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Welcome to Yale Cancer Center Answers with Dr. Francine Foss and Dr. Lynn Wilson. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Wilson is a Professor of Therapeutic Radiology and an expert in the use of radiation to treat lung cancers and cutaneous lymphomas. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1-888-234-4YCC. This week, Dr. Foss and Dr. Wilson are joined by Dr. Tobias Carling. Dr. Carling is an Assistant Professor of Endocrine Surgery and Director of the Yale Endocrine Neoplasia Laboratory.

Foss Let's start off by having you tell us a little bit about what the Endocrine Neoplasia Laboratory is?

Carling When I joined the faculty about four years ago, my role was both as a surgeon, but also as a scientist in cancer genetics, and we started this lab dedicated to understanding what the underlying genetics are of endocrine tumors and that is what we focus on in the lab and it has been very exciting so far.

Foss Can you define the word endocrine cancer for the audience?

Carling Endocrine cancers, or endocrine tumors, are tumors that arise in endocrine organs and endocrine organs are those that produce hormones. So typically, when we talk about endocrine tumors, those are tumors that arise in, for instance, the thyroid glands, the parathyroid glands, the adrenal glands, but you can also have endocrine tumors arising in endocrine cells of other organs. One example would be carcinoid tumors that arise in endocrine tumors of the GI tract or even the lungs, but what is common among endocrine tumors is that they arise either in endocrine cells or endocrine organs and sometimes, but not always, they overproduce hormones as well.

Wilson Dr. Carling, tell us a little bit about yourself, your background, and how you arrived at Yale?

Carling I am sure you can hear from my accent that I am not American originally, I am from Sweden. I grew up in a small town in the northern part of Sweden. From relatively early on I knew I wanted to dedicate my life to science and to medicine and I went to medical school in Uppsala and while I was in medical school, I came in contact and joined a lab that focused on endocrine tumors. So from relatively early on, I got interested in endocrine tumors, originally from the scientific point of view, and I ended up doing my PhD there in addition to my MD. The plan was then to stay at Uppsala and train as an endocrine surgeon, but before that I wanted to gain some more exposure to cancer genetics because cancer genetics at that time, this was about 10 to 12 years ago, was really very-very exciting with all the new technologies in understanding cancers. So, I did a postdoctoral fellowship in Southern California and then I met my wife in California, so the plan changed and ultimately I came here to Yale in 2002 for my general

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surgery training and then endocrine surgery training and I have stayed on the faculty ever since.

Wilson And Yale is a very large referral center for endocrine cases, is that correct?

Carling That is absolutely correct, and so was Uppsala, so it is interesting have been in two premiere centers both in the United States as well as in Europe. Yale has really become dominant and those are very, very rare cancers, but because of overproduction by its hormone, parathyroid hormone causes significant morbidity in many patients with osteoporosis and kidney stones and a lot of psychiatric problems. Those are more common in women than in men as well and those are more common in postmenopausal women, so the prevalence is about 2% to 2.5% of all women over the age of 55. So that is another common tumor we see. More rare tumors are for instance carcinoid tumor in the GI tract as well as for instance adrenal cortical cancers. We only see about 500 to 600 adrenal cortical cancers in the United States. So there is a wide range between very common and less common tumors.

Wilson Tobias, you mentioned that thyroid cancer became a lot more common in women over the last several decades, do you know why that might be?

Carling Not exactly, what we do not know is that it is becoming more common and initially it was thought that this was purely due to the fact that we identified smaller cancers earlier, but if you look at the data carefully, and when I talk about an increase in thyroid cancer, just be clear, this is solely due to a cancer called papillary thyroid cancer, there are three other types of thyroid cancers called anaplastic thyroid cancer, medullary thyroid cancer, and follicular thyroid cancer, and they have not shown an increase in incidence. This increase in thyroid cancers is purely due to papillary thyroid cancer, but if you look at the data of papillary thyroid cancer, it shows that if it was only due to earlier detection, you would anticipate that you saw smaller tumors becoming more frequent and larger tumors being less frequent, but that was not the case, also larger tumors. If you stratified based on size or based on aggressiveness, it is increasing in all groups and it is also true that it is increasing in both males and females and it is increasing in all different ethnic groups. So, there is a true increase of papillary thyroid cancer. We are not sure why that is the case, whether it is certain environmental factors, but what we do know is for papillary thyroid cancer, radiation exposure is the best known risk factor, but certainly there is going to be a lot more need for studies to understand this increase.

