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Welcome to Yale Cancer Answers with your host Doctor Anees Chagpar. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week it’s a conversation about pancreatic cancer with Doctor Mandar Deepak Muzumdar. Doctor Muzumdar is an assistant professor of genetics and medical oncology at the Yale School of Medicine where Doctor Chagpar is a professor of surgical oncology.

Maybe you can start by telling us a little bit about pancreatic cancer. It’s certainly not one of the Big 5. We talk about breast cancer and lung cancer and colon cancer and prostate cancer. Pancreatic cancer is a little bit rarer. Is that right? Yes, pancreatic cancer is...
somewhere between the 10th and 11th, most common cause of cancer in the United States. But it’s rapidly contributing to cancer deaths in the United States. It’s now the third leading cause of cancer death in the United States and is soon expected to be the second leading cause within the next few years. So I think it’s becoming a very important cause of cancer that we really have to deal with. Yeah, and that’s I guess because pancreatic cancer, although it may be rare, is often pretty fatal. Most patients with pancreatic cancer are diagnosed at advanced stages. Either it’s beyond surgical resection, which is our mainstay of therapy for cure or it is already spread to other organs, making it exceedingly challenging to treat at that point. And so the idea is to either find it early or prevent it altogether. So let’s take each of those in turn. I know that your lab is
really looking at prevention, but maybe you can talk a little bit before we get into that as the bulk of our discussion today, what are the signs and symptoms that people should be aware of so that they could try to catch it a little bit earlier? So pancreatic cancer unfortunately is challenging to actually diagnose early because many of the symptoms that are associated with it are quite nonspecific or associated with other different more common conditions. So some common symptoms include abdominal pain or discomfort, nausea, weight-loss. Many of these things can be caused by other factors that are more common, such as reflux for example. So that’s one of the challenges with diagnosing, but I think that one of the things we do know is that there are a number of risk factors associated with pancreatic cancer, in particular by 10% of all pancreatic cancers, are associated with some sort of genetic familial cause,
and so certainly in patients who have first degree relatives with a prior history of pancreatic cancer, multiple family members had pancreatic cancer that should alert more complete evaluation and discussion, at least with their physicians. But again, it doesn’t have very common symptoms that are unique, making it very challenging to diagnose early. A number of studies are being done now to try to identify factors that are involved in early detection. Hopefully some of those will lead to some blood based, tests that we can actually do to try to identify some markers that might give us an inkling that pancreatic cancer may be there. That would allow us to do some follow-up testing, but we’re still in the research phases of that. We’re getting there, but we’re not quite there yet. And so because the symptoms are so non specific people I would presume people don’t pay attention to that.
And by the time things have festered on for quite awhile, they then present and have are found to have disease that’s gone and spread to other organs making it more difficult to treat. You talked a little bit about genetics and you said that about 10% of all pancreatic cancer patients have a family history. That also means that 90% of people don’t. And so, even if you don’t have a family history of pancreatic cancer, should you be paying attention even to those non specific symptoms? If they don’t go away, or if they don’t have a reason behind them, maybe get checked out? That’s exactly right. If their symptoms that are persistent or you don’t have a great explanation for, a discussion with your doctor is always necessary. It’s always possible that it is pancreatic cancer. But it’s more likely that something else is going on. It’s better to be evaluated and check to make sure that pancreatic cancer wouldn’t be a cause of the symptoms. Tell us a little bit more about the genetics of pancreatic cancer. I mean, when we talk about a
family history, is it something that is age specific? Should it run on one side of the family or the other? Are there multiple family members who may be involved or should be involved in order for you to be a little bit more cautious? Does it affect other cancers? Tell us a little bit more about that whole space of the genetics of pancreatic cancer. About 10%, like we discussed, about 10% of all pancreatic cancers are associated with some sort of family history. And the things to be aware of, are multiple first degree relatives, so that is siblings, parents, children with pancreatic cancer, particularly first degree relatives who are diagnosed prior to the age of 50. There’s a greater risk of developing pancreatic cancer, and there’s a number of known gene mutations that have been identified in pancreatic cancer that are also seen in other cancer types such as colorectal cancer, breast cancer, ovarian cancer.
So certainly, if any of those have been found in family members, one should at least discuss with the geneticists getting tested for those types of mutations which might alter how to actually screen or to try and diagnose pancreatic cancer early. And so some of those mutations I know as a breast cancer surgeon, we think of BRCA. We think breast and ovarian cancer but BRCA also increases your risk of pancreatic cancer. If you have a family history of breast cancer and let’s say one of your family members has been diagnosed with a BRCA mutation, you’re at increased risk of carrying that same mutation. You go to a geneticists or genetic counselor and you test because testing now is pretty ubiquitous and actually fairly cheap. And if you carry that genetic mutation, most people think about all of the things that they can do to prevent breast cancer or ovarian cancer, and certainly prophylactic
surgery is in the cards.

