

Yale CANCER CENTER *answers*

WNPR Connecticut Public Radio



Hosts

Anees Chagpar MD

Associate Professor of
Surgical Oncology

Francine Foss MD

Professor of Hematology

Steven Gore MD

Director of
Hematological
Malignancies

Aspirin as a way to Prevent Pancreatic Cancers

Guest:

Harvey Risch, PhD

*Professor, Epidemiology and Chronic Diseases,
Yale School of Medicine*

Yale Cancer Center Answers is
a weekly broadcast on **WNPR**
Connecticut Public Radio
Sunday evenings at 6:00 PM.

Listen Live Online at
www.cpbm.org

OR

Listen to Archived Programs at
www.yalecancercenter.org

Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss, Anees Chagpar and Steven Gore. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at the Yale Cancer Center. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital and Dr. Gore is Director of Hematological Malignancies at Smilow. Yale Cancer Center Answers features weekly conversations about the research, diagnosis and treatment of cancer, and if you would like to join the conversation, you can submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week you will hear a conversation about the role of aspirin in preventing pancreatic cancer with Dr. Harvey Risch. Dr. Risch is Professor of Epidemiology and Chronic Diseases at Yale School of Medicine. Here is Dr. Steven Gore.

Gore Start off by telling me where you are in the field and what it is you do as an epidemiologist in pancreatic cancer.

Risch I have been an epidemiologist for three decades now, and I started off as a very quantitative person trying to use statistical techniques to understand the causation of disease. After about half of that time, I came to think that the biological processes of human disease was more important than the statistical so I have become much more of a biologist now, and that is kind of what I do, try to understand the causation of human disease and how to prevent it and ameliorate it. I got into pancreatic cancer a little over a decade ago because of a very peculiar paper that crossed my desk. I am an editor of a journal of the National Cancer Institute, and I received a manuscript to triage to send out for review concerning *Helicobacter pylori* and risk of pancreatic cancer.

Gore This is the bug that causes peptic ulcers right?

Risch That's right, and gastric cancer. And I tried to understand why in the world there could be an association between this organism, bacteria, which colonizes in about a third of Americans still even today and is asymptomatic for most people, why there would be an association between this and pancreatic cancer? I quickly discovered that it does not colonize the pancreas, it does not get into the pancreas, it only stays in the stomach, therefore, it had to be something biochemical or physiologic. And after working on this for about three months, I had some ideas about its biochemical processes that were involved and I got two studies funded by the National Institutes of Health to do large studies on pancreatic cancer and *Helicobacter* in Connecticut and actually in Shanghai because they have a different kind of *Helicobacter pylori* in their population and it works a little bit differently and that keyed into our hypothesis. We finished those studies actually this past fall, and we published two papers now that have shown the associations with *Helicobacter* and how they change the physiology of the stomach and how the acidity of the stomach is related to how the pancreas responds to that acidity and how that prompts the pancreas to be at higher risk or at lower risk in the case of China for risk of pancreatic cancer. It has been a fascinating journey.

Gore Wow! Maybe you can walk us through that point by point. You told me that a third, I think you said, of Americans are colonized by this particular bacterium, and what is that doing that is subsequently impacting what the pancreas is seeing?

3:52 into mp3 file <http://yalecancercenter.org/podcasts/2015%200201%20YCC%20Answers%20-%20Dr%20Risch.mp3>

Risch Well, humans have been colonized by Helicobacter for at least 50,000 years.

Gore How do we know that?

Risch We have evolutionary information about the strains and how they distribute across the entire western and eastern worlds. And, the evolutionary biologists characterize how the genetic changes in the organism occur and how they spread geographically.

Gore Wow!

Risch And so they can trace the evolution of Helicobacter as its own organism in parallel with the evolution of humans. It really is fascinating.

Gore Fascinating.

Risch And they have shown that Helicobacter has co-evolved with humans and spread with human migrations. So it is something we have had in us for a long time, and for most people, it is asymptomatic. Most people do not know that they are carrying it. It is a very few who actually have symptoms related to what the Helicobacter is doing in them.

Gore Okay.

Risch But it does do something. Helicobacter comes in two major strains; one that is more aggressive and one that is less aggressive. In the United States and western countries, it is about 50-50, about half the people who are carriers of this organism, and we do not say people are infected, we say they are colonized because it is such a natural thing, about half are colonized with the more aggressive strain and half with the less aggressive strain. Whereas in China, almost everybody, perhaps 90% of people who are colonized are colonized with the aggressive strain. Now I say the aggressive strain; it is a strain that is aggressive in its physiology, the way it interacts with the lining of the stomach. But what it does do for people is it shuts off their acid secretion in their stomach, the aggressive strain.

