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Cognitive Impairment in Gynecologic Cancers: A Systematic Review of Current Approaches to Diagnosis and Treatment

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Abstract

Purpose: To review the etiology and assessment of chemotherapy-related cognitive impairment (CRCI). To explore current treatment and prevention strategies for CRCI and propose future research goals in the field of gynecologic oncology.

Methods: Computerized searches in PubMed of cognitive impairment in cancer between 2000 and 2012 were conducted. The inclusion criteria were randomized control trials evaluating treatment of CRCI and search terms "cognitive function, cognitive impairment, cognitive decline, chemobrain, chemofog and cancer".

Results: To date, numerous modalities have been utilized for assessing CRCI in patients undergoing therapy. It has been proposed to move towards web-based assessment modalities as a possible standard. Few studies to date have aimed to elucidate possible treatment and prevention options for CRCI; even less in the field of gynecologic oncology. Only seven of these studies were subjected to randomized control trials. Only one of these studies looked at treatment in patients with gynecologic cancers.

Conclusions: The etiology of CRCI is multi-factorial. Following from this, there is no consensus on the best way to assess CRCI although objective measures are more reliable. One must extrapolate data from the non-gynecologic cancer literature, even venturing to non-cancer literature, to explore the treatment and prevention of CRCI. The methods found in these areas of research have not yet been applied to CRCI in Gynecologic Oncology.

Keywords: Gynecologic cancer; Chemotherapy related cognitive impairment; Treatment and prevention

Introduction

Chemotherapy-Related Cognitive Impairment (CRCI) is a distressing side effect of cancer therapy and can persist beyond the duration of treatment in the majority of patients [1]. CRCI is defined as cognitive decline experienced by those undergoing treatment of their cancer with chemotherapy. It is often referred to as 'chemo brain' or 'chemo fog' and for some it becomes the most troublesome survivorship issue faced [2]. Most describe it as being unable to remember certain things and having trouble finishing tasks or learning new skills [3]. The American Cancer Society defines CRCI as: forgetting things that you usually have no trouble recalling; trouble concentrating, remembering details, multi-tasking and remembering common words; and taking longer to finish things. Although studies associating cognitive changes with cancer chemotherapy have been reported since the mid 1970s [4], this phenomenon is poorly understood, especially in patients with gynecologic cancers [5]. A study of the most common symptomatic complaints experienced by ovarian cancer survivors showed that 69% of those patients involved reported cognitive impairment [6]. This is a greater incidence than what has been previously documented amongst breast cancer survivors [7]. As even mild cognitive impairment can impact a person's quality of life and interfere with carrying out daily activities [8], CRCI in patients with gynecologic cancer warrants further investigation.

This review is will summarize current data on the etiology of CRCI, explore the modalities employed to assess CRCI, and, with emphasis on treatment and prevention, demonstrate the gap in knowledge about CRCI as it applies to gynecologic cancers with suggestions for further research.

Etiology

The etiology of CRCI can be divided into four underlying mechanistic categories (Table 1). The direct effect of chemotherapy on the central nervous system will be explored here. Many studies have suggested that it is the toxic nature of chemotherapy, and its assault on neural substrate, that is responsible for the cognitive impairment in patients undergoing cancer treatment [9]. Some chemotherapeutic agents have been shown to preferentially exert their toxic effects on neuronal derivatives over cancer cells themselves. Dietrich et al. found that certain agents were more toxic to CNS progenitor cells and nondividing oligodendrocytes than too many cancer cell lines *in vitro* [10].

Several authors have shown that therapeutic levels of 5-Fluorouracil (5-FU) are associated with progressive delayed damage to myelin *in vivo* [11]. They also demonstrated increased apoptosis in specific brain regions along with decreased proliferation in the subventricular zone, the dentate gyrus of the hippocampus and the corpus callosum. These areas of the brain are important in learning and memory formation. Briones and Woods demonstrated an association with increased acetylation of histones leading to decreased cellular proliferation in mice treated with cyclophosphamide, methotrexate and 5-flurouracil [12]. Unfortunately, very limited data exists on the effects of carboplatin or paclitaxel, the mainstays of treatment in many gynecologic cancers, within the CNS. It has been well established that the paclitaxel can cause peripheral nervous system toxicities such as paresthesias, dysthesias, and muscle weakness. It follows from this that perhaps paclitaxel has similar effects on the CNS that could result in cognitive impairment. Studies using PET imaging have shown small amounts of radiolabeled