But what about pancreatic cancer?

How do you prevent that?

You can’t really remove your pancreas. There’s no surgical removal of

the pancreas that would be used.

The prevention, though there are certain screening programs that

one can get, a part of that would help you to find it earlier.

That would include things like image Ng and other things that can be done to find it.

There’s also a number of non genetic risk factors that we know can contribute

to pancreatic cancer and they likely will cooperate with gene mutations, and those are some of the lifestyle things that can be done to try and decrease your risk of pancreatic cancer.

For example, we know for quite some time now that smoking is associated with pancreatic cancer, two and a half fold increased risk of developing the disease over the general population, so quitting smoking might be one thing to do.

We know there’s several other modifiable risk factors including obesity,
which is soon to surpass smoking as the leading modifiable risk factor for pancreatic cancer and its associated with somewhere between 2 and a 1/2 fold increased risk again over the general population, and so losing weight may be helpful in terms of reducing risk. There are a number of dietary things that have been associated, but none of them are convincing, but there are lifestyle modifications in terms of tobacco cessation, stopping smoking. Or altering diets or losing weight that might be helpful. What about alcohol? So there are some studies that do see an association of alcohol with pancreatic cancer. Development of the studies are not conclusive. There’s also an association with excessive alcohol use. An inflammation of the pancreas, also known as pancreatitis and certainly chronic pancreatitis. That is inflammation that’s recurrent, can be a risk factor. But in terms of limited exposures of alcohol, there is some association,
though it’s not necessarily as strong as tobacco and or obesity so you make a good point.

We often talk about obesity and sitting is becoming the new smoking and the number of cancers that are increased with obesity.

Your lab has been looking at that in particular, with pancreatic cancer. Tell us a little bit more about the research that you do.

We’ve become interested in looking at non genetic factors that might be contributed to cancer development and this is in part due to the fact that we can study the cancer associated gene mutations in animal systems or model system such as the mouse and what we found is when we engineer the cancer associated mutations into mice while they do get the human cancers, we can engineer them in a large fraction of the pancreas. But we get very little tumor that develops and even the tumors that develop, most of them don’t progress to the advanced stages. So this suggested to us perhaps
non mutational factors, non genetic factors may be driving it or the environment or some other factors within the person might be contributing. And so we actually turned to epidemiological studies that had actually shown risk of increased pancreatic cancer development in obese individuals, and this has been known now for nearly two decades, in fact. Obesity is associated with 13 different cancer types, including many of the cancers in the gastrointestinal tract, including pancreatic cancer, and our research is really focused on trying to understand how obesity might contribute to cancer development in hopes of maybe identifying new ways of preventing and or treating the disease. And what we’ve found actually in studying obesity in mice in which we can engineer the mice to be obese or give them a high fat diet, for example, to make them dietarily obese, that the obesity itself can actually cooperate...
with gene mutations to promote the development and progression of pancreatic cancer. And we can actually do studies in mice to make them lose weight using either genetic or again dietary tricks, and we’ve found that if you do that at an early stage prior to the development of advanced tumors, you can actually use that as a preventative strategy to actually prevent the emergence of advanced pancreatic cancer. So what you’re basically telling us is that obesity kind of is synergistic with genetic mutations in pancreatic cancer in their progression and in their development. And so if you have a BRC mutation, one of the things you can do before you ever get pancreatic cancer as soon as you know about that genetic mutation, or even when you just have a family history is to lose weight because you will reduce your risk of getting pancreatic cancer, or at least having the pancreatic cancer be as aggressive as it otherwise could be. That’s right, that’s what our studies are suggesting.
both in humans from the epidemiology and also in our mouse models that actually weight loss might be helpful in reducing the risk of pancreatic cancer.

And so does the same thing apply to quitting smoking? That is less well studied in the realm of pancreatic cancer. We do know, for example, in heart disease that quitting smoking can have a dramatic improvement in reducing the risk of heart disease. And losing weight or reducing obesity also has cardiovascular benefits. So in terms of heart disease as well as cancer, as challenging as it may be to reduce or stop smoking and to lose some weight it might be very helpful in terms of not only improving general health, including cardiovascular disease, but also might play a role in cancer prevention. Yeah, it sounds like those two things if you want to live longer and better are two things that should be at the top of the ticket. You talked about genetically or doing
dietary tricks to get mice to lose weight and so we can make mice lose weight, it’s harder to get people to lose weight. Do you have any tricks or tips on studies that have been done that may have helped people to lose weight?

