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Editorial
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Is It Time for Gynecological Oncology to Widen Its Scope of Expertise?

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Editorial

Obesity is a reality for more women than ever before. In the US, 40% of women are obese (BMI 30 or above) and 10% are extremely obese (BMI 40 or above) [1]. The situation is not much better in the UK and other industrialized countries where obesity rates are 26% but increasing [2].

Obesity often co-exists with insulin resistance. It is estimated that only 12% of the US population are metabolically healthy [3]. It is disproportionately found in both poorer socioeconomic groups [4] and also ethnic minority groups [5,6].

Among the Gyn Oncology population, obesity is a specific concern at multiple levels. It is a risk factor for endometrioid adenocarcinoma of the endometrium *via* three separate mechanisms, one of which includes insulin resistance and which is preceded by endometrial hyperplasia. 40% of type I endometrial cancer is attributable to obesity. Insulin resistance is a causal factor in cardiovascular/ cerebrovascular disease; this is significant as the number one cause of death in obese patients with early stage endometrial cancer is myocardial infarction, congestive heart failure or cerebrovascular accident [7].

Obesity is often accompanied by insulin resistance, which has been implicated in the genesis of epithelial ovarian cancer, primary peritoneal cancer and breast cancer as well as endometrioid adenocarcinoma of the endometrium [8]. A surrogate marker for insulin resistance, higher random bloody glucose levels, has been shown as possibly prognostic in primary epithelial, peritoneal or tubal carcinoma [9]. Insulin receptors are found on epithelial ovarian cancer cells [10]. Starving cancer cells of glucose has been shown in the lab to retard their growth [11]. This is particularly striking when one remembers that epithelial ovarian cancer cells express GLUT-1 receptors, which mediate entry of glucose into the cells [12].

We also have evidence that choriocarcinoma growth is affected by insulin, given the presence of a large density of insulin receptors [13]. Obese women are less likely to receive the HPV vaccine and this may translate into higher incidences of premalignant and malignant HPV-related dysplastic disease [14].

Women may face delays to starting treatment, due to the need to deal with comorbidities, in order to decrease surgical risk. Peri-operatively, they face the risk of difficult intubation and its complications [15]. They will also face greater potential risks of intra-op and post-op complications [16].

Intra-operatively they face greater risks of complications related to conversion from minimally-invasive to open surgery, prolonged operating time, hemorrhage, injury to neighboring organs, abandonment of surgery and post-operatively , difficult extubation, wound infection, sepsis, thromboembolism and perioperative death as well as ICU admission [17]. Incomplete surgical staging may occur [18].

Post-operatively, patients may experience higher rates of wound infection and thromboembolic events [19]. Survival in ovarian cancer is adversely affected by obesity particularly in high grade squamous cancers [20].

Subsequent response to chemotherapy and RT may be affected; obesity is linked to increased cutaneous and GI toxicities from radiation therapy and up to 40% of obese patients having chemotherapy, will receive limited dosing not related to body weight [21]. Obesity is independently associated with lower quality of life post-gynecological cancer diagnosis and treatment [22].

The issue of obesity is a complex one but the root cause it can be argued, is a simple, one: The

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overconsumption of hyper palatable, ultra-processed foods, which have been shown to increase appetite and total caloric intake [23], are addictive [24] and increase the rate calories are consumed, thus affecting satiety levels. The factors that augment and precede the effects of that cause are complex; they include a history of sexual or physical abuse, eating or addiction disorders, chronic stress, medical illness, medication, environmental factors and sadly, the wrong eating advice. All of these variables have to be addressed if the problem is to be effectively dealt with.

Any woman who presents to a Gynecological cancer service with a malignancy, regardless of the stage or pathological type, will be under close follow-up for the next 5 years. This provides an excellent opportunity to maximize quality of life by addressing the general and specific health needs of this patient population. Issues include menopausal health [25], sexual dysfunction [26], and the amelioration of the modifiable risk factors present that may have contributed directly to the development of that disease e.g. insulin resistance and endometrial cancer [8,27].

