestyle interventions to increase EOC survival would be beneficial. A one hour long course will be offered for CME credit to expand the knowledge base of providers and equip them with the resources necessary to educate patients on healthy lifestyle modifications in order to minimize ovarian cancer recurrence.

Conclusions

With a lack of definitive cure and poor overall prognosis for women diagnosed with advanced stage epithelial ovarian cancer, there is a need for alternative treatment options when traditional methods fail. There is promising evidence that a diet high in carotenoids, cruciferous vegetables, flaxseed, and several other nutritional components is beneficial in preventing development of ovarian cancer. A diet containing processed foods, red meats, dairy, and high sugar content has been associated with increased ovarian cancer risk. It is possible that these dietary recommendations may apply to prevention of recurrence of EOC as well. The CME lecture will present the most up-to-date knowledge in the area of lifestyle interventions for the prevention of EOC. A curriculum for primary care and oncology health care providers will provide them with the tools necessary to provide their patients with nutrition and lifestyle recommendations that may prevent cancer recurrence.

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LIST OF ABBREVIATIONS

AAPA……………………...…..….American Academy of Physician Assistants

ACCME……………..…Accreditation Council for Continuing Medical Education

APST…………………………...…………Atypical Serous Proliferative Tumor

BMI…………………………………………...…………Body Mass Index

CME .... Continuing Medical Education

CRD………………………………………………..Calorie Restricted Diet

EGFR…………………………………………Epidermal Growth Factor Receptor

EOC…………………………………………......Epithelial Ovarian Cancer

GI……………………………………………………….…Glycemic Index

GL………………………………………………………Glycemic Load

Glut-1……………………………………………...…..Glucose Transporter 1

GWAS……………………………...………..Genome Wide Association Studies

HBOC……………………………………..Hereditary Breast and Ovarian Cancer

HED……………………………………………………...High Energy Diet

HGSC .... High Grade Serous Carcinoma

IGF-1…………………………………………………...Insulin Growth Factor 1

IRB……………………………………….……….Institutional Review Board

LGSC……………………………………............Low Grade Serous Carcinoma

MPSC…………………………………..Macropapillary Serous Borderline Tumor

NCCN…………………………………National Comprehensive Cancer Network

OM-3FA……………………………………………..…..Omega-3 Fatty Acid

OS……………………………………………………………..…..Overall Survival

PA………………………………………………………….…..Physician Assistant

PACs…………………………………………………..……….Proanthocyanidins

PARP……………………………………..…..Poly (ADP-ribose) polymerase

PGE2…………………………………………………………..….Prostaglandin E2

PI3K/Akt………………..……Phosphatidylinositol-3 kinase/Akt-mTOR pathway

PFS………………………………………..……….Progression Free Survival

RD…………………………………………………………………Regular Diet

ROS…………………………………………………...Reactive Oxygen Species

SGO……………………………...……………..Society of Gynecologic Oncology

SNP……………………………………...……Single Nucleotide Polymorphism

TIC………………………………………………..Tubal Intraepithelial Carcinoma

25-Hydroxyvitamin D……………………………………………………25(OH)D

INTRODUCTION

Background

Ovarian cancer is the most deadly gynecologic cancer in women[1] This statistic is attributed in part to late stage at diagnosis due to a lack of specific symptoms and effective screening methods[2]. The current standard of care includes chemotherapy treatment with carboplatin and paclitaxel with or without cytoreductive debulking surgery. Initial treatment with this chemotherapy regimen is effective in producing an expected response in 70-80% of patients[1].

Despite this initial treatment success, up to 75-85% of these patients will develop a recurrence of their cancer requiring additional treatment intervention[1–3] and many of them will not survive it. Though traditional treatment with chemotherapy and cytoreductive surgery produces a promising initial response and sparks hope in many patients, the overall five-year survival rate for advanced stage (III or IV) epithelial ovarian cancer (EOC) remains less than 30%[3]. Due to the extremely high rate of recurrence and lack of effective long-term treatment, recurrent ovarian cancer is viewed as a chronic disease[2]. Unfortunately, current therapies are not an effective option for most patients and overall survival (OS) rates have remained largely unchanged for the past 3 decades[3]. There is a tremendous need for therapies targeted at decreasing recurrence rates and sustaining remission, thereby increasing overall survival.

Nutritional and lifestyle modifications have been broadly studied in the context of improving overall health and decreasing risk for illness such as cancer. The American Institute for Cancer Research estimates that diet, physical activity, and maintenance of appropriate body weight can prevent up to 30-40% of all cancers[4]. While it is becoming more widely accepted that these lifestyle changes can prevent development of disease, there is a lack of knowledge of what effect these changes can have on patients that already bear a cancer diagnosis. Women undergoing treatment for ovarian cancer are left with limited options when traditional treatments fail and their cancer returns. While a cure is not yet readily available for patients suffering the diagnosis of this lethal disease, there is a need for research targeting dietary and lifestyle modifications specific to prevention of ovarian cancer recurrence.

Statement of the Problem

Healthy dietary habits, physical activity, and overall lifestyle contribute to our general health and help prevent illnesses such as heart disease, diabetes, and even cancer. Chemotherapy has been the mainstay of oncological treatment for years, with constantly improving regimens that strive to minimize toxicities and increase efficiency. While chemotherapy, radiation, and surgery remain the standard of care for many cancers, a role for nutrition and lifestyle intervention in the prevention of cancer has been suggested. Research in this area has focused on the impact of these modifications on primary prevention of malignancy. There seems to be a gap in knowledge of the effect of these lifestyle changes on prognosis of patients with a pre-existing cancer diagnosis. While chemotherapy improves prognosis and prolongs the lives of many cancer patients, it is rarely a cure, and patients are too often left with the impending threat of recurrence.

Advanced stage epithelial ovarian cancer frequently has a particularly promising response to initial treatment with chemotherapy and cytoreductive surgery. However, overall prognosis for these women remains poor. Attempts to improve outcomes for ovarian cancer patients have focused on primary prevention and early detection. With a lack of promising progress in this area, there is a need to focus on prevention of cancer recurrence. In this instance, where primary treatment is not effective in sustaining remission or improving overall survival, could dietary and lifestyle modifications improve overall outcome and prevent ovarian cancer recurrence?

Hypothesis

Dietary and lifestyle modification for specific nutritional elements and weight reduction will reduce the rate of ovarian cancer recurrence.

Objectives

The objective is to identify specific nutrients associated with a reduction in ovarian cancer recurrence risk in patients diagnosed with advanced stage (III or IV) high-grade papillary serous ovarian cancer. The primary goal is to summarize the most recent data to be presented to providers in the format of a CME lecture. The goal of the lecture will be to provide Physician Assistants (PAs) and other health care professionals with the information necessary to recommend dietary and lifestyle guidelines for ovarian cancer patients to reduce their risk of cancer recurrence.

Specific Aims

1. Identify specific nutrients and lifestyle interventions associated with decreased risk of epithelial ovarian cancer
2. Summarize the current data on dietary and lifestyle recommendations to decrease risk of EOC
3. Create a Continuing Medical Education lecture with the goal of providing Physician Assistants with information on the most recent updates on lifestyle interventions in the prevention of EOC

REVIEW OF THE LITERATURE

Overview

Epidemiology

Ovarian cancer is the leading cause of gynecologic cancer death in women[5]. In the United States, an estimated 22,280 new cases of ovarian cancer are diagnosed annually and the projected number of deaths from this disease in the year 2016 is 14,240[6]. The predicted overall five year survival for all types of ovarian cancer is approximately 46.2%[7], but this number varies significantly based on histological type, grade, and stage at diagnosis. For patients with localized stage I cancer at diagnosis, the five year survival is approximately 92.1%, while the survival for patients with stage III or IV cancer which has spread outside the ovary and regional lymph nodes drops to just 28.8%[7]. Unfortunately, ovarian cancer rarely presents with specific symptoms, and many of these cases are not diagnosed until they have already reached a late stage and therefore carry a poorer prognosis. The difference in survival rates at a localized early stage diagnosis compared to a late stage at presentation highlights the importance of early detection and preventive measures.