Gore And what does that do?

Risch That fact causes atrophy of the lining of the stomach. It causes the stomach lining to shrivel and undergo pathological changes that predispose toward gastric cancer and that is what is typically seen and that is why gastric cancer has a high frequency in China and Japan and other Asian countries because it is a very prevalent organism, perhaps 50 or 60 or more percent of people in China are colonized.

Gore Wow.

6:11 into mp3 file <http://yalecancercenter.org/podcasts/2015%200201%20YCC%20Answers%20-%20Dr%20Risch.mp3>

Risch Whereas in the United States, we have the two varieties, the less aggressive strain which increases gastric acidity, does the opposite of the more aggressive strain and that is the one that is associated with increased risk of pancreatic cancer in western countries and that is what we show that if you are colonized with the lesser aggressive strain that increases gastric acidity, you have a higher risk of pancreatic cancer. If you are colonized with the more aggressive strain that shuts off gastric acidity, you have a lower risk of pancreatic cancer but a higher risk for gastric cancer. So, these are the evil twins, pancreatic cancer and gastric cancer.

Gore I was going to say, either way you are not winning out.

Risch That's right. Yeah.

Gore How does this increased acidity put the pancreas at risk for developing cancer?

Risch There are more than two, but the two major jobs that the pancreas does is it makes enzymes to help in digestion of food constituents, and in a much larger way, it makes fluid and bicarbonate, which is a chemical that neutralizes gastric acidity. So when the acidity of the stomach is released into the duodenum, the next part of its pathway through the intestines, the acidity has to be neutralized and that is pancreas' job, and it makes up to 2 L of fluid a day that is very alkaline because of the bicarbonate that neutralizes the gastric acidity.

Gore Okay.

Risch And the pancreas recognizes how much acidity there is in the food products and responds to that, so that it makes more or less depending upon what it has to neutralize. But it turns out that the *Helicobacter* modulates that. It increases the amount of acidity even when the pancreas is resting if the less aggressive strain is colonized or it is totally shut off when the gastric acidity is shut off and therefore the pancreas is also shut off making this alkaline substance to neutralize the acidity that isn't there. The presence of this organism works to make the pancreas respond to the acidity that is being modulated. Now, what is really fascinating is that one would think, so why does this acidity matter and why does it matter for the pancreas even if it is changing its behaviors?

Gore Right.

Risch This was shown in experiments in hamsters in the late 1980s, that when carcinogens that are known to cause pancreatic cancer are given to hamsters, but in a dose that is too low to cause the cancers, but they were still given the hormone that is used by the intestines to tell the pancreas to make more bicarbonate at a physiologic level, then they overwhelming got pancreatic cancers. So the fact that the pancreas is stimulated to make more bicarbonate and more fluid, sets its ductal cells, the cells lining the glandular part of the pancreas that makes all this fluid, it sensitizes those cells to the presence of the carcinogens that get to the pancreas through the blood stream. Like from smoking and from other sources.

9:34 into mp3 file <http://yalecancercenter.org/podcasts/2015%200201%20YCC%20Answers%20-%20Dr%20Risch.mp3>

- Gore Wow! So, it seems kind of simple but complicated at the same time.
- Risch There are a few things going on, but it is all physiology, and physiology has scientific principles and when you kind of lay them out and see which factor affects what, it works out straightforwardly.
- Gore Do you know or is it known what percent of pancreas cancer is associated with colonization with this particular bacteria? Is it 100%?
- Risch No. In fact, it is not that large because the causes of pancreatic cancer are somewhat diverse and I would say perhaps 25% at the most, 20% maybe are caused in association with Helicobacter, but do not forget in China it is prevented by Helicobacter, so it is the opposite, but is a large fraction, that is why in China pancreatic cancer is a relatively rare disease and gastric cancer is very common; whereas here in the west, it is the opposite.
- Gore And does the Helicobacter colonization interact with other risk factors for pancreas cancer besides the carcinogens that you were talking about?
- Risch It probably does, but we do not know how. We know now that ABO blood group is also associated with risk of pancreatic cancer just like it is for gastric cancer or stomach. But how it works, we have no real ideas yet, but it is essentially proven, there are now at least 20 studies that have looked at ABO blood group both on the basis of measuring people's blood group from their red blood cells and looking at the genetics of ABO and seeing how the variations in the genes make the ABO blood group, and both kinds of studies all show the same thing, that people with blood group A have increased risk of pancreatic cancer and people with blood groups B and AB have increased risk if they live in western countries and do not have increased risk if they live in China.
- Gore So should people like myself who are group A, be doing anything different to assess our risk for pancreas cancer?
- Risch It is not a big ticket item.
- Gore Lots of people I would say have blood group A.
- Risch Correct. Our best estimate now of increasing the risk of pancreatic cancer is about a 30% increased risk. Now, the lifelong risk in western countries of pancreatic cancer is about 1 in 60. So, 1.5% about. So, a 30% increased risk is still going to be under 2% lifetime risk. By the age 40 or 50 it is there, and you probably know some relatives or friends or connections of people who have had pancreatic cancer.
- Gore Sure.