Interventions to improve insulin sensitivity and/or obesity will by definition, involve an element of body fat reduction. A meta-analysis looked at weight-loss interventions in endometrial cancer survivors [28]. No significant weight loss at 6 or 12 months was reported. At first sight this would suggest that pursuing weight loss in this group of patients is futile. On closer inspection of the individual papers however, it is clear that all no attempt was made to diagnose or treat underlying insulin resistance. There was a reliance on "traditional" weight loss caloric restriction, which is associated with lowering of the metabolic rate and rebound weight gain [29]. None of these papers assessed the role of abstention from ultra-processed foods in the diet, which independently lead to obesity [30] and whose consumption will affect any validated questionnaire looking to detect underlying eating disorders or triggers to excess consumption. A subsequent RCT found that in women with endometrial and ovarian cancer, the ketogenic diet resulted in significant decreases in body fat and increased insulin sensitivity [31].

Patients with both obesity and insulin resistance will not lose weight unless dietary manipulation consistent with the underlying pathology is undertaken and evidence suggests that this will involve manipulation of carbohydrate regardless of caloric intake which will generally self-regulate [32,33].

Compliance is always a concern in any dietary intervention trial. The RCT referred to above reported up to 80% compliance over a 12-week period. Data from the Virta trial in type 2 diabetics found that compliance with a ketogenic diet with ongoing support could be achieved in 78% of participants over a 2-year period with remission of type 2 diabetes (and hence the resumption of normal insulin resistance) in almost 50% of patients, and sustained weight loss on average of 10% body weight [34].

Historically, Gynecological Oncology began when gynecologists with an interest in managing gynecological cancer, began developing the necessary additional skill set. Their evolution into highly skilled, subspecialist surgeons was demonstrated when superior patient outcomes were observed at their hands as compared to others [35], leading to the consolidation of a new subspecialty.

I believe that the next stage in evolution of the specialty's to respond to societal changes by integrating an obesity service into the existing multidisciplinary model. The goal will not be merely weight loss, but also amelioration of the underlying insulin resistance that has proved itself a contributing factor in the pathogenesis of breast, endometrial and ovarian cancer. Diabetes, metabolic syndrome, cardiovascular and cerebrovascular all contribute to morbidity in this patient population and can also be affected by the same measures [36]. This will by definition involve weight loss, and can be initiated from the moment diagnosis of a malignancy occurs.

As an example of this, the ketogenic diet has been shown to be effective when it comes to weight loss [37] and metabolic disease both in the non-cancer and cancer populations. The diet has been studied in women with endometrial and ovarian cancer, where significant decreases in body fat were noted along with no adverse effects on biomarkers [38]. In other cancer settings, preliminary research has indicated that potential chemo-sensitization can occur in the setting of endogenous ketone body production secondary to the ketogenic diet [39] and that positive changes in quality of life of patients can occur [40]; there is also evidence that it may be of assistance in ameliorating the side effects of chemotherapy or radiotherapy. Other studies are ongoing [41].

There may be practical applications of such a diet in the field of ultra-radical surgical cytoreduction in ovarian cancer patients. In those with insulin resistance and obesity, a significant number may also have NASH (None-Alcoholic Steatohepatitis) which leads to hepatomegaly. Dietary manipulation has led to rapid reduction of *de novo* lipogenesis and demonstrable decrease in liver volume which theoretically may aid surgery in the upper abdomen in advanced cases of ovarian cancer where liver resection may be required [42].

We know from the breast cancer literature that in estrogen-driven cancers, a lower carbohydrate intake is associated with lower recurrence rates [43]. Might this also apply in cases of endometrioid adenocarcinoma of the endometrium or even epithelial ovarian cancer?

There is a tremendous amount of research waiting to be carried out in this area of adjuvant dietary manipulation, given the low quality of the trials that have been done to date that will complement the excellent work already being done on the surgical [44,45], chemotherapy and radiotherapy fronts. This work needs to be integrated into specialty-specific clinical/basic science research and cannot be outsourced.

Dietary manipulation will never replace the mainstays of surgery, chemotherapy and radiotherapy. As an adjunct therapy to improve quality of life or even to assist in chemosensitization however there may be tremendous potential [46]. We may ultimately find, after both clinical and basic science research, that there is no role for diet in gynecological cancer. But what if we do? What if we find that our patients tolerate chemotherapy or radiotherapy better as has been seen in other cancers? What if we find that recurrence rates are affected positively, no matter how marginally? What if we find that the quality of life of our patients is transformed by "in-house" management of health problems not traditionally falling under the remit of Gyn Oncology?

The focus of oncology was traditionally on survival; with our increasing success over the years in diagnosing, curing or palliating cancer, our patients are now living longer, overall. Quality of life issues have never been more important to consider. Gyn Oncologists are in a unique position to pioneer in this regard, and to advocate for Women's health issues, long after treatment for the primary cancer

is complete.

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