Foss Are most people with thyroid cancers symptomatic or do they mostly get picked up just incidentally on physical examination?

Carling Now-a-days it is certainly true that most of them are asymptomatic, or they feel a lump in their thyroid gland and because of that they seek medical attention and most patients then

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have an ultrasound. Other imaging techniques are becoming more common such as CT scans and MRIs and PET scans those can certainly pick up incidental thyroid tumors as well.

Foss I think the parathyroid tumor is one that most people are not familiar with, and is certainly difficult to diagnose. I am also surprised to hear that it is increasing in incidence. Can you talk a little bit about that?

Carling Just to give some background, in the neck you have the thyroid gland and next to the thyroid gland you have the four parathyroid glands and some of my patients sometimes confuse the thyroid gland with the parathyroid glands, but these are distinct organs with clearly distinct functions. The thyroid gland produces thyroid hormones, which controls the overall metabolism in your body, whereas the parathyroid glands produce parathyroid hormones, which control the calcium metabolism in your body and the most common scenario is that you develop one single tumor out of those four parathyroid glands. This tumor then is often benign, and it overproduces a hormone called PT, the parathyroid hormone, and that hormone then goes throughout your body and causes a lot of effects; one of the most common is kidney stones or osteoporosis. The reason I think parathyroid tumors have always been common, and the reason that we are detecting more is because of increased awareness and the fact that we now very easily can measure parathyroid hormones. So the diagnosis is relatively straightforward and involves checking calcium and a parathyroid hormone level.

Wilson Can you tell our listeners a little bit about the various treatments that are used? I know there are a lot of different types of tumors and the treatments can vary, but what are some of the major categories?

Carling What is true in almost all endocrine tumors is that surgery is by far the most common and most important treatment. Another type of treatment that is used widely and it is effective in thyroid cancer is radioactive iodine. The reason why that is so effective is because iodine is taken up almost exclusively by the thyroid gland. So the radioactive iodine you have and radioactive isotope that is tagged to the iodine is taken up by the thyroid gland and the residual thyroid cancer cells are then killed by the radioactivity and it has been used for many-many years and it is a very safe and very well tolerated treatment. For many of the other endocrine tumors, unfortunately, surgery is the only curative treatment and what is true for almost all endocrine tumors is that classical external-beam radiation therapy and conventional chemotherapy have in general very little effect and thus very little role in the treatment.

Wilson And some of the surgeries I can imagine when operating in the neck can be pretty complicated and tricky to do?

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Carling Yes, the neck is a delicate area of the body that has a lot of important structures including nerves and blood vessels. So what is true for these types of operations in the neck are that they tend to be very delicate operations, which is part of the reason that it attracted me, because I like those kinds of very delicate operations.

Wilson We are going to take a break for a medical minute. Please stay tuned to learn more information about endocrine surgery with Dr. Tobias Carling.

Medical Minute

The American Cancer Society estimates that the lifetime risk of developing colorectal cancer is about 1 in 20 and that risk is slightly lower in women than in men. Early detection is the key; when detected early colorectal cancer is easily treated and highly curable. Men and women over the age of 50 should have regular colonoscopies to screen for this disease. Each day more patients are surviving the disease due increased access to advanced therapies and specialized care. New treatment options and surgical techniques are giving colorectal cancers survivors more hope than they ever had before. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale to test innovative new treatments for colorectal cancer. New options included Chinese herbal medicines being used in combination with chemotherapy to reduce side effects of treatment and help cancer drugs work more effectively. This has been a medical minute. A more information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

Wilson Welcome back to Yale Cancer Center Answers. This is Dr. Lynn Wilson and I am joined by my co-host Dr. Francine Foss and today we are talking with Dr. Tobias Carling and we are discussing endocrine surgery. Tobias, you were telling the audience a little about some of the different treatments, operations, surgeries and how delicate surgery needs to be in the neck. You are operating on other parts of the body as well. Endocrine organs are not only in the neck. Tell us about some of the other locations?