12:36 into mp3 file <http://valecancercenter.org/podcasts/2015%20201%20YCC%20Answers%20-%20Dr%20Risch.mp3>

- Risch So, it is not rare, but on the other hand it is not that common. But the more important factors are things like cigarette smoking which is a major problem, it increases the risk of pancreatic cancer, chronic pancreatitis, and a few relatively rare familial genetic conditions.
- Gore So we know that cigarette smoking is kind of bad for everything, right?
- Risch For a lot of things, that is true.
- Gore Certainly in my field of leukemia, it is probably the best established leukemogen or cancer causing agent even though it is under-recognized in leukemias as relatively rare compared to some of these tumors that we were talking out. That is fascinating. How do you make these connections with patients, was the population screened for colonization with this bug? Did you have to do endoscopies, or serologic testing in the blood?
- Risch We use serologic testing. In our studies, we do case-control studies, we identify a representative sample of everybody with pancreatic cancer in a defined geographic area over a particular time period and interview them and get biological samples from them, blood if we can, and then for comparison purposes, we identify a random sample of the general population who are at risk of getting pancreatic cancer. Similar ages, gender, ethnicity and so on, and then we do the same, we interview them with questions about their medical history, occupational history and smoking history and things like that, and we get biological samples from the control people also. Then, we compare what is different between the cases and controls, and in particular for Helicobacter looking at serum or plasma assays to look at biochemical markers.
- Gore That is fascinating. Let's pick up on this and elaborate a little bit more so that I understand it better after the break. Right now, we are going to take a short break for a medical minute. Please stay tuned to learn more information about pancreatic cancer and eventually about aspirin and pancreatic cancer with Dr. Harvey Risch.

*Medical
Minute*

Genetic testing can be useful for people with certain types of cancer that seem to run in their families. Genetic counseling is a process that includes collecting a detailed personal and family history, risk assessment and a discussion of genetic testing options. Only about 5-10% of all cancers are inherited, and genetic testing is not recommended for everyone. Resources for genetic counseling and testing are available at federally designated comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven. The Yale Cancer Center cancer genetic counseling program is a new frontier in the fight against cancer. The program provides genetic counseling and testing to people at increased risk for hereditary cancer and helps them to make informed medical decisions based on their own personal risk assessment. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale New Haven. More information is available at yalecancercenter.org.

15:46 into mp3 file <http://yalecancercenter.org/podcasts/2015%200201%20YCC%20Answers%20-%20Dr%20Risch.mp3>

Gore Welcome back to Yale Cancer Center Answers. This is Dr. Steven Gore, and I am joined tonight by my guest, Harvey Risch, and he is educating me, and I hope you, about how epidemiologists study complex things like pancreas cancer. We have been talking in particular about the association between pancreas cancer and this bacterium. You were talking about case controlled studies where if I understand it correctly, you have got this group of patients who have pancreas cancer and you have got a control group who I guess are matched similarly?

Risch Yes.

Gore Who don't have pancreas cancer?

Risch They are matched on age, gender and ethnicity to some degree and so on.

Gore Then you do sort of a survey about what they have been exposed to and what they do habit-wise and stuff?

Risch Yes, that is correct. We develop questionnaires that are worked out to obtain as subjective information as we can on specific questions for a hypothesis that we create in order to try to get differences that we think are etiologic that are causal between the cases, what causes the cases to be cases.

Gore And you are drawing blood tests as well to look for examples of whether they have colonization with this bug?

Risch Yes, that is right.

Gore Then you are comparing the background or the associations in the people who develop pancreas cancer and try to find out what is different between them and the people who did not develop pancreas cancer, is that how it works?

Risch Correct.

Gore How many people are involved in such a study?

Risch In our Connecticut study we have about 400 cases and 700 controls and in our Shanghai study about 800 cases and 800 controls.