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Direct Effect of Chemotherapy	Indirect Effect of Chemotherapy	Effects Related to Cancer Biology Alone	Other
Damage to Myelin (MTX, 5-FU)	Inflammatory Process (paclitaxel, docetaxel, doxorubicin)	Fatigue	Stress
Histone Acetylation (Cyclophosphamide, MTX and 5-FU)	Oxidative Stress (doxorubicin, quinone containing agents, cyclophosphamide MTX)	Anemia	
Telomere Shortening(MTX)	Microglia Activation (MTX)	Pain	Hormonal dysregulation
Decreased levels of hippocampal catecholamines (MTX)	Cerebrovascular Obstruction (MTX)		

Table 1: Proposed etiologies of CRCI. MTX, methotrexate; 5-FU, 5-flurouracil.

paclitaxel in the brain after IV administration [13], making direct CNS toxicity a plausible mechanism for CRCI.

However, the existing clinical data make it difficult to draw conclusions about the direct effect of chemotherapy, especially taxane-based therapy, on the CNS. For example, one small prospective study was unable to demonstrate objective CNS dysfunction in women with ovarian carcinoma undergoing treatment with paclitaxel and carboplatin. Using Electroencephalographic Topography (EEG), Mayerhofer et al. [14] set out to monitor pre- and post-treatment effects of chemotherapy on the CNS. In the 28 patients they examined there was an overall increase in CNS vigilance after completion of 6-cycles of chemotherapy; in other words, no CNS toxicity was appreciated [14]. Alternatively, a later study by Kreukels et al. using EEGs showed significantly reduced processing speed four years after initial treatment in patients with breast cancer treated with high-dose cyclophosphamide, thiotepa, and carboplatin [15]. Although a comparison of these studies suggest that the divergent findings could be explained by the differing treatment regimens or dosing, Cheung et al. concluded that there is too little data available to evaluate the relationship between drug type and dosing and cognitive impairment in breast cancer patients [16]. This is contrary to what was originally suggested by Schagen et al., that higher doses of chemotherapy have been associated with greater incidence of cognitive impairment [17]. Other direct mechanisms that have been proposed, but not evaluated in a gynecologic cancer setting, include telomere shortening and decreased levels of hippocampal catecholamines [18,19].

Indirect Effects of Chemotherapy on the CNS

The indirect effects of chemotherapy are those exerted through resultant physiologic processes in response to cancer cell death. One proposed theory by Aluise et al. [20] stated that certain cytotoxic agents can produce a cascade of proinflammatory agents in response cell injury which subsequently cross the blood brain barrier. Prolonged activation of cytokine pathways can have adverse effects on the brain resulting in fatigue, lack of motivation and appetite, as well as disturbances in sleep and concentration. Paclitaxel and docetaxel in particular have been associated with increased levels of IL-6, IL-8 and IL-10 [21-23]. Some researchers have documented a positive relationship between increased circulating levels of cytokines and cognitive impairment [24]. Tumor necrosis factor-alpha has been shown to stimulate glial cells, local generation of reactive oxygen and nitrogen species, oxidative stress and mitochondrial dysfunction within the CNS after administration of doxorubicin [25].

Another process that has been implicated in CRCI is oxidative stress through the production of reactive oxygen and nitrogen species. Joshi et al. examined this process specifically with the administration of doxorubicin and were able to demonstrate increased levels of free radicals within brain tissues of mice [26]. Aluise et al. goes on to assert that sufficient build of these free radical species can ultimately lead to neuronal cell death [20]. In fact, when doxorubicin was co-administered with certain antioxidants, improved memory was observed in mice [27] further supporting oxidative stress as a plausible mechanism for CRCI. Other mechanisms proposed include microglia activation and cerebrovascular obstruction. Seigers et al. were able to demonstrate increased microglia activation and decreased cerebral perfusion in rats after administration of methotrexate [28].