Carling The most common other type of operation is adrenalectomy for adrenal tumors, the adrenaline glands and endocrine glands that sit right on top of the kidney, and I think a big advancement that has been made over the last 10 years or so is that now we can use minimally invasive surgery, meaning laparoscopic surgery, for this kind of tumor and adrenaline tumors are common but many adrenaline tumors do not need to be resected, but those tumors that overproduce hormones, and the hormone that they can overproduce is a hormone called aldosterone, and when it does that, it causes hypertension and low potassium, or it can overproduce cortisol, which causes a syndrome called Cushing's syndrome or it can over produce catecholamines, which is that fight-or-flight hormone of the body and those tumors are called pheochromocytoma and those can be very

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dangerous tumors even though they are benign because it overproduces stress hormones to the point where patients often have skyrocketing blood pressure and heart rates and can develop strokes and heart problems because of the hormone production.

Foss Tobias, I understand that sometimes it is very hard to find these endocrine tumors in some patients where maybe you can detect the hormone over secretion, but you cannot find the primary tumor.

Carling That is true, it is becoming less of a problem now-a-days though because we have better imaging technologies. Here at Yale, just to give one example, over the last few years we have continued to develop a new CT scan based technology for identification of parathyroid tumors that enables us to perform minimally invasive surgery because we typically know exactly where the tumor is because a normal parathyroid gland is just the size of a grain of rice and the tumor sometimes is not much bigger than that. So, we often depend on our colleagues in radiology to develop new technologies for us to do the surgery in better ways.

Wilson Tell our listeners what you mean by minimally invasive surgery? What is the difference between that and the traditional kind of operation where you have a big incision and you are opened up with good visualization.

Carling You can define minimally invasive surgery in different ways. When we're talking about a neck operation, minimally invasive parathyroidectomy for instance, that involves using a targeted approach, meaning figuring out where the tumor is before we do the surgery and instead of using general anesthesia, local anesthesia, with what is called a cervical block technique. This has many many advantages including that the patient can vocalize during the operation, which is very helpful because one of the risks with operating in the neck is injury to the recurrent laryngeal nerve, which is a very important nerve that controls the vocal cords. So, by having the patient vocalize during the operation, we can ensure that we protect the nerve. That is one example of minimally invasive neck surgery. Minimally invasive surgery in the abdomen or in the retroperitoneal space, meaning where the adrenals are, often involves a laparoscopic operation, instead of using a large incision it uses smaller incisions and with a video camera introduced through one of the ports we are able to do the operation.

Foss Say you have surgery and the tumor is removed, then the tumor maybe comes back in another spot. How successful is surgery then in looking for those metastases and is that the correct approach in that situation?

Carling I think the best example of this is probably thyroid cancer. So, thyroid cancer very commonly spreads to lymph nodes in the neck. Those lymph nodes can be either in what we call the central neck meaning right next to the thyroid gland or in the lateral neck

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where you have the sternocleidomastoid muscle. If the patient, when they present already have metastases, we remove all those lymph nodes as part of the initial operation. If they have a complete operation with all the lymph nodes removed, the recurrence rate is slow, but if they do recur, they still have an excellent outcome and if they do recur, repeat surgery is sometimes needed.

Wilson You mentioned a little bit about the incidence of these cancers among men compared with women, but can you give our listener a little bit more information about what age these occur and other racial differences, other certain patients who may be at higher risk for these cancers than others?

Carling For parathyroid tumors, it seems like it is about three times more common in women than in men and it tends to increase with age and you see that increase after 45 to 55 years. The other endocrine tumors, what is common among them, is instead they often affect relatively young patients, meaning patients that are in the middle of their life and often with young families, so it is not uncommon for thyroid cancer or adrenal tumors to affect 34 to 50 year old individuals.

Wilson Do you see these tumors run in families? Do family members have higher predilection for these types of things if one person gets it, is the other person thought to be possibly be at some risk?