Gore That is a lot, but it is not like I was picturing, tens of thousands or something.

Risch We actually are getting to that point. Many disease groups, people interested in a particular disease like pancreatic cancer, have now formed consortia in which we participate so that we can pool either the questionnaire information or the biological samples or both to do genetic studies

18:00 into mp3 file <http://yalecancercenter.org/podcasts/2015%200201%20YCC%20Answers%20-%20Dr%20Risch.mp3>

and risk factor studies. And in our consortia now we have a number of different projects that have garnered perhaps 10,000 cases and 15 or 20,000 controls to try to get much subtler effects, but the flipside of all this big science is that if you need such large studies in order to elicit small associations, the associations are probably not that relevant. They are interesting and they can point in directions but they do not capture a large part of what the disease is really doing.

Gore You are looking for a bigger signal really?

Risch That's correct.

Gore And I guess with the bigger signal, if there was an intervention that could change that, you would have a bigger bang for your buck I guess.

Risch That is true, but big studies do allow us to look in subgroups of people, for example, older females who have had diabetes or something like that where we then would still need a large enough group to be able to have some statistical power to make our associations.

Gore Do your surveys ask things about family history and things like that?

Risch Yes, there is a long line of development of these kinds of epidemiologic questionnaires for cancer studies dating back to the 1960s and each one has evolved with both methods for eliciting the information well and objectively and minimizing the amount of time that these things take because they can take an hour or two even for some complicated questionnaires. We do look at family history, we look at occupational exposures, sometimes we look at dietary exposures, past diets and medical history things that are related to people's behaviors, what medications they have used in the past and that is how we got to the aspirin results.

Gore Tell us about that. I know that people have been eager tonight to find out about aspirin in pancreas cancer since we have advertised that, tell me about that.

Risch Aspirin has been examined as a factor involved in the risk of a number of different cancers, particularly colorectal cancer, and when we did our study starting in 2006 or so, our first pancreas study, we knew that there was literature about aspirin use and the risk of pancreatic cancer, but it was unclear. There were some studies that showed a little bit of reduction in risk and some that showed no association and one or two that showed increased risk. But, given that the marginal cost of adding another question or two to an already long questionnaire is very small, we added questions about aspirin and other anti-inflammatory medications to our questionnaire, and so we got information about aspirin usage. And then, when we analyzed this information, we were a little bit surprised that there was as big and as consistent an association with decreased risk of pancreatic cancer as we found in our study.

Gore So, people who take aspirin are at a decreased risk?

21:09 into mp3 file <http://yalecancercenter.org/podcasts/2015%200201%20YCC%20Answers%20-%20Dr%20Risch.mp3>

Risch That's correct. Now, there is a literature that is not entirely correct, as I said there are other studies besides ours that show decreased risk and there are some that show no associations and there are some that show increased risk. However, one of the things about aspirin usage today and studies that have acquired cases recently, is that there is a natural experiment in the population about aspirin usage and that is the usage of low-dose aspirin for preventing cardiovascular disease. So, people who have chosen to do that have elected to do that generally because they feel that they are at increased risk of cardiovascular disease and so they take a low-dose aspirin every day, which is not at the level of treating a condition that would otherwise use regular aspirin multiple times a day.

Gore You mean like rheumatoid arthritis?

Risch Rheumatoid arthritis, chronic pain, something like that. So, this has become a natural experiment that has occurred since the mid 1980s and now we have both the fact that a sizeable proportion of the population have been taking aspirin as well as the fact that pancreatic cancer has a latency from the time that the initial cancerous changes occur until it is diagnosed. And we know that that time is somewhere between 10 and 15 years. So, to do a study in the mid to late 2000s applies to behaviors that were occurring around 1990 or 1995. And that was in the era when aspirin usage was on the uptake for this low-dose aspirin usage, and so we were placed in our study at the relevant time to examine whether this association exists or not and that is what we found, that aspirin usage for more than a year or longer was associated with a 50% chance of cutting the risk in half.

Gore That's big.

Risch Yes, it's substantial.

Gore Can you be sure? It would seem to me that the people who were taking aspirin are people who think or their physicians think they are at higher risk for cardiovascular disease, so could this not be an association between a protective effect of cardiovascular disease or risk of cardiovascular disease and pancreas cancer?