The overall lifetime risk of development of ovarian cancer for the general population is approximately 1.3% and the average age for a woman at initial diagnosis is 60 years old[8]. While many risk factors have been suggested for the development of ovarian carcinoma, the strongest risk is associated with a family history, with approximately 10% of patients exhibiting an inherited genetic predisposition[8]. The greatest of the genetic risks is associated with the presence of mutations in the BRCA1 and BRCA2 genes[9]. The average risk of developing ovarian cancer for a woman with a BRCA1 mutation is 39%, while the risk for a woman with a BRCA2 mutation is 11%[10]. A 1.5-2 fold increased risk for development of ovarian cancer has been observed with infertility, nulliparity, and late or early menopause[9]. Oral contraceptive use, multiparity, hysterectomy, and tubal ligation have been found to be protective against the development of ovarian neoplasm[9].

Surface epithelial ovarian cancer (EOC) is the most frequently diagnosed ovarian malignancy. High grade serous carcinoma (HGSC) is the most common EOC, accounting for 70% of all surface epithelial carcinomas diagnosed in North America[5]. Due to its aggressive nature, HGSC accounts for 90% of the surface epithelial cancers that present with stage III or stage IV disease and is responsible for the majority of deaths due to ovarian cancer[11].

With a lack of specific symptoms and effective screening, most women are not diagnosed until they present with advanced-stage disease. Current screening for primary ovarian carcinoma includes trans-vaginal ultrasound and Cancer Antigen 125 (CA125) biomarker detection. However, neither of these techniques have been found to reduce morbidity or mortality[3] and the survival rates have remained unchanged.

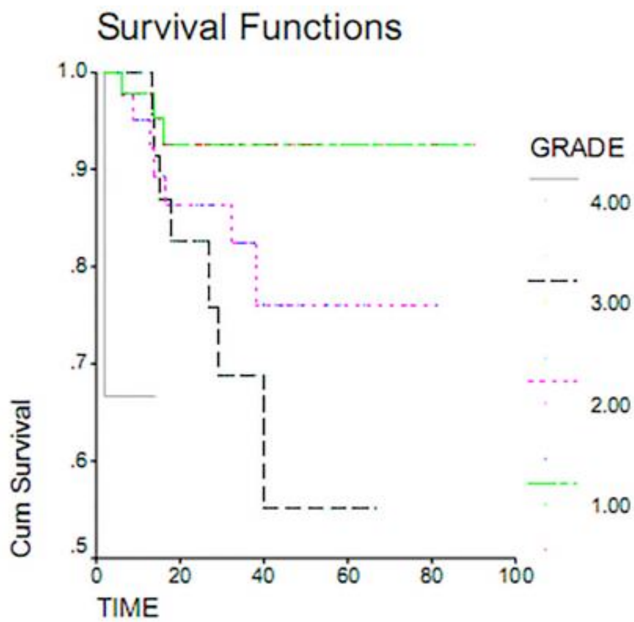

Figure 1. *Overall survival rate in patients with epithelial ovarian cancer by histologic grade,* Karimi-Zarichi, et al. (2015) [12]
In the above Kaplan Meyer curve by Karimi-Zarichi et al, the OS for ovarian cancer patients is shown over a time course in months. OS is greatest for Grade 1 disease, followed by Grade 2, Grade 3, and finally Grade 4 presenting with the worst overall survival.

Pathophysiology

Although ovarian cancer is often thought of as a single entity, it is more accurately described as a group of heterogeneous diseases, each with its own risk factors, presentation, natural history, and response to treatments. Epithelial ovarian carcinoma (EOC), which includes serous, endometrioid, clear-cell, and mucinous types, accounts for approximately 90% of all ovarian neoplasms [13]. Among the epithelial neoplasms, serous carcinoma is the most common and will be the focus of this literature review. Serous carcinoma is further divided into two sub-classifications, High Grade Serous Carcinomas

(HGSC) and Low Grade Serous Carcinoma (LGSC). These two subtypes differ greatly with regards to their pathology and pathophysiology and have been found to develop and progress via two distinct pathways (Figure 2)[14].

The LGSCs follow what is now known as the Type I pathway. Type I ovarian cancer includes low grade serous carcinoma, endometrioid carcinoma, mucinous carcinoma, and clear cell carcinomas[15]. Type I low grade serous carcinomas have been found to develop from precursor adenofibromas or borderline tumors and progress to serous carcinoma through a somewhat predictable and step-wise manner[14]. Via this Type I pathway, a serous cystadenoma or adenofibroma slowly progresses to an atypical proliferative serous tumor (APST) then to a non-invasive macropapillary serous borderline tumor (MPSC), and finally to an invasive MPSC[14]. The identifiable precursor lesions and the relatively slow, step-wise pattern of development often allow low grade serous tumors to be detected and diagnosed at a relatively early stage. LGSC are also associated with a certain group of genetic mutations. Specifically, they frequently exhibit mutations in the KRAS, BRAF, PTEN, and CTNNB1[15] and generally lack mutations of TP53[14]. Tumors that progress along the Type I pathway present with low-grade nuclei with infrequent mitotic figures[14]. The differences in genetic mutations, precursor lesions, and mitotic figures may provide some explanation as to why these tumors behave so differently than High Grade Serous Carcinomas of the ovary.

Ovarian High Grade Serous Carcinomas (HGSC) are thought to develop via what is known as the Type II pathway. Unlike the adenofibroma of LGSC, a consistent morphologically identifiable precursor lesion of HGSC has been more difficult to verify and the tumors have long been thought to arise de novo. However, there is mounting evidence to suggest that many of these HGSCs actually develop from intraepithelial carcinoma in the fallopian tube and therefore are not in fact strictly of ovarian origin[14].

While a morphologically identifiable precursor lesion for HGSC has not been recognized, it is becoming increasingly more accepted that many of these carcinomas may in fact arise from very early lesions in the fallopian tube known as tubal intraepithelial carcinomas (TIC)[14]. These lesions are found at the fimbriated end of the fallopian tube, in close proximity to the ovarian surface. Increasing evidence suggests that TICs may be the origin of at least a subset of these high grade malignancies. First, in women with BRCA mutations but no evidence of ovarian cancer undergoing prophylactic salpingo-oophorectomies, early serous carcinomas have been detected in the fallopian tube with no evidence of tumor in the ovary itself. Second, 92% of TICs contain an identical TP53 mutation as that seen in ovarian high grade serous carcinoma. Third, p53 is expressed in small foci of histologically normal epithelium, termed the p53 signature. It is thought that this p53 mutation leads to TIC, which ultimately progresses to HGSC of the ovary [14]. While it is possible that these tubal intraepithelial carcinomas may actually be metastases from a primary ovarian cancer, TICs have been found to have shortened telomeres compared to HGSC. These shortened telomeres are an early sign of carcinogenesis leading to chromosomal instability, which is a key trait of HGSC [16], suggesting that the TIC develops prior to HGSC.

