

Dr. Harvey Risch, Epidemiology Research in Pancreatic Cancer June 27, 2010 Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Dr. Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Foss is a Professor of Medical Oncology and Dermatology specializing in the treatment of 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 1888-234-4YCC. This evening Ed and Francine welcome Dr. Harvey Risch, Dr. Risch is a Professor in the Division of Chronic Disease Epidemiology at Yale School of Public Health and he joins us to talk about pancreatic cancer. Here is Ed Chu. Chu Why don't we start off by defining for our listeners out there what pancreatic cancer is? Risch Pancreatic cancer is a cancer that occurs in the pancreas, obviously. The pancreas is an organ that is just underneath the stomach and makes enzymes to digest food and fluid to help with neutralization of stomach acid. Chu How common is pancreatic cancer as a public health problem? Risch It's not a major problem, but it is a significant one. Probably about 1% of the population will get pancreatic cancer over their lifetime, and that translates to about 42,000 cases in the US per year, and about 35,000 deaths from pancreatic cancer per year. Foss Harvey, what are the ages and gender of patients with pancreatic cancer? Risch It mostly occurs in individuals over age 50, especially over 60 and in their 70s, and it used to be that it was more a disease of males than females, but in the last few years women are now getting pancreatic cancer at the same rate as men. Chu What do we know about the underlying risk factors for pancreatic cancer? Risch The classical risk factors have been identified as tobacco smoking, mostly cigarette smoking, which perhaps accounts for 20% of cases. There are some rare genetic mutations, and also chronic pancreatitis, which is inflammation of the pancreas, and together those may account for perhaps 10% of the disease, so overall we know about 30% of what causes pancreatic cancer and the remaining 70% is unknown. Recently, there has been some work showing evidence for ABO blood group, AB and AB blood groups, compared to group O as being associated with risk and that's just a developing story. 2:43 into mp3 file <http://yalecancercenter.org/podcast/jun2710-cancer-answers-risch.mp3> Foss There was a paper in the New England Journal a number of years ago about coffee and the risk of pancreatic cancer, has that ever been proven? Risch No, and like many findings we have in epidemiology, we tend to believe our own findings until the next paper comes out that refutes it, so when one puts together the whole literature, there is no other evidence really to show that. Chu And is there any linkage say between other diseases of the pancreas such as diabetes and the development of pancreas cancer? Risch Diabetes is an interesting story because there is an increased risk that one measures in studies, but on the other hand, within about three years before the diagnosis of pancreatic cancer, there is also an increased incidence of diabetes that we believe is the result of the cancer itself developing, so it's unclear which direction the cause goes, whether diabetes causes pancreatic cancer or vice versa, and we do not really know yet. Foss Harvey, you mentioned smoking is a risk factor. I

do not think many people in the audience connect smoking with pancreatic cancer. Risch Smoking causes a number of different kinds of cancers, not just lung cancer, there's a whole class of smoking related cancers and pancreas is one of them. The carcinogens for pancreatic cancer reach the pancreas from the lungs to the blood stream rather than being deposited in the lungs directly, but it's still an important source of carcinogenic material that's in the tobacco smoke that causes the cancer. Foss Likewise with passive exposure to smoke, is that also a risk? Risch I think that's harder to prove. There may be, in theory there could be, but we do not really know that. Chu What's remarkable is that, as you say, pancreatic cancer may effect about 40-45 thousand patients in the United States each year, but yet just within the last few years there is so much publicity about sports stars and Hollywood personalities that have developed pancreatic cancer and so you get the sense that it really is a pretty significant issue. Risch It's hard to know, once you turn 40 you know people who had some of the more rare kinds of cancer, either among your friends, acquaintances, or relatives. And in general I think that these are noteworthy kinds of occurrences, and so we pick up on that. It's hard to know whether it was just not talked about as much in past generations, or that the risks have been5:07 into mp3 file <http://yalecancercenter.org/podcast/jun2710-cancer-answers-risch.mp3>increasing, but they certainly have not been increasing dramatically. Foss Do you think that many pancreatic cancers are not picked up on early enough? This is always a question we have about screening and detecting cancers early so that we can actually impact the survival. Risch That is true. The cancers that occur deep in the abdomen, are in general, unless they have some root at the outside, not diagnosed early so it's mostly late stage disease, which has poor survival. Foss And is it also true that many patients do not have symptoms until they are very advanced? Risch That's correct. Chu For our listeners out there, for breast cancer we have screen mammography, for colorectal cancer, we have screening colonoscopy. For pancreatic cancer, as of yet there is no screening or early detection method that has been developed. Risch That's largely correct; one would have to have an index of suspicion, a reason to look for pancreatic cancer, and in any cancer like the pancreas, ovarian and others where the rates are sufficiently low, like 1-2 percent of a lifetime risk, there is no reason that you would screen because the number of people who would be falsely diagnosed after you do more invasive tests would be too large to compare to the number you would actually find as truly having pancreatic cancer, so it's not effective. Foss Can you tell us if there is an association with other cancers, say patients who may have colon cancer or breast cancer, are they going to be at an increased risk for pancreatic cancer? Risch Not that I know of, unless they carry a BRCA2 mutation, which would put them at increased risk for breast cancer, pancreatic cancer, ovarian cancer and a few others, but that's relatively rare. Foss You study the epidemiology of pancreatic cancer. Can you talk a little bit about what epidemiology is for our audience? Risch Epidemiology is the study of human diseases or conditions by using representative samples of people from the population; both people with the disease and people