Process Related Directly to Underlying Cancer

This category arose after studies were able to demonstrate the presence of cognitive dysfunction prior to the initiation of treatment [22,23,29], suggesting that it is the effects of cancer itself on physiologic processes that account for cognitive dysfunction. For example, pain, fatigue and anemia have all been shown to have detrimental effects on neurocognitive testing [30]. Fatigue and pain have been described as the most severe symptoms experienced by patients with ovarian cancer [6]. With regard to pain specifically, a prospective cross-sectional multicenter study in 2011 by Kurita et al. [5] assessed the prevalence of cognitive dysfunction in a large sample of opioid-treated patients with cancer. Although they found that those patients requiring the highest doses of opioids for pain control were more likely to score lower on the MMSE, there was no association with pain intensity and cognitive functioning [31]. Interestingly, breakthrough pain was associated with higher cognitive performance as assessed by the MMSE when compared to patients without breakthrough pain. They concluded that it is the anti-sedative nature of acute pain that accounts for this finding.

Process Related to Hormone Regulation

This category includes processes related to stress and hormonal dysregulation. It has been documented that increased circulating levels of gluccocorticoids trigger damage to structural and functional areas of the brain including the hippocampus [32]. Given that psychological stress can often be a significant part of a cancer patient's struggle [24], this warrants consideration as a contributor to CRCI. Studies looking at the role of hormonal regulation in cancer treatment response and patient survivorship have produced conflicting evidence. Studies have shown that low levels of Insulin-like growth factor are associated with age-related cognitive decline and possibly predispose patients to a cancerous state [33]. Estrogen deficiency has been associated with cognitive impairment as demonstrated by studies assessing impact of prophylactic oophrectomy at time of hysterectomy for benign disease [34]. On the contrary, multiple studies showed that estrogenic therapy could be associated with cognitive decline, especially in verbal memory and processing speed [35,36]. This evidence is based on smaller studies with cross-sectional data. Interestingly, breast cancer patients who underwent both chemotherapy and estrogenic therapy showed the most deterioration and the most persistent decline in cognitive function [36].

Diagnosis and Assessment

Three modalities have been utilized to assess cognitive functioning as it relates to treatment of cancer (Figure 1). Patient-reported data and cognitive measures are responsible for accumulating most of what

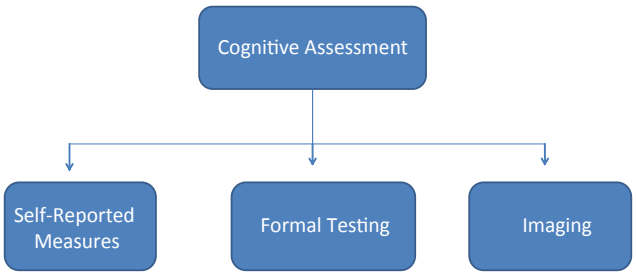

Figure 1: Categories of cognitive assessment.

is known today about CRCI. Unfortunately, a divergence between subjective and objective outcomes has made fully appreciating CRCI difficult. As Dutta et al. discussed, psychological stress, fatigue, and anxiety confound subjective measures [37].

A small pilot study by Hess et al. demonstrated a statistically significant decline in cognitive functioning over the course of treatment for advanced ovarian cancer. This study compared self-reported cognitive impairment to the results of web-based assessments of cognitive functioning. When using objective measures, 90% of participants demonstrated decline in attention, processing speed, or response time [38]. Another similar study performed in patients with being treated for breast cancer showed no correlation between self-assessments and the results of objective tests [39]. These authors also concluded that the self-perceived cognitive decline could be accounted for by underlying co-morbidities such as depression or anxiety, or more toxic chemotherapy regimen and negative affectivity traits.

Some have proposed that objective measures are more reliable. However, as Vardy et al. indicated that many researchers employ different batteries of neuropsychological testing, often at different time points during or after treatment, and have varying cutoffs for what constitutes cognitive impairment [1]. Exemplifying this point, Hensley et al. examined the effects of treating ovarian cancer patients with paclitaxel, carboplatin and gemcitabine. No cognitive impairment was documented when using objective measures [40]. They used the Trails A and B tests (cognitive flexibility and psychomotor speed), the Wechsler Adult Intelligence Scale-R Digit Span subtest (attention and concentration), and the Center for Disease Studies-Depression (CES-D) scale, after cycles 3 and 6, and at 6 months after completion of chemotherapy. No other studies reviewed employed the same combination of tests.

