Hello, I am Sai-Ching Jim Yeung. I am an Associate Professor in the General Internal Medicine, Ambulatory Treatment, and Emergency Care Department at MD Anderson Cancer Center. Today, in this module of this Professional Oncology Education Series, I’ll be discussing endocrine issues in cancer survivors and this is the Part B of my presentation and I will discuss diabetes and obesity in the context of cancer survivors.

And, of course, the opposite end of the spectrum that is hypoglycemia and cachexia are also significant clinical problems, but here I would focus on hyperglycemia and diabetes because of time constraint.

Over the last couple of decades, the prevalence of type 2 diabetes and obesity steadily increases. This data from between 1990 and the year 2000 show that the prevalence of diabetes type 2 paralleled the increase in the mean body weight of the US population.

Diabetes type 2 and obesity are related and often coexist, perhaps due to risk factors that they have in common. Obesity and diabetes type 2 before cancer are independent risk factors for cancer. Cancers of the colon, breast (especially in postmenopausal female), ovary, endometrium, kidney, gallbladder, pancreas, and esophagus are associated with obesity. And cancers of the colon, breast, hepatoma, liver, endometrium, kidney, pancreas, and non-Hodgkin’s lymphoma are associated with type 2 diabetes.

Obesity and type 2 diabetes before and after cancer would also worsen the prognosis of the patient. Being overweight is a much more widespread problem among cancer survivors. And cancer survivors have weight gain and increased incidence of type 2 diabetes or glucose intolerance.

Obesity and weight gain after cancer therapy is well described in three malignancies in particular: ALL or acute lymphocytic or lymphoblastic leukemia, craniopharyngioma, and breast cancer.

A syndrome of hypothalamic obesity has been described in cancer survivors. And this syndrome is characterized by inability to transduce peripheral hormonal energy balance signals, overactivation of the parasympathetic nervous system, which promotes an obligate insulin hypersecretion and energy storage. There is a defect in the activation of the sympathetic nervous system leading to decreased lipolysis and decreased energy expenditure.

In the Women's Healthy Eating and Living Study: chemotherapy was shown to significantly increase the odds of weight gain among more than 3000 survivors of both pre- and postmenopausal breast cancer. And only 10% of the women studied had returned to their previous weight six years later.

And this is the graph from that study and this is the number of years. So after six years these people --- these women that had the gained weight still kept that increase in body weight and did not lose it back.

High weight gain can worsen the prognosis of breast cancer in terms of relapse-free survival.

In the Nurses' Health Study, nonsmoking breast cancer survivors who gained up to 14 pounds were 40% --- 40% more likely to have recurrence than those who maintained their weight. And survivors who gained an average of 20 pounds faced the 53% increase in recurrence. And weight gain increased the overall mortality. You can see here that there is a difference in the survival curve among the people that have more weight gain compared with the people that have less weight gain.

Non-smoking breast cancer survivors gaining up to 14 pounds were 40% more likely to have recurrence than those who maintained the weight. And again the survivors with the average of 20 pounds faced a 53% increase in recurrence and weight gain increased the overall mortality.

Diabetes can also occur or get exacerbated during and after cancer treatment. The common causes would involve the pancreas as well as drugs; drugs that involve steroids and drugs that are toxic to the -- beta cells.

Many medications used in cancer patients would worsen the diabetes causing the blood glucose to get out of control. And glucocorticoids: they increase the hepatic glucose production; they reduce the peripheral glucose usage and overall increase the insulin resistance. Interferon α2: It may cause an immune-mediated toxicity to the beta cells. And Octreotide: it is an analog of somatostatin, which can inhibit the insulin secretion from beta cells. Tacrolimus: it inhibits insulin secretion and interferes with intracellular signaling of insulin and cause insulin resistance. L-asparaginase is a protein synthesis inhibitor that can inhibit the synthesis of insulin and/or the insulin receptors.

The frequency of diabetes amongst cancer survivors is higher than the US --- general US population and this is based on a study done in our own hospital. The cancer survivors with diabetes were more likely to report that cancer affected their overall health, 42.3% versus 34.3%, and their ability to work. So, in another words, the diabetes would
worsen or exacerbate the impact of cancer on the general health of the person as well as the overall functionality of the person.