for control purposes who are selected randomly from the 7:18 into mp3 file <http://yalecancercenter.org/podcast/jun2710-cancer-answers-risch.mp3> general population to be a comparison to the cases. It's the representativeness that characterizes epidemiology because everything else that we do could be done in any kind of medical research study. We could study genetic factors, behavioral factors, exercise or hormonal factors, diet, occupation, environmental factors, and we can measure all sorts of things such as chemicals in the blood and bacterial colonization and so on, so what we actually measure is the same as other kind of research studies, but it's the representativeness and the large sample size to get enough statistical power to make conclusions that characterizes epidemiology.

Chu Harvey, what made you develop this interest in trying to understand the epidemiology of pancreatic cancer?

Risch This is really a very interesting story. I am an editor of the Journal of the National Cancer Institute and I received a manuscript to consider for publication looking at the risk of pancreatic cancer and colonization by the bacterium *Helicobacter pylori*, and I wondered why in the world should there been an association between *Helicobacter* and pancreatic cancer? I asked a few experts about whether *Helicobacter* colonizes the pancreas, whether it gets into the pancreas, and everybody uniformly said no, and to me that meant that there had to be some physiological reason why what the bacterium was doing in the stomach was somehow related to digestion and therefore causing the pancreas to do what it was doing, and I spent about six months reviewing the literature and trying to figure out why this process was going on until I had a clear hypothesis about it and published that and that started the studies that I have been doing.

Chu It's interesting because *Helicobacter pylori* has been associated with other kinds of cancers that typically arise within the stomach.

Risch That's correct, with gastric cancer predominantly, stomach cancer, and we believe that's a direct effect of the bacterium on the lining cells of the stomach, along with carcinogenic substances that are taken in mainly from diet.

Foss Most patients don't actually know they have *Helicobacter*, is that correct?

Risch Most of it is asymptomatic, that is it's only a very small fraction that causes heart burn or reflux that gets to be diagnosed. Most people don't know they have it.

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Chu How does one develop that infection?

Risch *Helicobacter* is typically acquired in childhood or adolescence and in the United States perhaps a third of individuals are colonized, which is relatively low. In Europe and in Asia it's perhaps 60% or even higher, as high as 80-85% of individuals that carry *Helicobacter*.

Foss In the United States, if a person knows that they have *Helicobacter*, how worried should they be about developing pancreatic cancer?

Risch It is still not a huge risk. The major risk from *Helicobacter* is more stomach cancer than pancreatic cancer because it causes both. It also is associated with cancer of the esophagus and it's a complicated organism behavior because it may reduce risk of asthma and have other health related risks and benefits, and so we don't think of it as an infection, we think of it as a colonization because so many people carry it and because most of its course is silent and it does not do that much, but it does raise the risk of stomach