Type II HGSC are clinically aggressive and often not discovered and diagnosed until they have already reached an advanced stage[15]. The progression of HGSC is rapid with characteristic high grade nuclei and numerous mitotic figures [14]. The common mutations of KRAS, BRAF, or ERBB2 seen in LGSC are uncommon in HGSC, but TP53 mutations are seen in 80%, indicating a significant genetic difference between the two types of serous carcinomas. Additionally, germline mutations of BRCA1 or BRCA2 are found in 15% of all serous carcinomas in North America, and are much more frequently noted in HGSC than in LGSC[14]. Both BRCA and TP53 serve a tumor suppression function and therefore mutations in these genes allow for development of tumor activity and carcinoma progression. The increased likelihood of BRCA mutations in Type II ovarian cancer correlates with an increased risk for hereditary breast and ovarian cancer (HBOC)[15].

The type I and type II pathways described are generally thought to be mutually exclusive, each following a distinctly different natural progression and resulting in unique presentations of disease. However, there is a possibility that a small subset of HGSC (type II) may actually arise from LGSC (type I). In a study carried out at Johns Hopkins Hospital, 3% of all serous carcinomas contained components of both high and low grade serous carcinoma[17]. Of the tumors with shared components, none of them contained a mutation of TP53, the mutation commonly seen in typical high grade serous carcinomas[17]. The lack of TP53 mutation suggests that the HGSC may have actually evolved from LGSC, a carcinoma that commonly lacks TP53 mutations[14], rather than from the type II pathway traditionally seen in HGSC.

LGSC and HGSC, arising from separate precursors and evolving via different mechanisms, present very different prognoses for patients. LGSC, developing via the

Type I pathway is typically composed of slow growing tumors and therefore often present at an earlier stage, where early intervention can occur. In contrast, HGSC typically presents with rapidly progressing aggressive tumors and patients are generally not diagnosed until late stage, where intervention is less effective. Unfortunately, the majority of all serous ovarian cancers are of the high-grade type, where treatment options for recurrent disease are limited and information is sparse on how to prevent recurrence.

In the instance of low-grade serous carcinoma, where a precursor lesion can be identified and genetic mutations can be targeted, early treatment provides for a much better prognosis for many women. However, in the instances of HGSC, where genetic mutations are not identified and a precursor lesion cannot be detected early in the clinical course, there is a need for additional targets of therapy.

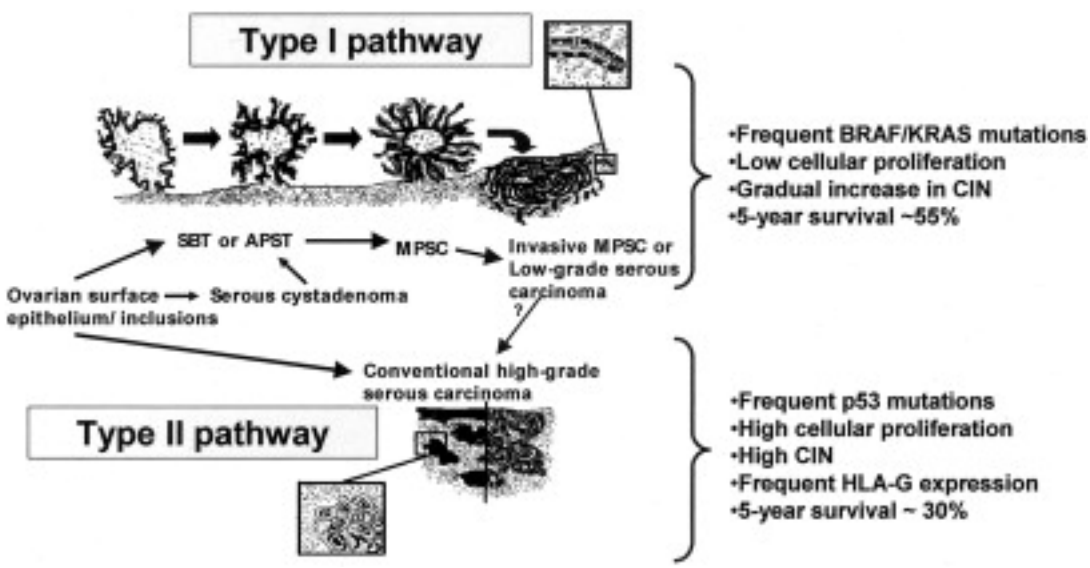

Figure 2, Shih et. Al (2004).[18] *Schematic representation of the dualistic model depicting the development of ovarian serous carcinomas, the most common type of ovarian cancer.* [18]

Treatment

The current treatment of primary ovarian cancer most often consists of a combination of cytoreductive surgery with a carboplatin and paclitaxel based chemotherapy regimen[19]. Cytoreductive surgery is performed with the goal of achieving no gross residual disease post-operatively. It has been demonstrated that a visibly disease-free outcome after surgery is a more significant prognostic indicator of survival than degree of metastasis prior to surgery[20]. Patients with high grade serous carcinoma typically have a promising response to chemotherapy treatment, with 70-80% exhibiting an expected initial response[1].

Recurrence of ovarian carcinoma following initial treatment is often difficult to detect. Patients reported to be in remission are generally asymptomatic, living high quality lives. Similarly to the presence of primary ovarian cancer, recurrence often presents with only vague abdominal symtoms[2]. Due to the lack of specificity of the physical symptoms, recurrence is frequently detected clinically via CA125 measurement or CT scans prior to the patient noticing any changes[2].

Treatment options for recurrence of ovarian cancer are often dependent upon the level of platinum sensitivity. Platinum sensitivity is defined as having a platinum-free interval (time between the last dose of platinum-based chemotherapy and evidence of cancer progression) of greater than or equal to 6 months. If the platinum-free interval is less than 6 months, the cancer is considered to be platinum resistant[13]. It has been found that treatment of recurrent ovarian cancer with paclitaxel plus platinum-based chemotherapy improves survival and progression-free survival compared to conventional platinum-based therapy[21]. For patients who no longer respond to platinum-based chemotherapy, treatment choice should consider patient preference, toxicity profile, ease of administration, and availability[19]. Single treatment regimens with paclitaxel, topotecan, or pegylated liposomal doxorubicin should be considered as they have shown to be reasonably effective in patients demonstrating platinum-resistance[19]

Clinical Course

More than 80% of patients with advanced stage ovarian cancer will experience recurrence of their cancer at some point after initial treatment[13] and will require additional therapy[2]. Patients whose recurrence presents as isolated metastatic cancer that can be fully resected with an additional cytoreductive surgery have a better prognostic outcome. Unfortunately, this presentation is rare[13]. Due to the lack of effective options, treatment of patients with recurrent epithelial ovarian cancer is now viewed by physicians as management of a chronic disease[2].

Despite the extremely high recurrence rate, an effective screening measure to identify relapse of ovarian cancer and improve outcomes for these patients does not yet exist. The most frequently identified initial sign of ovarian cancer recurrence is an increase in CA-125 serum level. It is a glycoprotein that serves as a biomarker for ovarian cancer. An increase in CA-125 level can be seen approximately 2 to 6 months before cancer recurrence is detectable via imaging studies or before the patient becomes symptomatic[22].