In a large prospective US cohort of a million people, diabetes is a predictor of cancer mortality.

A random effects model meta-analysis of 23 articles show that diabetes was associated with an increased mortality hazard ratio of 1.41 with the 95% confidence interval of 1.28 to 1.55 compared with normal glycemic individuals across all cancer types. And subgroup analysis by the type of cancer showed increased risk of --- for the cancers of the endometrium, breast and colorectum.

In a cohort study of colon cancer patients who underwent adjuvant chemotherapy, diabetic patients have higher cancer recurrence and mortality.

In another study done in our hospital people with hyperglycemia during induction chemotherapy for acute lymphocytic leukemia with hyper-CVAD regimen were found to have a shorter complete remission duration. They experienced a significant increase in overall mortality, and have --- are at increased risk for developing complicated infections.

So why do diabetes and obesity worsen cancer survival and outcome? Hyperinsulinemia, high IGF-1, low IGF-BP1, hyperglycemia: these are characteristics of diabetes. And these two here, hyperinsulinemia and high IGF-1 and low IGF-BP1, are characteristic for insulin resistance. And in obesity, we also have the cytokine secreted by fat cells, the adipokines, the leptin, IL-6, TNF-α, PAI-1, adiponectin, etc. Diabetes and obesity will also change the impact of the sex hormones --- change the sex hormones. For example changing the levels of estrogen, progesterone and androgens as well as the sex hormone-binding globulins leading to changes in the free levels of these hormones. There are dietary factors that are common to both cancer formation as well as diabetes and obesity, for example high fat diet.

There’s also a difference in the cancer treatment due to the comorbidities associated with diabetes and obesity. For example, with heart disease and kidney diseases and neuropathy, these factors or comorbidities can limit the amount or the type of chemotherapy that a cancer patient can receive. There can be poor response to cancer therapies such as having complications of infections and intraoperative mortality associated with diabetes and obesity. And cancer management is very much involved, very taxing to both the clinician and the patients. And the cancer management can distract the management of diabetes and obesity and leading to lack --- poor control.

Why do cancer cells love sugar? In 1931, Otto Warburg published that cancer cells exhibit increased glycolytic metabolism compared with normal cells and, therefore, depended on glucose supply. But contrary to what Warburg originally thought, the shift from oxidative phosphorylation to glycolysis is not a requirement for malignant transformation.

In fact, glycolysis is associated with a higher metastatic potential and survival advantage. And clinicians these days have taken advantage or exploited this characteristic of the cancer cells and used the \[^{18}F\] of fluorodeoxyglucose as a tracer to use in the PET scan or positron emission tomography scan to detect metastatic disease or for staging cancer and diagnosing cancer.

There are six hallmarks of cancer: evade apoptosis, persistent growth, limitless replication, insensitive to growth arrest, angiogenesis, invasion, and metastasis.

And just like all roads lead to Rome, we have reviewed the current literature and found that the majority of the carcinogenic events, the oncogenes and loss of tumor suppressor genes, led to a coordinated activation of three transcription factors --- two transcription factors and suppress one transcription factor. So, the one --- two transcription factors that were activated are MYC and HIF-1. The one that got suppressed is p53. And there is complex interaction among these three transcription factors. But the bottom line is a coordinated change in these transcription factors would lead to up-regulation or transcription of multiple genes involved in the glycolytic metabolism.

Hyperinsulinemia and high IGF-1 in diabetes and obesity can activate the insulin and IGF-1 receptors in cancer cells. And activation of this receptor can lead to activation of AKT signaling, which may reinforce the switch to glycolytic metabolism in cancer cells. AKT signal regulates the transcription and translation of glucose transporter 1 or GLUT-1, and AKT would activate the hexokinase-2, and causing it to associate with the mitochondria and promote phosphorylation of glucose to glucose-6 phosphate to be metabolized via glycolysis or the pentose phosphate pathway. An AKT phosphorylate the ATP-citrate-lyase or ACL, stimulating the cleavage of citrate to oxaloacetate and acetyl-CoA or acetyl-coenzyme A to supply downstream de novo fatty acid synthesis through the fatty acid synthase. AKT suppressed the expression of β-oxidation enzymes, the CPT-1A or carnitine palmitoyltransferase-1A. And
modulation of CPT- IA expression by this AKT signaling is the mechanism to suppress β-oxidation during cancer growth. And AKT activation would also lead to activation of HIF-1 and make and suppression of p53, up-regulating the expression of nearly all the genes that are involved in the glycolytic pathway.