To date, over 17 different neuropsychological tests have been employed to assess cognitive performance in patients undergoing, or who have undergone treatment for their cancer (Table 2). This number does not include the many combinations of tests administered as part of neuropsychological testing batteries.

Recently, the role of certain imaging modalities has become an area of focus as in understanding CRCI. This represents evidence that CRCI is a true pathophysiologic process. A reduction in the volume of brain structures important for cognitive functioning and changes in the integrity of white-matter tracks that connect brain structures have been associated with changes in cognitive functioning, and have been seen using structural Magnetic Resonance Imaging (MRI) on patients after chemotherapy [4]. Multiple studies have demonstrated these changes in breast cancer patients who have received chemotherapy and subsequently shown a positive correlation to poor performance on standardized assessments of cognitive functioning. Patients with breast cancer who had been treated with adjuvant chemotherapy had slower processing speed and significant decreases in Fractional Anisotropy (FA), a measure of white matter integrity, in the genu and corpus callosum [41]. Positron emission tomography imaging studies demonstrated lower resting brain metabolism and a larger area of frontal cortex activation in breast cancer patients treated with chemotherapy [42].

Treatment

As the underlying pathophysiology of CRCI is still undergoing investigation, finding effective treatment can be challenging (Table 3). Knowing that fatigue in particular can adversely effect objective measures of cognition, treating the fatigue with a stimulant like D-MPH (D-methylphenidate) seems a logical place to start. D-MPH has shown significant improvement in fatigue in subjects previously treated with cytotoxic chemotherapy [43]. However, when Mar Fan et al. set out to test D-MPH as an investigational drug for fatigue and cognitive decline in patients undergoing treatment for breast cancer, they found no difference in cognitive performance in the D-MPH group [44]. Unfortunately this study was underpowered to detect a difference on the High Sensitivity Cognitive Screen, the test they employed to monitor cognition.

Modafinil, a eugeroic drug, is commonly used in the treatment of several fatigue related disorders and was also examined in a similar context. Kohli et al. found enhanced performance in memory and attention in women who had previously undergone chemotherapy for breast cancer when randomly assigned to receive additional Modafinil after initial therapy course [45]. Cognitive function was assessed using the Cognitive Drug Research (CDR) computerized cognitive assessment program. The results from this study showed statistically significant improvement in the cognitive domain of memory, but not in attention. Lundroff et al. confirmed these findings but were also able to demonstrate improved attention [46].

Researchers have also examined administration of erythropoietin, a glycoprotein commonly used to treat anemia of chronic disease. In a double-blind, placebo controlled pilot study performed by O-Shaugnessy, epoetin-alpha was shown to cause a moderate improvement in Executive Control Function (a frontal lobe–mediated cognitive process that coordinates the multiple simple ideas and tasks that must come together in order to execute complex behaviors) during chemotherapy for breast cancer [47]. However, in a follow-up study by Fan et al. no improvement in cognition in the epoetin-alpha group was noted at 12 to 30 months after completion of treatment [48].

Other pharmacologic interventions for CRCI that have been examined in randomized control trials include Donepezil with Vitamin E, Traditional Chinese Medicine (TCM) , and ginkgo biloba [49-51], all of which showed no improvement in cognitive performance. The only one of these interventions to be examined in gynecologic cancer population was TCM. A study out of Hong Kong looked at the role of TCM in improving quality of life in patients undergoing chemotherapy for Ovarian Cancer. As one of the secondary outcomes, cognitive function was assessed and found to be either the same, or slightly worse in the TCM group [50].

One area of extensive research that has yet to be examined in the cancer population is that of neuropharmacologic modulation through nicotinic receptors. Acute intake of nicotine is known to enhance cognitive function in many domains [52]. This fact has been exploited in the investigational treatment of cognitive decline in schizophrenia and Alzheimer disease. In the Journal of Clinical Pharmacology

Cognitive Assessment Tools	
Patient Reports Measures	**Formal Cognitive testing**
• The Questionnaire of Experienced Deficits of Attention • The Cognitive Function Scale of the European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire C30, version 3.0, 26, 27 (EORTC-CFS) • Perceived Cognition Questionnaire • The Cognitive Failures Questionnaire • Patient Assessment of own functioning scale (PAF).	• The CLOX test • High Sensitivity Cognitive Screen • Exit 25 test/Executive 25 Interview • Web Based Cognitive Stability test • Mini Mental State Exam • Hopkins Verbal Learning Test –Revised • Finger Tapping test • Trail A&B test • Cognitive Drug Research Computerized Cognitive Assessment • Digit Span Test • Revised Rey-Osterrieth Complex Figure Test • F-A-S test • California Verbal Learning Test-II • Cog state • Wechsler Memory Scale • Wechsler Adult Intelligence Scale • The CANTAB

*Cognitive assessment tools cited in various studies reviewed in this article

Table 2: Cognitive assessment tools cited in various studies reviewed in this article.