However, the recommendation on how often to monitor this biomarker varies depending on the source. According to the Society of Gynecologic Oncology (SGO), a review of clinical symptoms and physical examination of patients following initial treatment for ovarian cancer should be completed every 3 months. If there is clinical suspicion of recurrence, an optional CA125 test and CT, PET, or MRI imaging should be perfeormed[23]. The National Comprehensive Cancer Network (NCCN) guidelines recommend follow-up visits every 2-4 months for 2 years with routine measurement of CA125 levels and additional radiographic imaging in cases where recurrence is suspected[24].

While CA-125 levels allow for detection of possible recurrence earlier than presentation of symptoms or detection of disease via imaging studies, it is not clear if treatment based solely on elevation of CA-125 is justified. Treatment in asymptomatic women with a detected elevation in CA-125 has not been found to significantly impact survival[22]. In a study conducted by the European Organization for Research and Treatment of Cancer, women in clinical remission were randomized to treatment either based on detection of elevated CA-125, or after the onset of symptoms. It was found that there was no significant improvement in survival regardless of if treatment was initiated immediately following CA-125 detection or following onset of symptoms[22]. Thus, while it allows earlier detection for ovarian cancer recurrence, CA-125 elevation may not hold much value in improving survival in patients with recurrent cancer. This suggests that recurrence of ovarian cancer carries an overall poor prognosis, regardless of when treatment is initiated.

The high recurrence rate, ineffective screening measures, and limited treatment options for recurrence all reinforce the need for development of new therapies and techniques focused on maintenance of progression-free survival (PFS). Dietary and lifestyle interventions have been studied in the context of prevention of primary development of cancer, but there is a gap in the knowledge of how these interventions impact the prognoses of patients post-diagnosis. A universally recommended guideline outlining specific nutritional components to optimize patients' diets to prevent the recurrence of cancer may be the next step in improving the clinical course of ovarian cancer.

Prevention

Known risk factors for ovarian cancer, as mentioned previously, include family history, nulliparity, infertility, hormone replacement therapy, and early or late onset of menopause. For women with a genetic predisposition or with the presence of a precursor lesion in the fallopian tubes, prophylactic salpingo-oophorectomies are available to reduce the risk of ovarian cancer development. The Society of Gynecologic Oncology recommends that all women aged 35-40 who have germline mutations in high risk genes should undergo risk-reducing surgery[25].

For the general female population, however, prevention is typically aimed at avoidance of the known risk factors. It is believed that ovulation plays a role in ovarian carcinogenesis, supported by the significant reduction in ovarian cancer risk seen with the use of oral contraceptives as well as increased parity [16]. It has been proposed that hemolyzed blood from retrograde menstruation and the release of follicular fluid during ovulation causes increased free radicals, predisposing to carcinogenesis[16]. Therefore, ovulation suppression may have a protective effect against EOC development.

Due to the heterogeneity of ovarian cancer as a disease, it is becoming increasingly evident that the treatment and management of these malignancies must be individualized in order to achieve the most effective outcome. Genomic Wide Association Studies (GWAS) have been carried out to compare the genotype frequencies of common variants seen in ovarian cancer throughout the genome[15]. Through these genomic studies, Single Nucleotide Polymorphisms (SNPs) have been identified that show an association with increased ovarian cancer risk. If more of these polymorphisms can be identified, it would open a window of opportunity for prevention of recurrence via targeting specific genetic components and may have implications on the future of EOC treatment.

Lifestyle

An estimated 30-40% of all cancers can be prevented by lifestyle and nutritional measures alone[26]. A healthy lifestyle includes a nutritional diet, physical activity, and maintenance of a healthy weight. Given the poor prognosis and extremely high recurrence rate of ovarian cancer, there is a need to identify additional options for patients to reduce their risk of recurrence and increase progression free survival. While trials for new therapies continue to evolve, a lifestyle intervention that could potentially improve prognosis would be extremely valuable to patients currently suffering from this disease. Unfortunately, the nutritional and lifestyle guidelines for ovarian cancer survivors are not well defined and can be confusing.

There is a significant body of research on several different nutritional elements that may play a role in reduction of cancer risk. However, a universal guideline is not available to ovarian cancer survivors wishing to optimize their diets to minimize cancer recurrence risk. In this literature review, the goal is to compile a list of recommended nutrition guidelines for ovarian cancer patients in remission in order to decrease their risk of recurrence.

Obesity remains a risk factor for much morbidity, including several types of cancers. Higher body weight has been positively associated with a higher death rate in esophageal, colon, rectal, liver, gallbladder, pancreatic, renal, gastric, prostate, breast, uterine, cervical, and ovarian cancer[27]. Several factors including genetics, sedentary lifestyle, and poor dietary habits contribute to the development of obesity.

Increased physical activity is believed to be protective against many cancers. Little research has been done, however, on the impact of physical activity on long-term survival and prevention of cancer recurrence in ovarian cancer survivors. Several studies have supported the hypothesis that obesity and hormone replacement therapy increase the risk for ovarian cancer while oral contraceptives decrease the risk[28]. Physical activity, with the goal of maintaining a healthy body weight, may be protective against obesity and therefore reduce the risk of cancer.

It has been proposed that energy balance of calorie intake and expenditure has implications on cancer risk. A positive energy state, with a high body mass index (BMI) and increased obesity has been associated with higher risk of development of many cancers. This positive energy balance promotes tumor growth by creating an environment that favors tumor-promoting factors. These modify growth signaling, inflammation and angiogenesis[29], making an ideal environment for tumor development and growth. High levels of insulin and insulin growth factor (IGF-1) increase the risk of cancer development and serve as a poor prognostic factor[29]. The insulin-insulin growth factor pathway activates downstream signaling to lead to the activation of the phosphatidylinositol-3 kinase/Akt-mTOR (P13K/Akt) pathway, regulating cell survival and proliferation. The PI3K/Akt pathway is commonly activated in all cancers[29]. Therefore, a diet that restricts the amount of insulin released, thereby reducing the extent of activation of the PI3K/Akt and similar pathways may reduce cancer risk and improve prognosis for patients with cancer. An increased activation of these pathways has been found in high-energy diets and decreased activation seen in calorie restricted diets[29], suggesting a protective role of calorie restriction.

Over-consumption of calories has been positively associated with cancer risk, while Calorie Restriction with Optimal Nutrition (CRON) has been found to inhibit tumor growth [26]. CRON emphasizes a reduction in the total amount of calories consumed by about 20-30% of the amount required to maintain a “normal” bodyweight while still emphasizing necessary amounts of vitamins, minerals, and other nutrients. Therefore, the CRON diet does not simply restrict all calories, but restricts excess calories, while maintaining necessary healthy nutrients.

Furthermore, it is possible that a calorie restriction diet alone provides anti-cancer benefits, regardless of nutritional content. Women with anorexia nervosa, exemplifying a low caloric intake as well as decreased nutrient intake, have been found to have a lower incidence of breast cancer[26], suggesting that perhaps a low calorie diet is sufficient in decreasing cancer risk regardless of the quality of nutrients consumed. It is possible that a low-calorie diet is protective against insulin resistance. Obese individuals often have increased levels of insulin and IGF-1 in their blood, a phenomenon known as hyperinsulinemia or insulin resistance. In addition, obesity also predisposes to an increased amount of estrogen, due to high production of this hornome in fat tissue. Estrogen has been associated with several types of cancers, including breast cancer and some types of ovarian cancer. While a high-energy diet is associated with hyperinsulinemia and increased estrogen production predisposing to cancer, calorie restriction and reduction in body fat, as seen in women with anorexia nervosa, seems to create a hostile environment for tumor development.