So this is a big problem. And how do we get people to lose weight? And a lot of it is genetics? Some of it can be genetic, some of it is trying to maintain the weight when people have already lost weight. I can’t speak to any specific tricks or tips that would be very helpful.

There are clinics now, including here at Yale, obesity clinics that do use adjunctive medications that can be very helpful in reducing weight and keeping the weight off. I would suggest that for those individuals that are having a hard time through just altering their diet or exercising to lose weight that trying to take advantage of some of these opportunities, including potentially going to some of these clinics might be very helpful. There’s a lot of focus from a public health standpoint in reducing obesity.
I don’t think anyone has a Magic Bullet, but I do think that there are dietary, exercise as well as medications that might be helpful for a large fraction of people. And as I’ve discussed already, I think that is really important, not only for general health outcomes, but I think it actually plays an important role for cancer prevention. For again, a large fraction of cancers.

Well thank you so much for that. We are going to take a quick break for a medical minute please stay tuned to learn more about pancreatic cancer, the role of genetics and the environment with my guest doctor, Mandar Deepak Muzumdar.

Support for Yale Cancer Answers comes from AstraZeneca, dedicated to advancing options and providing hope for people living with cancer. More information is at astrazeneca-us.com. This is a medical minute about lung cancer. More than 85% of lung cancer diagnosis are related to smoking and quitting even after decades of use can significantly reduce your risk of developing lung cancer. For lung cancer patients, clinical trials are currently under way to test innovative new treatments.
Advances are being made by utilizing targeted therapies and immunotherapies. The battle 2 trial aims to learn if a drug or combination of drugs based on personal biomarkers can help to control non small cell lung cancer. More information is available at yalecancercenter.org.

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Welcome back to Yale Cancer Answers. This is doctor Anees Chagpar and I’m joined tonight by my guest doctor Mandar Deepak Muzumdar. We’re discussing pancreatic cancer and the role of genetics and the environment in cancer, and one of the things that we talked about right before the break is that while pancreatic cancer is pretty rare, 10th or 11th, most common cancer in the United States, it is rapidly becoming one of the most common causes of cancer related death. Getting up there into the second or third leading cause of cancer related deaths.

So something really to think about and what you had mentioned was that there are a number of things that increase our risk.
Some things we can’t control.
Our genetics, our family history.
Some things we can control,
quitting smoking,
losing weight
to reduce your risk
developing pancreatic cancer
and reducing the stage at which it’s likely going to present at.
But I wanted to go back and talk about genetics.
We had talked about the fact that people have a family history.
Tell us a little bit more about the work that you’ve been doing looking at genetics and pancreatic cancer and how that might actually affect people.
So a number of mutations have been identified in pancreatic cancer and specific cancer genes that’s given us a great understanding in terms of how pancreatic cancers develop.
One of the hallmark genes in the disease is really the gene KRAS which is mutated in more than 90% of all human pancreatic cancers.
And it’s clear that it’s important in the development of pancreatic cancer when we engineer mice with KRAS, mutations in the pancreas, they get pancreatic cancers that look and behave just like the human disease. We also know that KRAS mutations can promote the growth and development of tumors in many other organs, including the lungs and the colon. In fact, 30% of lung cancers and in about 50% of colon and rectal cancers. And we know from cell studies that KRAS really promotes cell proliferation, their ability to duplicate themselves is a hallmark of cancer development. Now importantly, KRAS has been known for nearly four decades now, and we know from other tumor types in which we’ve identified the hallmark genetic mutations that we can often target those mutations with therapies that can be quite effective. Unfortunately, for KRAS it’s actually been very hard to develop drugs that can block its function,
and so one of the things that is actually emerged recently is new developments in drugs and one of those is a specific drug that targets a specific flavor or mutation of KRAS, which we call the G12C Mutation, which is found in about 14% of all lung cancers, but only about 2 to 3% of pancreatic cancers. Nonetheless, this class of drugs is now being tested in clinical trials and in lung cancer at least the data are quite promising that they can lead to shrinkage of the tumors in a large fraction of patients. Now it remains to be seen whether the effect will be true in pancreatic cancer, but we’re excited that now for the first time, we actually have a drug that can target at least a specific mutation in pancreatic cancer, so I just wanted to clarify for our listeners out there, there’s a difference in terms of genetics that are germline genetics and cancer genetics. Can you clarify that a little bit?
we’ve talked about, you know, going and if you have a family history, seeing a geneticist and seeing if you carry a genetic mutation like BRC and so on, and then we kind of transitioned and we talked about looking at cancer genetics, and the genetic mutations of a cancer cell. Can you talk about and clarify that difference just so that I make sure that everybody out there understands that difference? Absolutely so germline genetics is really based on mutations that are rise from the very beginning that you inherit or have been there from the very start. So those are mutations that are found in all of your cells. And we think some of them predispose to cancer development because they affect the ability of your body to maintain fidelity or to maintain the DNA without creating new mutations. So these are what we call DNA repair genes. They get when they get mutated. Now when the cells duplicate themselves during development, they make errors. And new mutations can occur. So that includes genes such as BRCA1 and 2 has been discussed, as well as other genes that are involved in DNA repair pathways.
and we’ve gotten to actually be able to take advantage of these mutations. From a therapeutic standpoint because it turns out certain chemotherapeutic agents in certain drugs can actually be more helpful in patients who have those mutations. So one of the things that’s emerged is that as we sequence more and more pancreatic cancers, we’re finding that we’re starting to find more and more of these DNA repair gene mutations in those cancers such that we actually believe as a community that everyone who is diagnosed with pancreatic cancer should have their tumors looked at for these particular mutations with the hope of potentially using that again to guide therapy.