TRIALS	Cancer Type and/or Stage	Comparison	Measurement of CRCI	Effect/Outcome/Finding
Jatoi et al. [49], 2004	Small Cell Lung Cancer	Double blind, placebo controlled trial of donepezil and Vitamin E	1. Mini Mental Status Examination 2. Blessed Dementia Scale	Study terminated prematurely secondary to side effects of treatment arm
Oh et al. [56], 2012	Multiple	Randomized trial of Medical Qigong versus usual care	1. perceived cog impairment 2. European Organization for Research and Treatment of Cancer, 3.The Functional Assessment of Cancer Therapy-Cognitive	Significant improvement in Cognitive functioning in the Medical Qigong group
Mar Fan et al. [44], 2008	Breast Cancer	Randomized trial of DMPH versus placebo in women being treated with Chemotherapy	1. High Sensitivity Cognitive Screen 2. Hopkins Verbal Learning Test-Revised	No difference in cognitive function but underpowered study
Kohli et al. [45], 2009	Breast Cancer	Randomized trial of Modafinil v. placebo in patients who been treated with chemotherapy and/or radiation	1. Cognitive Drug Research 2. Computerized cognitive assessment	Improved memory and attention in Modafinil group
O'Shaughnessy et al. [47]. 2002	Breast Cancer	Pilot study of patients randmonized to Epoetin alfa v. placebo during chemotherapy	Executive 25 Interview	Trend towards improved executive control function in the treatment group
Lundorff et al. [46]. 2009	Multiple	Randomized, Double blind, placebo controlled trial of Modafinil	1. Finger Tapping Test 2. Trail Making Test 3. Edmonton Symptom Assessment System	Modafinil was superior in two cognitive domains; psychomotor speed and attention.
Fan et al. [48]. 2009	Breast Cancer	Follow-up evaluation @ 12-30ms after treatment with epoeitn alfa during chemotherapy	1. HSCS 2. HVLT-R	Epoetin alpha did not protect against delayed cognitive dysfunction
Chan et al. [50], 2011	Ovarian Cancer	Double-blind randomized control trial comparing TCM to placebo during	EORTC-QOL C30	No difference in QOL - trend toward worse cognitive functioning in study group, but no statistical difference.
Attia et al. [51], 2011	Multiple (patients requiring brain irradiation for brain metastases or primary tumors)	Phase II Clinical Trial of Ginkgo biloba	1. MMSE 2. Trail Making Test Part A and B 3. Digit Span Test 4. Revised Rey-Osterrieth Complex Figure Test 5. F-A-S test 6. California Verbal Learning Test-II	Improvement in attention and concentration but no significant change was found for global cognitive function, attention/concentration and working memory, verbal fluency , or in Long-Delay Free Recall. Poor retention, increased toxicity and no perceived benefit
Galantino et al. [58], 2012	Breast Cancer	Patients attended Yoga twice a week for 12 weeks during chemotherapy	1. Perceived Cognition questionnaire 2. CogState	No pattern of cognitive decline or improvement Limited by N = 4

Trials looking at Interventions for CRCI (chemotherapy related cognitive impairment) in cancer. HSCS; high sensitivity cognitive screen, HVLT-R; Hopkins Verbal Learning Test-Revised, BR; breast, GU; genitourinary, GI; gastrointestinal, TCM; traditional Chinese medicine, EORTC-QOL C30; European Organization for Research and Treatment of Cancer–Quality of Life survey C30, QOL; quality of life, MMSE; mini mental status exam

Table 3: Trials looking at Interventions for CRCI (chemotherapy related cognitive impairment) in cancer.