While a low-calorie diet is thought to effectively starve tumor cells and therefore decrease tumor growth and development of cancer, it is important to recognize specific nutritional elements that put people at particular risk for tumor growth as well as elements that appear to be protective. Cancer development has been associated with alterations in cell metabolism. A commonly recognized property of cancer cells is their ability to utilize glucose at especially high rates[30]. Hexokinase is the enzyme involved in converting dietary glucose to glucose-6-phosphate. It has been found that hexokinase has increased activity in cancer cells via an increase in the gene copy number of the enzyme[30]. With an increased amount of hexokinase working to utilize glucose to promote cancer cell growth, malignant cells have developed a proliferation strategy supported by a diet high in glucose-rich foods. The enzyme is activated by glucose, insulin, hypoxic conditions, and phorbol esters. Therefore, ingestion of sugary foods feeds the metabolic strategy of cancer cells, favoring rapid proliferation and prolonged survival[30].

Concentrated sugars and refined flour products further impair normal glucose metabolism. Glycemic index (GI), which takes into account the blood sugar response to a standardized amount of carbohydrate in a certain food, and glycemic load (GL), which additionally accounts for the amount of the food eaten, have been positively associated with cancer development[26]. The higher the glycemic index of a certain food, the more insulin is released as a response to increase in blood sugar. Therefore, a high GI increases the levels of insulin and IGF-1, predisposing to hyperinsulinemia. Ovarian cancer has been directly associated with dietary glycemic index, suggesting a possible role of hyperinsulinemia and insulin resistance in ovarian cancer development[31]. Therefore, there may be a role in insulin-sensitizing agents similar to those encouraged in a diabetic diet in cancer patients.

Resveratrol, an insulin sensitizer, has been found to interrupt glucose metabolism in specific cancer cells[32]. It has selective cytotoxicity for ovarian cancer cells through glucose metabolism regulation via regulation of glucose transporter 1 (GLUT1), which is overexpressed in ovarian cancer[32]. A study performed by Gwak et all found that resveratrol inhibits GLUT1 transport to the plasma membrane, therefore impairing glucose uptake and inducing apoptosis[32]. This data suggests that the phytochemical resveratrol, found in fruits such as blackberries, blueberries, and red grapes may have a role in prevention of ovarian cancer development via interruption of glucose metabolism.

Much of the research in the area of nutrition and oncology has included the role of antioxidants and free radicals in the progression of carcinogenesis. Free radicals are created during the transfer of energy when an atom or molecule either gains or loses an electron. This happens naturally as a byproduct of normal human processes, but causes damaging oxidative stress in high concentrations. Reactive oxygen species (ROS) created in this process damage nucleic acids, amino acids, and other cellular components predisposing to cancer development[33]. These are neutralized naturally by the body's antioxidant system, which consists of enzymes and other compounds[33]. Antioxidants work to inhibit oxidation, or the loss of an electron, thereby decreasing the amount of free radicals created.

Many foods contain antioxidant properties and may help prevent carcinogenesis by minimizing free radicals when they reach dangerous concentrations. Dietary antioxidants have been found to be useful in supplementing the effects against carcinogenesis caused by arsenic[33]. This concept may be generalizable to other types of cancers affected by free radicals and ROS and may hold value in the prevention of ovarian cancer. More research is needed in the area of antioxidants and ovarian cancer specifically, but several antioxidant-containing foods have been associated with decreased cancer risk.

In addition to their resveratrol content and effects on glucose metabolism, red grape seeds and skins contain beneficial antioxidants. They are thought to have anticancer activity through a wide range of mechanisms. These antioxidants specifically target epidermal growth factor receptor (EGFR) and its downstream pathways, inhibiting over-expression of COX-2 and prostaglandin E2 (PGE2) receptors, as well as modifying estrogen receptor pathways, resulting in cell cycle arrest and apoptosis. This function in prevention of replication and resultant apoptosis could allow for targeted limitation of rapidly dividing malignant cells, suggesting a role of red grape products in the reduction of cancer occurrence.

Fruits and vegetables provide countless health benefits. It remains controversial, however, whether a diet high in fruits and vegetables has a significant impact on ovarian cancer risk specifically. Several studies have failed to show an association, while others have suggested a possible relationship but remain inconclusive. It may be that certain vegetables are beneficial in preventing ovarian cancer while others fail to have an effect. It has been proposed that increased intake of yellow and cruciferous vegetables, such as broccoli, brussel sprouts, and collard greens, as well as carotenoid-containing vegetables improve survival in ovarian cancer patients.

Carotenoids are known for providing health benefits via antioxidant properties, inhibition of malignant tumor growth, and induction of apoptosis[34]. A high intake of foods containing carotenoids has been associated with reduced risk of breast, cervical, ovarian, and colorectal cancers[34]. They can be found in foods such as carrots, spinach, bell peppers, kale, and several other vegetables. The major carotenoids that seem to have the greatest antioxidant effect include B-carotene, lycopene, lutein, zeaxanthin, crocin, and curcumin[34]. A significant increase in both alpha and beta carotenoids has been associated with a diet composed of low fat, high fiber, encapsulated fruit and vegetable juice concentrates, and a soy-based beverage[35]. Their antioxidant activity inhibits cell growth and malignant transformation and may be associated with improved prognosis among ovarian cancer survivors[35].

The poor prognosis of patients with advanced EOC is attributed in large part to the late stage at diagnosis and the tendency for early metastasis even prior to diagnosis. Hens have been found to closely model the human response to ovarian cancer. Hens fed flaxseed-rich diets have a significant reduction in ovarian tumor severity, with more tumors confined to the ovary and decreased metastatic spread[36]. Flaxseed contains omega 3 fatty acids (OM-3FA) and phytoestrogen lignans, which have anti-inflammatory, anti-cancer effects [36]. OM-3FAs and phytoestrogen lignans target the inflammatory prostaglandin pathway, most notably PGE2[37]. Ovarian cancer has a significantly better outcome at early stages with containment to the ovary and decreased metastatic spread. If flaxseed can reduce ovarian tumor severity and metastasis, it opens the possibility of treating more women in an early stage of cancer, thus improving their prognosis significantly. Additionally, there could be a role of flaxseed in preventing ovarian cancer recurrence at more distant sites, favoring a more localized presentation and therefore a better prognostic outcome.

Vitamin D deficiency has a potential role in promoting development of many different types of cancers. Conversely, higher Vitamin D levels may improve overall prognosis of ovarian cancer patients. It has been found that higher serum 25-Hydroxyvitamin D (25(OH)D) concentrations at the time of diagnosis of ovarian cancer are associated with increased survival, independent of other prognostic factors such as age, stage, and post-operative residual disease[38]. Increased intake of Vitamin D was found to be strongly inversely associated with serous borderline and endometrioid tumors in particular[39]. More research is needed to determine a direct effect of Vitamin D on serous tumor development, but vitamin D supplementation may improve survival outcomes for women with all types of ovarian cancer.

The effect of dairy products on cancer development has been controversial. Some studies have suggested an increased risk of cancer associated with high dairy intake while others have proposed an inverse relationship. One study found that high intake of certain dairy foods is in fact associated with increased ovarian cancer risk while others demonstrate a protective property against ovarian carcinoma. In particular, it was observed that intake of skim/low fat milk, yogurt, and cheeses decreased ovarian cancer risk while whole milk and cream cheese increased risk[39]. When the specific components of dairy nutrients were examined, calcium was found to have a strong inverse association with ovarian cancer risk overall, with a particularly strong effect on decreasing risk of serous borderline and mucinous tumors. More studies are needed to determine a possible effect of these two components on high-grade serous carcinoma risk.