cancer and may increase the risk of pancreatic cancer. Chu People have been talking about this association between Helicobacter and stomach cancer. I think there is also an association between this organism and lymphoma, a special type of lymphoma which is Dr. Foss's domain, but I guess it kind of highlights this association that people have been increasingly aware of relating to inflammation, and then the development of cancer down the road. Risch It's very interesting how we think the Helicobacter works for pancreatic cancer. Helicobacter comes in lots of different varieties which we refer to as strains. Some of the strains are more virulent and some are less virulent. The more virulent strains of Helicobacter shut off stomach acid production, and over time lead to an inflammation of the lining of the stomach and increased risk of stomach cancer, but the milder strains do not do that and they tend to increase the production of stomach acid and in response the pancreas increases its production of fluid and bicarbonate which is a chemical that neutralizes the stomach acid. When the pancreas does this it becomes more sensitive to the effects of carcinogens, which are these chemicals, for pancreatic cancer they are of a class called nitrosamines, which arise in tobacco smoking and also in smoked and processed meats like bacon, salami, baloney, and so on. And these chemicals get to the pancreas through the blood stream and the pancreas is sensitized to the effects of the chemicals more so because it's been turned up because of the Helicobacter effect, and so that's the total picture that we think is why the 12:53 into mp3 file <http://yalecancercenter.org/podcast/jun2710-cancer-answers-risch.mp3> Helicobacter is involved in pancreatic cancer. Foss So the Helicobacter does not itself actually infect the pancreas? Risch No it does not. Foss That's interesting because the pancreas is actually connected to the whole stomach system through ducts. Risch That's right, but there are other species of Helicobacter that do colonize the pancreas, but not Helicobacter pylori, not the one that does with stomach cancer. Foss You talked about nitrosamines and certainly nitrosamines are in a lot of the food that we eat, particularly the hot dogs at baseball games. Can you talk a little bit about the risk, and how much nitrosamine will put a patient at risk? Risch Like most human behaviors, it's things that you do regularly that matter. If you have hot dogs once or twice year, it's not a big deal, but multiple times per month is what matters. Foss And you specifically also mentioned bacon. Risch Any of those together multiple times per month is where the risk increases. Foss This was really useful to hear this information about pancreatic cancer and we would like to continue our discussion after a short break. Please stay tuned to learn more information about pancreatic cancer with our guest Dr. Harvey Risch. 14:55 into mp3 file <http://yalecancercenter.org/podcast/jun2710-cancer-answers-risch.mp3> chemotherapy to reduce side effects of treatment and help cancer drugs work more effectively. This has been a medical minute and more information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network. Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am here with my co-host Dr. Ed Chu. Today our guest is Dr. Harvey Risch who joins us to discuss pancreatic cancer. Right

before the break Harvey, we were talking about nitrosamines as a risk for pancreatic cancer. Are nitrosamines also a risk for other kinds of cancer? Risch Nitrosamines are mainly a risk for pancreatic cancer and gastric cancer. It is possible that they may be involved in other cancers, but the evidence is strongest for stomach cancer and pancreatic cancer. Foss Is there any kind of racial or genetic predilection to sensitivity to nitrosamines? Do certain people need to watch out for this? Risch I would say no we do not know that to be a factor in the risk for nitrosamines. There are some racial ethnic differences and risks for pancreatic cancer. It is seen a little more frequently in whites and African-Americans and a little less frequent in Asians. Chu Harvey, maybe we can go back to the basics of pancreatic cancer for those who may have missed the first part of the show. Based on your research have you observed any changes in the incidence of pancreatic cancer over the recent years? Risch Pancreatic cancer has been slowly increasing in frequency over the last say two decades. It's more or less leveled off for men, but it has been increasing more for women who have caught up with men. Probably the reason for this increase is cigarette smoking among women. Foss In terms of looking at smoking, does it make any difference how young a person starts to smoke, or is it total pack years of smoking that impacts the incidence? Risch The most interesting thing about smoking is it matters what you have done in the last few years and therefore, for pancreatic cancer, quitting is important because the risk goes down to almost that of a nonsmoker in 5-10 years after quitting. And it goes down the fastest, the sooner you quit. As soon as you quit, it start to drop and after 10 years it is almost all the way17:30 into mp3 file <http://yalecancercenter.org/podcast/jun2710-cancer-answers-risch.mp3>download and after 15 years it's distinguishable from a lifelong nonsmoker. So quitting really matters for this disease. Chu Again, like the patients that you studied in your research, did you notice that the incidence of pancreatic cancer increased in those who smoked and who also had this underlying Helicobacter infection? Risch Yes, definitely. Each one of them contributes to the risk and the combined picture of risk between smoking and Helicobacter colonization and blood groups, as I mentioned, that we can perhaps talk about more, can get to 5 to 10 fold increased risk if one has the whole combination of risk factors. Foss Can you talk about the blood group data? Risch This is another interesting story. It's been known for almost fifty years that ABO blood group is involved in certain diseases, they are involved in ulcers of the stomach and duodenum and gastric cancer and now we have some recent evidence that they are involved in the risk of pancreatic cancer as well. It also is curious that Helicobacter pylori colonization is involved in the risk of stomach cancer and stomach ulcers, gastric ulcers and duodenal ulcers, and we believe also in the risk of pancreatic cancer. So the four conditions seem to be related to both ABO blood group and to Helicobacter pylori colonization. Now why in the world should ABO blood group be related to something that occurs in the stomach or the pancreas? The answer to this is that the molecules that define the blood groups do not just sit on the surface of red blood cells but they also sit on the surface of the cells that line the stomach, and it turns out that these