Carling Absolutely, and what is true for most endocrine tumors is that genetics play a big role and some of the genetics we know very well, and some of it is still being sorted out. As examples of a genetic tumor susceptibility syndrome that causes endocrine tumors, is multiple endocrine neoplasia type I and type II. Type I is caused by a gene called the MN1 gene and it is inherited in autosomal dominant fashion, meaning that the offspring of a carrier has about a 50% risk of developing the multiple endocrine neoplasia type I or type II syndrome, they are inherited in the same way. For patients with MN1, almost all of them develop parathyroid tumors, but they also develop endocrine pancreatic tumors, those are endocrine tumors of the pancreas, as well as pituitary tumors, whereas those with type II develop parathyroid tumors, pheochromocytoma, and those are the tumors of the adrenal and sometimes parathyroid tumors as well. But also some of the more common endocrine cancers can be familial, for example, we know that papillary thyroid cancer is familial in about 10% of the cases, but in those cancers we still do not know what the cause of the gene is. For instance, for pheochromocytoma, we have identified now up to 10 different genes that produce familial pheochromocytomas, and those are just some examples. For many of the endocrine tumors, there is an inherited genetic predisposition.

Foss We talk a lot about genomic sequencing now and sequencing in the human genome and for a lot of tumors we now have specific sequence information for. Is this relevant in endocrine tumors, and can you explain what exome sequencing is?

Carling When we talk about exome sequencing, it is good to have some background about the human genome. The human genome has about 300 billion base pairs, or letters, and 1.5% of our genome is protein coding, meaning those give rise to genes that give rise to proteins that are important in our body, whereas 98.5% of the genome is what we call junk DNA. We do not really know what the function of that DNA is. So when you do exome sequencing, you sequence all the exomes, which is the protein coding region of the genome. When we started the lab about four years ago, I worked very closely with Rick Lifton in genetics and he has been a great mentor in genetics and they had developed this technique of exome sequencing to sequence constitutional DNA, meaning inherited DNA. So, we figured let us try to apply this to understand endocrine tumors as well. One of the first projects that we launched was to try to figure out what the molecular pathogenesis of aldosterone producing adrenal tumors is. And the reason why we chose those tumors is those are benign tumors, but cause a lot of problems because of the hormone production of aldosterone, but the reason we started with the benign tumor is we figured that if we sequence these tumors, it will be less likely that we identify a lot of passenger mutations as opposed to driver mutations. When you do large scale genomic studies of cancers, you often find lots of different mutations and it is difficult to know which ones are the drivers, meaning they cause cancers and which ones are the passengers, just a mutation that happens within the cancer that has no functional consequence. By starting with a benign tumor, we figured there would be less passenger mutations and we would be more likely to identify the driver mutations. So what we did is we recruited patients and we compared the constitutional DNA, which is the normal DNA in their body, to the tumor DNA. And what we found was that a large percentage, close to 50 % of these aldosterone producing tumors, have a mutation in one gene called KCNA5 and it turns out that this gene controls the potassium channel, which is very important in the adrenal gland and when you have a mutation that you acquire this produces not only self proliferation, which causes the tumor, but also aldosterone hypersecretion and that is the reason why patients develop these tumors. So, exome sequencing has been crucial in understanding these tumors for us. We are now moving on to other both benign as well as malignant endocrine tumors as well, and the reason we're very excited about this is that for cancers where surgery or other conventional therapies are not possible anymore, there are not many treatment options available, so we are hoping we can identify genes and pathways where targeted therapy will be possible.

Foss That was the question I was going to ask, which is how does just knowing this information help us in our approach to patients? Now that we have identified some of these genes, what is the next step?

Carling For some of the endocrine cancers, we still do not really know what genes are involved so what we are working very hard on is identifying that and the whole point of

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identifying what genes and what pathways in the DNA are more effected is to be able to develop therapies and drugs that can target these pathways that have been altered to treat the tumors.

Dr. Tobias Carling is Assistant Professor of Endocrine Surgery and Director of the Yale Endocrine neoplasia laboratory. If you have questions or would like to add your comments, visit yalecancercenter.org, where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.