In addition to their role in direct prevention of cancer, there may be a role of certain foods in promoting chemo-sensitivity. Often times, recurrent ovarian cancer presents with platinum-resistant disease. There is mounting evidence that certain nutritional elements may have sensitizing effects on chemotherapy drugs, amplifying response. One study isolated individual cranberry flavonoids to examine their effect on ovarian cancer cells. Two flavonoids with the most promising results were quercetin aglycone and cranberry A-type proanthocyanidins (PACs). Poly (ADP-ribose) polymerase (PARP) is a family of enzymes involved in DNA repair. When DNA damage is severe, such as in cancer cells, PARP translocates apoptosis inducing factor (AIF) from the mitochondria to the nucleus, increasing the apoptotic threshold and favoring cancer cell survival[40]. Pharmacologic inhibition of PARP has been proposed as a therapy option for several types of cancers[40]. Treatment of ovarian cancer cells with quercetin aglycone and PAC DP-9 led to the induction of increased apoptosis, causing caspase-3 activation, PARP deactivation, and amplification of cisplatin antitumor activity [41]. Therefore, dietary flavonoids, particularly quercetin aglycone and cranberry A-type proanthocyanidins, seem to be protective against ovarian cancer and may have potential to prevent recurrence.

Table 1. Nutritional Elements and Ovarian Cancer Risk

Protective Factors	**Risk Factors**
Flavonoids	Red and processed meat
Cruciferous vegetables	High glucose diet
Calorie restriction	High calorie diet
Flax seed	Obesity
Carotenoids	Concentrated sugars
Vitamin D	High fat diet
Fiber	Refined flour products

Table 1. *Nutritional Elements and Ovarian Cancer Risk*. Table 1 summarizes some of the proposed nutritional elements and their effects on ovarian cancer risk. Both protective factors and risk factors for development of ovarian cancer are listed.

Existing research

Obesity has been studied extensively in the context of cancer risk. It has been found to be associated not only with an increased risk of developing cancer but also with an increased risk of death from various cancers. One prospective study found that women with a BMI greater than or equal to 40 had a relative risk of dying from cancer of 1.62, with a 95% confidence interval 1.40-1.81[27]. In women with ovarian cancer, those with a BMI of 35.0-39.0 had a relative risk of death from their cancer of 1.51, compared to women with a BMI 18.5-24.9, with a 95% confidence interval, 1.12-2.02[27].

It is thought that a positive energy balance, or excess intake of calories, promotes tumor growth and thus predisposes to cancer development, while a negative energy balance with caloric restriction delays cancer progression. One study showed that a positive energy state attained by a fat-rich diet encouraged an aggressive ovarian cancer growth pattern, while a negative energy state achieved by a 30% calorie restriction diet resulted in limited and restrained ovarian cancer growth pattern in vivo in mice[29]. Mice were injected with ID8 cells to generate ovarian tumors and the differences in tumor progression were analyzed between a group fed a regular diet (RD), a high energy diet (HED), and a calorie restriction diet (CRD)[29]. They found that the mice in the HED had a significantly higher number and size of tumor nodules in the diaphragm and bowel compared to those in RD and CRD, while the CRD mice had the lowest overall tumor burden ($p<0.001$)[29].

A calorie restriction diet, on the other hand, has been found to have an inverse relationship with tumor development. In an observational cohort study, O'Brien, et. al (2016) found that women with a history of an eating disorder were less likely to develop breast cancer than women who had never had an eating disorder (HR=0.62, 95%CI: 0.42-0.92)[42]. Women with a past diagnosis of anorexia nervosa have a history of following an extreme calorie-restriction diet. This supports the idea that calorie restriction may indeed be protective against breast cancer, and may have implications on other types of cancer as well.

There may be a role of hyperinsulinemia in promotion of cancer development. A case-control study conducted in Italy analyzed the effect of glycemic index (GI) and glycemic load (GL) on ovarian cancer risk. They studied 1031 women with epithelial ovarian cancer with a median age of 56 and compared them to a control group of 2411 women with a median age of 57 years with no history of cancer. Using a questionnaire to assess dietary habits, they determined that ovarian cancer was directly associated with dietary glycemic index (OR 1.7, 95% CI 1.3-2.1) and with glycemic load (OR= 1.7, 95% CI 1.3-2.1)[31]. Therefore, foods with high GI, such as sugary and fatty foods, which increase insulin response to blood sugar and predispose to hyperinsulinemia, increase risk of ovarian cancer. Women diagnosed with ovarian cancer should be urged to avoid food with a high glycemic index in order to prevent progression and recurrence of their disease.

A study conducted to determine the outcomes of three different dietary styles examined women with different nutritional habits to determine the effect on ovarian cancer risk. The three groups were defined as “meat and fat”, which included women who reported high consumption of processed meat, eggs, fat spreads, and sweets, “snacks and alcohol”, which included women with high consumption of alcohol, pizza, nuts, and other snacks, and “fruit and vegetable”, with high consumption of fruits, veggies, and whole-grains[43]. The women with a diet high in red meats, processed meats, and fat had a 2.5 fold increased risk of ovarian cancer[43]. The same study found a 40% lower risk of ovarian cancer in women in the “snack and alcohol” diet. After adjusting for confounders, the protective effect of the snack and alcohol diet was ultimately attributed to an inverse relationship of red wine consumption with ovarian cancer risk[43]. This supports the hypothesis that flavonoids and resveratrol found in red wine reduce ovarian cancer risk.

The antioxidant properties of foods containing a large amount of carotenoids have been found to be protective against EOC risk. A case-control study conducted in China by Zhang et al found a significant inverse association between intake of specific carotenoids and ovarian cancer risk. They examined 254 patients with EOC confirmed by histology and 652 age-matched controls. They compared the highest vs. lowest quartile of intake for alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein, and zeanthin, and total carotenoids. Results supported a lower incidence of ovarian cancer for the highest quartile of all carotenoids; alpha carotene (OR 0.39, 95% CI 0.23-0.66), beta-carotene (OR 0.51, 95%CI 0.31-0.84), beta-cryptoxanthin (OR 0.51, CI 95% 0.31-0.84), lutein and zeanthin (OR 0.45, 95%CI 0.27-0.76), and total carotenoids (OR 0.33, 95% CI 0.20-0.56)[44].

Flax seed, which has an inherent antioxidant property, has been found to significantly impact the risk of EOC development, showing involvement in restricting ovarian tumors to more localized presentation. Eilati et al studied hens fed a flaxseed-enriched diet and compared them to a control group to analyze for ovarian cancer risk. In the 3.5 year old hens, 50% of those fed a control diet developed ovarian cancer, while only 20% of those fed a flaxseed enriched diet developed ovarian cancer ($p<0.05$)[37]. Additionally, hens in the control group were more likely to develop late stage (T3 and T4) tumors, presenting with ascites and metastases, than the group fed a flaxseed rich diet[37]. The protective property of flaxseed in ovarian cancer risk seems to be largely tied to its ability to decrease levels of PGE2. In the hens studied by Eilati et al, PGE2 concentration was significantly decreased in cancerous ovaries in hens fed flaxseed enriched diets than in those fed a control diet ($p<0.001$)[37]. Increased dietary flaxseed seems to have a protective effect on ovarian cancer risk, a property that may be attributed to its ability to decrease concentrations of the inflammatory agent PGE2.