Now there’s a second class of mutations, not germ line, but these are mutations that occur in individual cells in the body at some point after birth, and these are what we call somatic mutations. These are mutations that can drive the growth and development of tumors. One of these mutations that falls into this class is the mutation in KRAS and
so these are mutations that we think are integral to the formation of particular cancer types. KRAS and pancreatic cancer. But they are not there from the very beginning. From when you’re born, they emerged at a later time point, but clearly play an important role in cancer development and play a potentially important role in guiding treatment. Again using targeted drugs that target these specific mutations and you make a very good point about when you’re diagnosed with cancer, like pancreatic cancer, getting that evaluated to look for these genetic mutations because there may be drugs that can target that specifically. You mentioned in lung cancer the fact that we have drugs against KRAS that have shown promise and that the data are out in terms of that fact with pancreatic cancer. Are there clinical trials looking at that? There are clinical trials using those same agents in a broad array of cancer types that have KRAS mutations. Specifically with that one particular
mutation, that G12C mutation, and so there are clinical trials that might be available. Again, it’s not that common in pancreatic cancer, so a lot of patients would not be eligible. There is clearly a push to develop KRAS drugs that target a larger number of KRAS mutations and there is a tremendous amount of research to develop this. In fact, the National Cancer Institute has a whole KRAS initiative which is really focused on developing more fundamental understanding. Of KRAS and other proteins and trying to develop new structures and drugs that we can use to target these. In the lab, we’ve tried to model what would happen if you inhibit KRAS using genetic technologies because we did not have these drugs for many years and so we can actually use genetic tricks to disrupt or knockout all function. And we’ve done that in pancreatic cancer. We see that it can be quite effective in reducing the growth of many pancreatic cancer cell lines. But a subset of them
0:23:07.41 –> 0:23:09.811 seem to continue to survive
0:23:09.811 –> 0:23:11.509 despite complete loss of KRAS,
0:23:11.51 –> 0:23:13.52 suggesting that even with these drugs
0:23:13.52 –> 0:23:16.299 there is likely to be some resistance now.
0:23:16.3 –> 0:23:17.29 The encouraging
0:23:17.29 –> 0:23:20.02 part is we can use these models to
0:23:20.02 –> 0:23:22.456 study how cells aid KRAS inhibition,
0:23:22.46 –> 0:23:23.483 how they resist,
0:23:23.483 –> 0:23:25.188 how they continue to survive,
0:23:25.19 –> 0:23:27.286 and using this data we can now
0:23:27.286 –> 0:23:29.546 use that to bring it into our clinical
0:23:29.546 –> 0:23:31.672 trials and try and design better
0:23:31.672 –> 0:23:33.56 combination therapies that might
0:23:33.56 –> 0:23:35.448 overcome the resistance mechanisms
0:23:35.45 –> 0:23:37.73 that developed with KRAS.
0:23:37.73 –> 0:23:38.702 Now we’re excited
0:23:38.702 –> 0:23:40.646 we finally have drugs that target
0:23:40.646 –> 0:23:42.713 KRAS to really test these hypothesis
0:23:42.713 –> 0:23:44.926 and really see whether we can
0:23:44.926 –> 0:23:45.87 overcome resistance.
0:23:45.87 –> 0:23:47.982 But because of the genetic studies
0:23:47.982 –> 0:23:50.12 that we and others have done,
0:23:50.12 –> 0:23:52.052 it gives us some advanced insight
0:23:52.052 –> 0:23:54.144 into how to really combine drugs
0:23:54.144 –> 0:23:56.34 into ways that might help patients
0:23:56.34 –> 0:23:58.578 even earlier in terms of overcoming
0:23:58.578 –> 0:24:00.378 resistance to KRAS inhibitors
0:24:00.378 –> 0:24:01.799 as they continue to
0:24:01.8 –> 0:24:04.928 emerge. So now that we have these inhibitors
0:24:04.928 –> 0:24:07.805 against the G12 mutation of KRAS,
0:24:07.81 –> 0:24:10.394 have you looked at mice who have that
mutation and see whether these drugs work?