little molecules that are on the stomach lining cells are immediately next to the parts of the cells that bind to the *Helicobacter pylori*, to the bacterium that sits in the stomach, and so it matters which of these blood group molecules is present because they interact physically, or they may interact physically, with the bacterium that they are adjacent to and because of that they have an effect on risk and that is how we believe the ABO effect occurs through the bacterium.

Foss For our listeners, can you tell us if there is a specific blood type that is at highest risk?

Risch We believe that the non O blood groups are at the most increased risk. We are talking about A, B, and AB, it's not a dramatic risk, perhaps 40 % increased risk for individuals who carry those blood groups, but on the other hand there is the interaction with *Helicobacter pylori* and we have to sort that out and that's a very hot topic for research.

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Chu Have you or others found that perhaps there is a linkage between the blood type and the development, or presence of *Helicobacter* infections?

Risch It does not appear that ABO blood group is related to the likelihood of developing infection and colonization with the bacterium, but when the blood group is present it changes a little bit how the bacterium operates and we think that is how it is working.

Foss On the flip side, if you have type O, is your risk lower?

Risch Yes, it would be a little bit lower.

Foss Does that make any difference in terms of how clinicians approach patients with *Helicobacter pylori*? Because as you have said, a lot of patients are colonized with this, so should physicians be thinking about a matrix in terms of how to approach patients who are positive?

Risch In my opinion if somebody is known to be positive for carrying *Helicobacter pylori* they should be treated. The treatment is a course of three antibiotics over a short, two or three week period, and it cures about two thirds of individuals on the first pass and perhaps if you need a second pass at it, it would get to 95%. One interesting study that took a cohort of about 13000 individuals who were carrying this bacterium and treated them, showed that of the two thirds that were successfully eradicated, they had a 40 percent lower risk of subsequent pancreatic cancer, so that's almost like a human experiment showing the association.

Chu Harvey, how is *Helicobacter* infection colonization initially diagnosed and how is it followed for treatment?

Risch Well, for an adult who has never been colonized, if they get it in adulthood they will have an episode of gastritis, that is acute inflammation of the stomach. It could be painful and they will wonder what happened to them and they may seek medical attention. For individuals who get it in childhood and adolescence, they would never know they had it and it might be totally asymptomatic, they would never know. They might have had a slight bout of gastritis, but in childhood there are any number of childhood illnesses that would appear the same and so it would not be remarkable.

Chu Is there a blood test to detect the infection or does a procedure have to be done to actually gather the bacterial organism?

Risch Actually, it is quite easy. There are blood tests, but even easier, one can