In a study of patients with surgically resected colorectal cancer, higher pre-diagnosis plasma C-peptide, that is an indicator of hyperinsulinemia, and lower levels of pre-diagnosis plasma IGFBP-1, or higher free concentrations of the IGF-1 or insulin growth factor-1, are associated with increased mortality after colorectal cancer resection.

In a retrospective analysis of data from an Adjuvant Breast Cancer Clinical Trial, Goodwin et al., reported that elevated fasting insulin concentration was correlated with decreased survival and higher rates of cancer recurrence and mortality. And this is the reference. In a different study similar results were obtained for the IGFBP-1, but it was not independent of the insulin.

To further support the theory of stimulation of cancer cell growth by high insulin and IGF-1 in diabetes and obesity, multiple in-vitro studies of various cancer cell lines have shown that cancer cells have functional insulin and IGF-1 receptors on the plasma membrane and that insulin and IGF-1 promote growth of the cancer cells.

Thus far, there is ample evidence to support the theory that the characteristics of diabetes or insulin-resistant state, that is hyperglycemia, hyperinsulinemia, high IGF-1, to worsen the prognosis of cancer. However, many questions remain. For example, "Like in obesity, do leptin or the other cytokines or adipokines add to the impact of the above factors?" Many of these patients also have dyslipidemia and thus, "Does the free fatty acid function as a signaling molecule and can add to these factors and cause the synergistic effect and worsening the survival of the cancer survivors?"

Now that we know weight gain and obesity are bad for cancer survivors, "How should obesity be managed?" There are no specific recommendations regarding weight control for cancer patients in the literature. "How aggressive should the treatment be? Should we consider surgical options? Does weight loss impact on cancer prognosis? Does improvement in the insulin aspect improve the cancer prognosis? Or do the cytokines confer resistance to cancer therapy? And if so, are there any ways, or how can we counteract this chemo-resistance or radioresistance?"

The treatment of obesity involves diet and lifestyle management. We can use drugs as in pharmacotherapy and undergo surgery.

This is a list of the current anti-obesity drugs in the United States. There are only two drugs approved by the FDA for the long-term use, Sibutramine and Orlistat. The thiazolidinediones and biguanides are primarily used to counteract the insulin resistance and biguanide, metformin, does lead to a modest weight loss of around 5% body weight. And the incretin mimetics are antidiabetic agents that can suppress appetite. And clinical studies are underway to study whether they can be useful in patients for weight loss.

Anti-obesity surgery include liposuction and various forms of bariatric surgery. And together with diet and lifestyle modifications, bariatric surgery is effective in reversing morbid obesity. And since many cancer patients are expected to gain weight after cancer therapy, "Should anti-obesity surgery be incorporated in the surgical treatment of cancer?"

There is a need for effective weight management strategies. Hopefully, future work would shed light on some of these questions, such as, "Can medications that improve insulin resistance block the impact of obesity on cancer growth?" Or, "Are adipokines druggable therapeutic targets?"

Now on the other hand, similar to obesity, there are no specific guidelines for the management of diabetes in cancer patients. And there are no specific recommendations regarding the glucose control for cancer patients in the literature.

There are many unresolved questions. "Should clinicians just follow the sick day guidelines?" Or, "Does tight glycemic control impact on cancer prognosis?" Or, "Are some of the medications used for diabetes better than others with respect to cancer survival? Does type 2 diabetes confer resistance to cancer therapy; and if so, how can this chemoresistance or radioresistance be overcome?"