The association between circulating 25(OH)D and ovarian cancer risk has not been well defined. Zheng et al performed a case-control study among seven prospective studies in order to evaluate this relationship. They found no statistically significant effect of circulating vitamin D levels and EOC risk. However, when stratified for individual factors, an inverse association between 25(OH)D and ovarian cancer risk was suggested for women with a BMI >25kg/m2 ($p<0.01$)[45], suggesting that there may be a role of increased vitamin D concentration in preventing ovarian cancer in overweight women. Webb et al examined the effect of serum 25(OH)D concentration on overall survival of women with ovarian cancer. It was found that at diagnosis, higher serum 25(OH)D levels were associated with increased overall survival, with a HR 0.93, 95% CI 0.88-0.99 per 10nmol/L 25(OH)D)[38]. In addition to serving a protective factor against ovarian cancer risk in overweight women, vitamin D levels may also prolong ovarian cancer survival rates.

A longitudinal follow up study by Dolecek et al analyzed the effect of pre-diagnosis diet on survival among 341 women diagnosed with EOC. They found that higher vegetable intake in general was associated with longer survival (HR 0.66, 95% CI 0.43-1.01, $p<0.05$)[46]. Additionally, when analyzed specifically for yellow and cruciferous vegetables, survival was significantly better with increased intake. Higher meat intake, particularly red and processed meats, was found to have an inverse association with survival (HR 2.28, 95% CI 1.34-3.89). Dolecek et al also examined the effect of dairy on long term survival and found that milk consumption to be associated with decreased survival (HR 2.15, 95% CI 1.20-3.84, $p <0.05$)[46]. Pre-diagnosis diet may therefore have a significant effect on the long-term outcomes of ovarian cancer patients, with a diet high in cruciferous vegetables improving survival and red meats and dairy products decreasing survival. More research is needed in this area on the effect of changing to a diet based on these findings to determine the effect of a post-diagnosis diet on recurrence rates and long-term survival.

METHODS

Study design

A lecture-based curriculum on nutrition and lifestyle recommendations for patients with ovarian cancer will be developed and presented to Physician Assistants (PAs) and other health care providers working in primary care and oncology. A review of the most up to date findings on the effects of nutrition and lifestyle interventions on ovarian cancer will be summarized and presented to the audience. The goal is to educate providers on information about dietary and lifestyle modifications specific to decreasing risk of ovarian cancer development. The hope is for attendees of the lecture to leave equipped with the knowledge necessary to feel comfortable engaging in a conversation with patients about lifestyle modifications to reduce their risk of cancer recurrence. This curriculum will be presented at Continuing Medical Education (CME) conferences and offered for one hour of CME credit.

Study population and sampling

The lecture will be given as a CME course at both national and local conferences with the goal of a total of 200 attendees. Assuming an estimated attendance of 100 providers at the national conferences and 10 providers at each of the local conferences, the course will need to be offered at least one national conference and ten local conferences in order to reach the sample size goal. The information will be presented as a one hour long lecture directed toward health care providers at the level of PA, but will be available to physicians, nurses, and other health care workers who are interested in acquiring information to provide their patients.

Study variables and measures

In order to assess the efficacy of this curriculum, all those in attendance will perform a pre-test and a post-test to quantify baseline knowledge and evaluate the amount learned during the lecture. The pre-test will consist of 15 multiple-choice questions and will be formatted as a digital response Turning Point style quiz. Each attendee will be provided with a clicker for response purposes upon entering the lecture hall. Answers to the pre-test questions will not be provided. At the end of the lecture, the same questions will be presented to the audience for response. The goal is to achieve a passing score of 80% for the post-test. In order to achieve the passing score of 80%, participants will need to provide the correct answer to 12 of the 15 questions.

Recruitment

The lecture will be offered at CME national and local conferences and made available to all health care workers, particularly emphasizing the attendance of physician assistants working in a primary care or oncology setting. Information about when and where the course will take place will be available on the CME website. Institutions interested in hosting the lecture will be given a flyer with a brief outline of the course as well as the time and location the lecture will take place to email to health care employees to encourage attendance.

There will be a sign in sheet located at the door to the lecture hall for all attendees to sign in. This will allow all health care providers to gain CME credit for their participation in this course. The CME credit as well as the unique opportunity to gain access to information regarding updates on nutrition and oncology will serve as incentive for attendance.

Curriculum

The curriculum will take the format of an hour-long lecture accompanied by a PowerPoint presentation. The learning objectives (Table 2) will be presented at the beginning of the lecture and will highlight the key aspects of the course. They will serve as the outline for the talk and will provide the audience with the key take-away points.

Table 2. Learning Objectives

At the end of the lecture, the learner will be able to:
1. Recognize the limited effective treatment options and poor prognostic outcome for women with type 2 advanced ovarian cancer
2. Identify the proposed differences between the type 1 and type 2 pathways of EOC and recognize treatment differences.
3. Apply the most recent data on dietary and lifestyle modifications and EOC to their clinical work

4. Create a provider-patient dialogue to educate patients about recommendations and guidelines pertaining to nutrition and lifestyle in the prevention of EOC recurrence
5. Recognize the need for additional studies on type 2 EOC to solidify evidence pertaining to nutrition and lifestyle and the prevention of recurrence

Presentation Outline:

- Introduction to the epidemiology of ovarian cancer, focusing on poor prognosis of advanced stage disease
- Description of the differences between type 1 and type 2 disease, with emphasis on the lack of treatment options for recurrent aggressive type 2 cancer
- Overview of the current treatment options, including the chemotherapy regimen and cytoreductive surgery
- Presentation of recurrence rates statistics and poor survival even after promising response to therapy
- Outline of the most recent findings in nutrition and lifestyle and the role in prevention of ovarian cancer development
- Reinforce the need for additional studies on the effect of nutrition on the prevention of recurrence in women previously diagnosed and treated for EOC

Curriculum Assessment

The pre and post-test will serve as the main assessment of the ability of the curriculum to meet the learning objectives. The pre-test will assess health care provider's baseline knowledge on ovarian cancer and the role of nutrition and lifestyle on preventing cancer development. As mentioned previously, the pre-test will be administered to all people in attendance prior to the start of the PowerPoint lecture using the Turning Point clicker system. Similarly, when the lecture has been completed, the post-test will be administered to the audience using the clicker system. Additionally, the participants will be given a paper survey asking asked how the knowledge acquired during the session will change their current practice (with up to 3 concrete examples). The survey is to be turned in prior to exiting the lecture hall.

The content of the pre and post-tests will have basis in the learning objectives and will include questions on nutritional elements and their effects on ovarian cancer development. The question topics are displayed in Table 3.

Table 3. Question Topics

1. Types of ovarian cancer
2. Pathway of type 1 vs type 2 EOC
3. Overall prognosis of ovarian cancer
4. Five year survival for advanced stage EOC
5. Chemotherapy regimen for EOC
6. Outcomes of cytoreductive surgery
7. Effect of BMI on ovarian cancer development
8. Effect of obesity on cancer mortality rates
9. Effect of flaxseed on development of EOC

10. Effect of carotenoids on development of EOC
11. Effect of cruciferous vegetables on development of EOC
12. Effect of red meats on development of EOC
13. Glucose metabolism in cancer cells
14. Effect of dairy products on development of EOC
15. Extent to which audience feels comfortable discussing dietary and lifestyle interventions for cancer patients in their practice

Study variables and measures

The main measure of the competency of the lecture to provide useful information and effectively teach the attendees will be the pre and post-tests. A series of 15 questions will be presented for the pre-test to assess the baseline knowledge of the attendees. After the lecture has been completed, the same 15 questions will be presented again, with the goal of an increase in score to at least 80% correct for the audience in total. The questions will be based on the learning objectives listed in Table 2 and will include the topics in Table 3.