Risch It seems unlikely. We do know from some recent work that we have been doing that aspirin usage, both low-dose and regular, decreases inflammatory cytokine levels in the blood. So we know that it is having a physiologic effect and it is in the direction we think it should be that it works as an anti-inflammatory agent and inflammation is hypothesized to be an instigating agent for changes of cells from normal to precancerous to cancerous kinds of changes because cells under inflammatory circumstances tend to multiply more frequently and each cell multiplication conveys a slightly increased risk of transformation to a cancer cell, and so the more that happens or the faster that happens, the more risk at a cellular level. And, eventually if that happens to a large degree, it

24:15 into mp3 file <http://yalecancercenter.org/podcasts/2015%200201%20YCC%20Answers%20-%20Dr%20Risch.mp3>

could transform the risk to some sizeable amount, whereas the aspirin prevents that by reducing inflammation. So, we think that is the mechanism involved.

- Gore Makes biological sense as well as kind of an empiric observation. I mean this sounds almost too good to be true, should everybody just be doubling down and getting themselves some aspirin and should everybody be taking aspirin, do you think?
- Risch Aspirin, for most people, is okay, but there are people who have negative side effects from it. Either from bleeding, strokes and so on, GI bleeding, that are serious risks, serious side effects, but for only a small minority of individuals. So one has to weigh ones own personal risk of the different conditions that you have to deal with. If you have a risk or a family history of increased risk of cardiovascular disease and you are taking aspirin in order to prevent cardiovascular disease, presumably because of its effects on clotting, reducing blood clotting, then the fact that you are taking aspirin is good for prevention of pancreatic cancer. But to take aspirin to prevent a disease that occurs in 1% in 60 whereas it increases risks of clotting-related disorders like strokes and intestinal bleeding, I would say the balance is not clear-cut. If somebody is at high risk of say colorectal cancer and is taking aspirin for that, then they are preventing pancreatic cancer. But, one has to evaluate in I think a really quantitative way what the real risks are that a person is facing and then evaluate how much risk and benefit adding aspirin to that regimen actually causes, how beneficial it would be under that circumstance.
- Gore Even though aspirin is over the counter and a 81 mg aspirin seems pretty innocuous like any other medical intervention people should really be discussing this kind of choice with their physicians or their healthcare professionals it would seem.
- Risch So on an individual basis, it is pretty innocuous, but we as epidemiologists see an entire population and so we know that in a population any particular individual is unlikely to be affected, but there will always be some people in the population who will have negative adverse events from taking aspirin. So we have to base our conclusions on a quantitative way of evaluating things and that is how we think people should optimize their own personal choices by looking at things quantitatively.
- Gore Haven't there been studies of aspirin in preventing I think it was colorectal cancer if I am not mistaken, and I don't really remember how those studies worked out, but I seem to remember they were kind of disappointing, am I remembering that incorrectly?
- Risch No, I think that aspirin usage is beneficial for reducing the development of polyps that are precancerous stages for colorectal cancer, and I am pretty sure that that is accepted now as a beneficial effect of aspirin. And I think that it applies to the low-dose baby aspirins that people take as well. How much it prevents colorectal cancer in a quantitative way, I don't know, but I am sure that it has a beneficial effect.

27:38 into mp3 file <http://valecancercenter.org/podcasts/2015%200201%20YCC%20Answers%20-%20Dr%20Risch.mp3>

- Gore This shows my living too much in the world of leukemia and liquid tumors and not keeping a pulse so much on other common solid tumors. So it is interesting and I believe they have also studied sort of the aspirin-like drugs like some of the so-called COX-2 inhibitors.
- Risch We also ask people about what are called NSAIDs, non-steroidal anti-inflammatory medications.
- Gore Like Advil.
- Risch Like Advil, right, naproxen and there is a whole spectrum of them. And what we found is no associations at all.
- Gore Really?
- Risch As opposed to aspirin. Now, there are two possible reasons for that. One is that they are involved in the biochemistry of clotting and the other effects of aspirin differently than an aspirin itself is. And the second is, there has been no natural experiment to take those medications like there has been for low-dose aspirin. So in the general population, people take those medications for indications for inflammatory problems that they are trying to prevent, just like regular dose aspirin, they are not taking it in a more casual way and in a much more widespread way like low-dose aspirin which is as I said the natural population experiment that we can tap into for our studies. So for both reasons, the NSAIDs do not seem to be involved in disease risk in the same way that aspirin itself is.
- Gore And we are going to have to have to wrap up here. In my understanding, perhaps that is because the people who are taking these non-steroidals already have a very inflammatory environment that is hard to suppress.
- Risch That is entirely possible.

Dr. Harvey Risch is Professor of Epidemiology and Chronic Diseases at Yale School of Medicine. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC and as an additional resource archived programs are available in both audio and written format at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another addition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.