There are many antidiabetic drugs available in the United States. And broadly these can be classified into two major categories, the insulins and the insulin secretagogues versus all others. And this slide shows the insulin, insulin analogs, and the insulin secretagogues. The insulin analogs are genetically-engineered insulins with modified structures to change their pharmacokinetic behavior. And the insulin secretagogues are sodium channel modulators that enhance the secretion of insulin from β-cells and they can be classified chemically into sulfonylureas or meglitinides, based on the chemical structures.
Apart from the insulin and insulin secretagogues, the other drugs include alpha-glucosidase inhibitors, thiazolidinediones, and biguanides, incretin mimetics, the DDP-4, the dipeptidyl peptidase, and amylin analogs.

The thiazolidinediones and biguanides are the two types of antidiabetic drugs that may have beneficial effect for the cancer patients. The thiazolidinediones are agonists of PPARγ or peroxisome proliferator-activated receptor-Y. They increase --- they decrease cellular proliferation and induce apoptosis of various cancer cell lines. And in pancreatic cancer cell lines the IC50, the concentration that inhibits 50% of the pancreatic cancer cells, is around 20 microM. And it may work through by induction of a tumor suppressor called PTEN. The biguanides activate, AMPK or AMP-dependent protein kinase through another kinase called LKB1. And they inhibit the cell growth by decreasing mTOR and S6 kinase activation. And the IC50 concentration that inhibits 50% of the breast cancer cells are in the range between 5 to 20 milliM.

If you do a PubMed search on thiazolidinediones and cancer, many articles will show up and this is a list of the titles of selected articles.

The point that I want to make is that there is a body of preclinical lit --- preclinical data in cell culture and in animal models demonstrating the inhibitor effects of thiazolidinediones on various types of cancer.

This article reports that thiazolidinediones reduce the risk of lung cancer. Yet, the epidemiological evidence for a beneficial effect of thiazolidinediones for cancer patients is scanty compared with metformin.

Now if you do a PubMed search on metformin and cancer, again, many articles will show up. And this is a list of the titles of selected articles. The point I want to make again here is that there is a body of preclinical data in cell culture and in animal models demonstrating the inhibitory effect of metformin on various types of cancer.

A case-control study suggested that metformin was associated with reduced risk of cancer in diabetic patients with an unadjusted odds ratio of 0.86.

And patients with type 2 diabetes exposed to sulfonylureas and exogenous insulin had a significantly increased risk of cancer-related mortality compared with patients exposed to metformin. And the authors were uncertain whether this increased risk was related to a deleterious effect of sulfonylurea and insulin, or a protective effect of metformin or due to some unsure --- unmeasured effect.

Our case control study showed that metformin use was associated with reduced risk, while insulin and insulin secretagogues were associated with increased risk of pancreatic cancer in diabetic patients.

Our colleagues in Breast Medical Oncology did a retrospective chart review and they found that diabetic patients with breast cancer receiving metformin and neoadjuvant chemotherapy had a higher pathological complete remission rate than diabetics not taking --- or not receiving metformin.

There is not enough time for me to go into details about our laboratory investigation. But here, I will just provide a summary of our laboratory findings, which is published in an article that is in press. We found that insulin promotes proliferation of cancer cells. Glucose also promotes proliferation of cancer cells, but they are dependent on high insulin concentrations. The antidiabetic drugs such as rosiglitazone and metformin have suppressive impact on cancer cell growth. While exenatide, which had been used as control, which is one of the incretin mimic – incretin analogs, has no such direct impact. The combination of gemcitabine or doxorubicin with rosiglitazone or metformin would result in extra inhibition of cancer cells.

At this point, there is no definite clear data to guide the clinical management of diabetes in cancer patients. And future work we will need to address these two key questions: "What are the diabetic treatments that are most beneficial for diabetic patients with cancer?" "What are the appropriate diabetes treatment targets for cancer patients?"

Now to conclude my presentation, here are some of the key points to remember. Type 2 diabetes and obesity are potentially modifiable factors that impact on cancer patient survival. There is no clear data to guide a clinical management of type 2 diabetes in cancer patients and obesity at this point. And diet and lifestyle changes are fundamental. Some pharmacotherapies, anti-insulin resistance medications for diabetes, may be beneficial for cancer patients or more beneficial for cancer patients than other agents. And more research is needed to change the standard of care to optimize the cancer patient survival. This concludes my presentation on endocrine issues in cancer survivors and thank you for your attention.