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take in a small amount of chemical that will add bacteria, if they are present it will

convert to hydrogen gas and that can be measured in breath and so there is a breath test that can be done. Chu That's interesting. Foss Let's get back to the question about nitrosamines again and talk about other potential carcinogens. We have heard, and continue to hear on the radio, about the risk of pesticide exposure from fruits and vegetables and I am wondering, are there other chemicals that are specifically associated with pancreatic cancer? Risch The major animal models that have looked at pancreatic cancer for at least 30 years have used nitrosamines. They work in the animal models and they were thought to characterize human exposures from smoking and that's probably why they were originally developed. To my knowledge, pesticides, and for example overcooked food and burned food are another class of chemicals that are also thought to be a carcinogen although they may not be as important as nitrosamines, have been looked at, but there is very little convincing evidence of their associations. Chu Harvey, what do we know about the role of alcohol and pancreatic cancer? Clearly there is an association between alcohol and some chronic pancreatic diseases. Risch Yes, there is an association but it appears only at the very highest levels of alcohol intake, people who have six or more drinks per day on the average. Less than that, there is no significant evidence of an association. Foss So the average social drinker, for instance, should not really have to worry as much about this. Risch Not unless they smoke. Foss You mentioned that chronic pancreatitis is associated, so if you do not have chronic pancreatitis, and you drink for instance, what is your risk, is that a marker? The chronic pancreatitis, is that a marker? Risch Chronic pancreatitis is a serious disease, but it's infrequent. Less than 2% of people in the general population will have had chronic pancreatitis at some time. 25:03 into mp3 file <http://yalecancercenter.org/podcast/jun2710-cancer-answers-risch.mp3> Chu You focus on the epidemiology of pancreatic cancer. What's your sense about where things have evolved with respect to our understanding of the biology and treatment advances that have been made in pancreatic cancer? Risch Treatment is very difficult primarily for the reason that most cases are diagnosed after the disease has spread from the pancreas, and the pancreatic enzymes are very caustic chemicals that will digest parts of the body if they get out of the pancreas. This makes it a very serious disease in the later stages, so it's very important to get it at an early stage when there is some hope for surgical cure; today that characterizes perhaps 20 or 25 percent of cases that are diagnosed. That means the majority are too late to save that way and our chemotherapy and radiation treatments help a little bit, they prolong life, but in general they do not cure the patients, so prevention is really the big item for pancreatic cancer. Chu Are there specific genetic tests that could be done to predict risk for pancreatic cancer? Risch Only for the rare individuals who carry BRCA1 or BRCA2 mutations and even for them the risks for breast and ovarian cancer are much higher compared to pancreatic cancer. Chu You just mentioned the potential role of prevention, so what are the types of chemo preventive strategies that people are taking or thinking about to prevent pancreatic cancer from developing? Risch For pancreatic cancer the best thing to do is to try to minimize the consumption

of smoked and processed meats, it is not something to obsess about, but just in general to be prudent try to have them relatively infrequently. Also stop smoking if one smokes, or do not start in adolescence and if one has heartburn at least be tested for *Helicobacter* coverage and treat it if it is present.

Foss Are there clinical trials, epidemiologic trials going on at the national level looking at pancreatic cancer?

Chu I am in the process of organizing a large study, consortial study, of case control and large epidemiologic studies to try to put together a picture of how the ABO blood group, *Helicobacter* colonization, nitrosamines in the diet, smoking and so on are involved in the cause. We do this by collaborating with scientists all over the world who have done individual studies and we know have a collection of studies that involve

27:41 into mp3 file <http://yalecancercenter.org/podcast/jun2710-cancer-answers-risch.mp3> approximately seven thousand cases and seven thousand controls. We are seeking grant funding from the NIH to be able to do a combined analysis.

Foss And all of these patients have had extensive questionnaires about lifestyle and diet and all other factors that might be important?

Risch Yes, that's correct.

Foss Just for the audience to understand, these epidemiologic studies do require huge numbers of patients.

Risch We certainly value when patients participate in our studies. In general we try to identify everyone that we can find with the disease in a defined area from the state of Connecticut, but we identify for comparison purposes normal people in the population and we do this by calling people on the telephone or mailing them letters and so on. And this is not something that people are used to and we have to convince them that we are not doing market research and we are not selling things, we are doing medical research, and it's important that they participate and in general we have been very successful with that.

Chu Harvey, it has been great having you on the show to share with us your really interesting research on the epidemiology of pancreatic cancer and hopefully we will have you back on a future show and you can tell us where you are in your large clinical trial, and how that study is doing.

Risch Thank you very much.

Chu Until next week, this is Dr. Ed Chu from Yale Cancer Center wishing you a safe and healthy week. If you have questions or would like to share your comments, visit yalecancercenter.org, where you can also subscribe to our podcast and find written transcripts of past programs. I am Bruce Barber and you are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.