Whether there is a significant proportion of them that are resistant, or whether most of them actually will respond like the lung cancer patients have?

so there are studies that have been done using human cell lines that have particular disk error. Gee, 12 Mutation and put them into mice and then treated the mice with the drugs and they can be quite effective in shrinking the tumors. Now we do see that again.

Subset of those tumors will recur, and a lot of work is being done now to try to identify those resistance mechanisms and then hopefully bring that quicker to the clinic. That’s something we’ve really learned from targeting other mutations and other cancer types like lung cancer that cancers will often find ways to escape the inhibition, but we now know and study that in advance and hopefully design clinical trials and better ways to bring those combination therapies sooner and hopefully prevent the emergence of resistance to these drugs. So given the choice,
if a patient is diagnosed with pancreatic cancer, there are standard chemotherapy regimens that are given, and we know that these may or may not be effective, but if a patient has a particular mutation and there is a clinical trial that is offering them a medication targeted against that mutation, are they better off just statistically to take the clinical trial over the standard of care? Or is it better to do the standard of care? Wait till you fail and then try a targeted therapy? Many of these targeted therapies, when their first introduced and tested in patients, are often used after the standard of care is already been given and there may be a point once we show that they are efficacious or they work that they then are brought up to earlier stages. That’s true for example, in lung cancer and specific types of mutations in lung cancer that we’ve observed. But at this point most of these trials, at least the early phase trials, are after the standard of care, so I think that right now standard of care...
care chemotherapy is really our best bet. How we tailor which chemotherapy to give it may depend a little bit on whether there are mutations in DNA repair genes that we can detect in cancer. So I think it’s important to talk to your oncologist or doctor about looking at the sequence, because that could affect how you choose the chemotherapies that we typically give and then hopefully down the line some of these targeted drugs will make their way to where they might be helpful in the first line prior to what we have currently, and maybe replace the current therapies in terms of standard of care. I don’t think we’re quite there yet, and pancreatic cancer for targeted therapies, so when we talked about germline mutations and some people may have, for example a mutation, are you using that information to tailor your therapy as well and if so, can you tell us a little bit about that? We do know that DNA repair pathways are abnormal in patients who have two mutations and it turns out certain chemotherapy therapies that we give
can be more effective in that context. Those cells can’t repair the DNA. It actually induces, which leads them to be more sensitive to those chemotherapies, and so we are tailoring our chemotherapy a little bit in terms of having that mutation. We also know that there is a certain class of drugs called PARP Inhibitors that have been quite helpful in breast and ovarian cancers with RCA mutations that now have shown some efficacy in patients who have be RCA germline mutations in pancreatic cancer and recently was FDA approved actually for that indication in the last month. And so again, the knowledge of these mutations and their presence in the tumors is helping us guide how we treat our patients. Tell me how that impacts overall survival. If we give standard chemotherapy, how efficacious is it? And if we can target something, how much does that improve outcomes? So in terms of overall survival, in standard of care chemotherapy, in which we use really four drugs, three of which are chemotherapies,
A regimen which has been around now for nearly a decade, is still the standard of care. It was important when the initial results came out nearly a decade ago, because it really showed that combinations of chemotherapy could be better than a single chemotherapy. In the 2000s, we did a number of trials in which we combined chemotherapies and none of them were better than one drug alone, and so that really showed us that combination chemotherapy can be helpful in pancreatic cancer, and I think those are still the standard of care at this point. Though again, we can tailor a little bit based on the sequencing and the presence or absence of these general permutation.

Deepak Muzumdar is an assistant professor of genetics and medical oncology at the Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at Yalecancercenter.org. We hope you’ll join us next week to...
0:29:26.576 –> 0:29:29.313 learn more about the fight against cancer here on Connecticut public radio.