In addition, the demographics of the audience will be recorded using a Turning Point survey. The survey will consist of three questions, listed in Table 4.

Table 4. Audience Demographics Survey

1. Which of the following most accurately describes your current profession? a. Physician Assistant b. Nurse Practitioner c. Physician d. Nurse e. Other
2. Which of the following most accurately describes the specialty in which you currently practice? a. Primary care

b. Oncology c. Gynecology d. Other
3. How many years have you been practicing medicine? a. less than 1 year b. 1-5 years c. 5-10 years d. more than 10 years

Data collection

The pre-test will be presented directly prior to the initiation of the PowerPoint presentation and the post-test will be administered immediately following the conclusion of the presentation in order to include the maximum number of attendees in data collection. The responses from these tests will be recorded digitally using the Turning Point clicker system. The attendees will also be given a paper survey asking them how the knowledge they acquired during the presentation will change their current practices. The survey will have space for the attendees to provide 3 examples of this. The pre- and post- test scores will be examined, with the goal passing score of 80% (12 out of the 15 questions correct).

Data Analysis

The mean of both the pre-test and the post-test will be calculated. The pre-test mean will reflect the baseline knowledge of the providers in attendance prior to the lecture on the material. The post-test mean will reflect the knowledge that the providers have on the topic following the lecture. The goal is to achieve an overall mean score of at least 80%

on the post-test. There is no goal mean score for the pre-test as it is a function of baseline knowledge.

A paired t-test will also be run comparing the mean of the pre-test to the mean of the post-test. This will allow us to interpret the improvement in knowledge from baseline. Because the baseline knowledge of the audience may vary significantly depending on the demographics of each particular lecture, there will not be a minimum anticipated value for score improvement. However, this value will be useful if the audience as a whole does not achieve the mean score goal of 80% on the post-test. In that case, the paired t-test will reflect whether or not the post-test results were significantly different from the pre-test results. If they are, then the audience knowledge improved from pre-lecture to post-lecture. However, it the paired t-test is not significantly different, the lecture did not provide an appropriate intervention to adequately improve the audience's knowledge on the subject matter.

Timeline and Resources

In order for the curriculum to be presented at CME conferences to PAs, physicians, and other providers, it must be submitted to and approved for CME by the Accreditation Council for Continuing Medical Education (ACCME) and the American Academy of Physician Assistants (AAPA). We will anticipate that approval from ACCME will take 12 to 18 months to be completed and the application for AAPA approval will take 3 weeks. Applications to each will be submitted in the summer of 2017, with expected approval from both by fall of 2018. We anticipate it will take one year to present the lecture at one national conference and 10 local conferences. The anticipated completion of data collection will be in the fall of 2019.

Institutional Review Board

The curriculum will be submitted to the Institutional Review Board (IRB) for approval for educational research.

CONCLUSION

Discussion

The majority of the research conducted on improving EOC survival has focused on early detection and primary prevention of the disease. Due to the presence of identifiable risk factors and known precursor lesions for Type 1 LGSC, these cancers have been the target of much of this research. However, Type 2 HGSC, with a lack of specific risk factors, a clinically aggressive course, and a worse prognosis, needs to be studied more extensively with regard to prevention of both initial development and recurrence to improve survival.

The data on nutritional elements and prevention of ovarian cancer development may not be generalizable to all types of EOC. Because of the earlier presentation and more identifiable risks, women with LGSC may be easier to identify and recruit for research studies than those with aggressive HGSC. Additionally, many of the dietary and lifestyle changes described in the literature focus on modulating estrogen levels, which may not play a significant role in some types of ovarian cancer, but not HGSC specifically. Thus it is not clear whether these data are generalizable to both women with LGSC and those with HGSC. More studies are needed examining the effects of these interventions, specifically in HGSC.

Additionally, much of the research that has been published focuses on nutritional components and the prevention of primary development of ovarian cancer. While this is clinically useful in the general population and in women at risk for developing EOC, the implication on patients who already have disease is not clear. There is a need for additional studies focusing on the effect of these interventions on recurrence rates in women with previously diagnosed and treated HGSC in clinical remission.

Summary

Ovarian cancer is the leading cause of gynecologic cancer death in women. With an overall five-year survival rate of less than 30%, the diagnosis of stage III and IV EOC carries a poor prognosis and aggressive clinical course. Given the poor prognosis and high recurrence rate for women diagnosed with advanced stage EOC, there is a need for additional treatment interventions focusing on increased survival for this population. In particular, type 2 HGSC presents with clinically aggressive, difficult to treat disease with limited therapeutic options for recurrent disease. A dietary intervention to reduce ovarian cancer recurrence and increase overall survival would be extremely valuable in this population.

Cruciferous vegetables, carotenoid-containing foods, flavonoids, flaxseed, and other antioxidants have been the subject of many studies researching the effect of nutritional components on ovarian cancer development. Additionally, obesity has been directly associated with ovarian cancer development as well as mortality. There is a broad range of potential foods, nutritional elements, and lifestyle factors that have been proposed to be effective in reduction of ovarian cancer development, progression, and recurrence. Historically, much of the research in this area has focused on reduction of primary cancer risk, failing to specifically study recurrence rates after clinical remission has been achieved. While there is a need for further research in this particular cohort, a CME course to provide health care providers with the most recent data on the topic is the first step in creating awareness of this potentially life-altering intervention for ovarian cancer patients.

Clinical and/or public health significance

As the leading cause of gynecologic death, with survival rates that have remained largely unchanged despite chemotherapy and surgical interventions, ovarian cancer is in need of an intervention to prolong survival. A CME course outlining the most promising nutritional elements and their effect on cancer development, emphasizing the potential to decrease recurrence rates and prolong survival, would be beneficial in creating awareness in this area of research.

The CME will equip PAs and other health care providers with the knowledge of the most recent advances in the area of nutrition and ovarian cancer. It will serve to spread awareness to the medical community as well as allow them to provide patients with the most up to date information. Attendees of the CME course will be able to provide their patients with nutritional and lifestyle recommendations to minimize development and recurrence of EOC.

LIST OF JOURNAL ABBREVIATIONS

Adv Anat Pathol.	Advances in Anatomic Pathology
Am J Epidemiol.	American Journal of Epidemiology
Am J Hum Genet.	The American Journal of Human Genetics
J Am Diet Asso	Journal of the American Dietetic Association
Am J Obstet Gynecol.	American Journal of Obstetrics & Gynecology
Am J Surg Pathol.	The American Journal of Surgical Pathology
Ann Oncol	Annals of Oncology
Br J Pharmacol.	British Journal of Pharmacology
Curr Oncol Tor Ont.	Current Oncology
ESMO	European Society of Medical Oncology
Front Oncol.	Frontiers in Oncology
Gynecol Oncol.	Journal of Gynecologic Oncology
Int J Womens Health.	Journal of International Journal of Women's Health
J Bioenerg Biomembr.	Journal of Bioenergetics and Biomembranes
J Int Cancer	International Journal of Cancer
J Natl Compr Cancer Netw JNCCN.	Journal of the National Comprehensive Cancer Network
Mol Carcinog.	Molecular Carcinogenesis
NEJM.	New England Journal of Medicine
Nutr J.	Journal of Nutrition

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CURRICULUM VITAE

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