Therapy, Raffa suggests that there is significant indirect evidence that the selective α7 nAChR (nicotinic acetylcholine receptors) drugs may be useful in cancer chemotherapy-related cognitive impairment [53].

Behavioral interventions have also been explored. Meditation has demonstrated improvements in the areas cognition, pain, anxiety, psychological well-being and overall quality of life [54]. Beigler et al. suggested that meditation potentially has a role in managing CRCI [55]. Taking this one step further and using several patient administered surveys and questionnaires, Oh et al. were able to demonstrate improved cognitive functioning in patients assigned to incorporate Medical Qigong as part of their cancer treatment regimen [56]. Medical Qigong is a practice of aligning breath, movement, and awareness for exercise, healing, and meditation [57]. A small case series performed in breast cancer patients undergoing treatment looked at the role of Yoga in CRCI and overall quality of life [58]. The findings of this study, however, are inconclusive at best and ultimately assert that yoga 'may impact various aspects of cognition'. Although more aerobic exercise has not been examined on the clinical level with regard to a possible intervention for CRCI, Fardell et al. examined the role of scheduled physical activity in mice receiving 5-FU and Oxaliplatin. They demonstrated improved cognition and suggested that physical activity can actually prevent cognitive decline [59].

Lastly, Ferguson et al. have been examining a novel cognitive behavioral therapy intervention in treating CRCI. Memory and Attention Adaptation Training (MAAT) has not only demonstrated improvements in objective measures of cognitive function, but has also improved stress management in dealing with memory problems in everyday life at two, and six-month follow-up in patients who have cognitive complaints after treatment for breast cancer [60].

Prevention

In the area of CRCI prevention, some authors have concluded that few clinical recommendations can be made secondary to the paucity of available data [61]. Most of we what know about preventing cognitive decline in general stems from Alzheimer and dementia literature. For example, flavinoid administration (tannic acid) has been shown to prevent cognitive impairment in the domains of hyperactivity, decreased object recognition, and defective spatial reference memory in transgenic mice with cerebral pathology that mimics Alzheimer disease [62]. Several studies have highlighted the correlation between higher education level and decreased cognitive impairment on formal neurocognitive testing when looking at age-related cognitive decline. Sattler et al. followed individuals over a 12 year period and monitored cognitive performance with psychogeriatric examination and neuropsychological testing. Patients with higher baseline education levels had lower levels of mild cognitive impairment [63]. The same relationship has been demonstrated in individuals with a high level of physical activity. Perhaps physical activity is not only a means of combating cognitive decline associated with chemotherapy, but a means of neuroprotection against CRCI [64]. In the same vein of monitoring the effects of healthy behaviors, a survey was administered to colorectal cancer survivors that included measures of fruit and vegetable intake, physical activity, smoking status and alcohol consumption. Fruit and vegetable intake was the only factor associated with higher cognitive function [65]. In fact, research examining foods high in polyphenol concentration has shown a neuroprotective effect against inflammation, oxidative damage, and cell death, all mechanisms previously implicated in CRCI [66].

Lastly, a randomized double blinded study has demonstrated decreased cognitive impairment and increased executive functioning in older hypertensive patients treated with angiotensin receptor blockers [67]. Previous studies have demonstrated a link between hypertension and ovarian and endometrial cancers [68]. Given this, patients with gynecologic cancers whose mean age of incidence is highest, HTN could be of significant prevalence to justify use of this antihypertensive as a potential adjunct to standard treatment to help prevent CRCI.

Summary/Future Research Directions

The etiology of CRCI is multi-factorial. There is evidence to suggest that immune dysregulation through cytokine release plays a primary role - especially when examining those agents more commonly used in the treatment of gynecologic cancers. Our understanding of this phenomenon has been limited by the lack of uniformity in assessing cognitive function. Although patient reported measures are often confounded by underlying co-morbidities or psychosocial predispositions, they may have a role in serving as a screening mechanism for patients complaining of cognitive decline. With regard to objective assessments, a task force has been developed to address the issue of non-standardized test administration. Recently, there has been movement towards web-based assessment tools [69]. The most promising interventions thus far include Modafinil and lifestyle modifications- although none specific to gynecologic oncology patients. Preventative measures have not been studied on a clinical level in gynecologic cancers. Further research such as that into diet and exercise should consider the non-cancer literature for future directions.

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