

Support for Yale Cancer Answers comes from AstraZeneca, dedicated to advancing options and providing hope for people living with cancer. More information at astrazeneca-us.com. Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. I am Bruce Barber. 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 is a conversation about pancreatic cancer research with Dr. Harvey Risch. Dr. Risch is a Professor of Epidemiology and Chronic Diseases at the Yale School of Public Health and Dr. Gore is a Professor of Internal Medicine and Hematology at Yale School of Medicine and Director for Hematologic Malignancies at Smilow Cancer Hospital.

Gore Epidemiology is one of those words that people see in the newspaper and I think many people do not have a clue. What exactly is epidemiology?

Risch That's interesting because everybody out there in the science world thinks they understand it without knowing anything about it.

Gore I am going to claim ignorance.

Risch It is interesting that what makes epidemiology scientific is that we would like to study the entire population, the entire world of everybody and every disease, everybody with every disease, but obviously, that is impossible.

Gore That's a big chunk.

Risch So, what we do instead is we take samples of people from the population, we take samples of people with the diseases we are interested in and we try to conclude from studying samples of people that they represent what the disease actually does and how it works and how to fix it and so on, and how it applies to everybody in the population, and so what makes us scientific is how we can generalize from our restricted samples of people and samples of measurements to the whole population, and there is some very subtle science involved in that. The world thinks we just study people with disease and people without, and my colleagues, even my own doctoral students do not realize that that is what make it scientific until I actually start discussing with them why they think epidemiology is scientific.

Gore Sounds a little bit like polling where the polling people take samples and extrapolate from that or am I totally off base there?

Risch That is true except that the polls can change the next day and the polls know that they are obviously going to be wrong half the time as much as they are right, and they move 2:47 into mp3 file https://cdn1.medicine.yale.edu/cancer/2019-YCA-0113-Podcast-Risch_349501_5_v1.mp3on, whereas we put everything in the literature and our colleagues cite us and when we get it wrong, we are wrong forever. So, we have to be more careful.

Gore How does that actually translate in somebody who is interested particularly in pancreas cancer, is that what happened in your case, you were looking at pancreas cancer or did interesting things about pancreas cancer fall out of other things you were looking at?

Risch This happened quite by accident, my study in pancreatic cancer. About 2000 or 2001, I am an editor of the journal of the National Cancer Institute and a manuscript came my way to send out for review on the stomach bacterium *Helicobacter pylori*.

Gore That causes peptic ulcers, right?

Risch Yes, and why it should also cause pancreatic cancer. And I discovered pretty quickly that *Helicobacter pylori* does not colonize the pancreas, it stays in the stomach. Most people, many people have it, a third of the American population has it. It does

not do anything for them, it does not affect their health appreciably for most people who have it, and so how could an organism, a bacterium that sits in the stomach, affect risk of pancreatic cancer where it does not invade, does not live? After thinking about this for a while, I came up with hypothesis about how the stomach functions and indirectly how the pancreas responds to it. And I got 2 large studies funded to study this, one in Connecticut and one in Shanghai, and the hypothesis that I had proposed back in 2001 directly supported the hypothesis that I had made and that was kind of fun spending 7, 8 or 9 years doing studies and then when you get the data and 15 minutes later you know whether the result that you had proposed 7-10 years in the past actually is true or not. Gore That is a lot of deferred gratification in the meantime. Risch That's correct. We knew that aspirin was involved in effecting the climate of acidity in the stomach. Aspirin is not a totally benign medication, it has side effects in a small minority of people; the erosion of the lining of the stomach or intestines and causes bleeding there in addition to potentially in the brain, although it is not common. Gore Yeah, many people cannot tolerate it. Risch Right. So, we included the questions on aspirin use as part of the general questionnaire looking at *Helicobacter pylori* and pancreatic cancer, and the extra effort of putting in a few questions on something you are interested in into a questionnaire that you have already set up for a different purpose is very small, so we included questions on aspirin, 5:41 into mp3 file https://cdn1.medicine.yale.edu/cancer/2019-YCA-0113-Podcast-Risch_349501_5_v1.mp3 and what we found when we did this is that in both the Connecticut study and the Shanghai study, people who said they used aspirin regularly and now we are talking about low-dose aspirin, the kind that is not used because of pain or arthritis or something like that, but just to prevent cardiovascular disease or reduce its risks, also turned out to reduce the risk of pancreatic cancer by about a third. Gore Who were you polling, I mean what was the population that you were doing the study in? Risch One of the studies was done in Connecticut where over about a 4-year period, we interviewed everybody we could get to who had been diagnosed with pancreatic cancer and then we also took a sample of people from the population that we randomly chose from the population, we sent letters and then we called up and asked them if they would participate in the study. Gore And they didn't have pancreas cancer, those people presumably? Risch Presumably, we did not ask them whether they had pancreatic cancer, but because pancreatic cancer is uncommon, none of them as far as we knew at least at the time we interviewed them. And we did the same study in Shanghai starting 2 years or 3 years later because the *Helicobacter pylori* in Asia is slightly different than the varieties that are present in Connecticut and we wanted to get a handle on some variation in *Helicobacter pylori* to see if that affected how this theory about what it was doing with gastric acidity could be manifested. So, we had the same study there with the same questionnaire translated into Chinese and we also asked about aspirin. Aspirin there, low-dose aspirin for the same reasons was being used, it is a kind of natural population experiment in both countries that people are using it because of media messages and educational messages that they get thinking that it will be helpful for them, but it is otherwise not related to par-

ticular disease, and so people who choose to use are more or less similar to other people who choose not to use it. So, it is a great way of getting information about an exposure that should not be biased because its relationship to other things that would be more related to risk of pancreatic cancer than the aspirin use. So, it is a good measure of aspirin usage and we saw the same reduced risk both in Connecticut and in Shanghai. Gore And how did you know whether the patients in the control population had the Helicobacter or not, is that not something you could know from the study? Risch We took blood samples from everybody and we did testing of their plasma samples from their blood and so we know not only whether they had Helicobacter once in their lives and now had immunity to it, because it is tolerated by the immune system, that it 8:30 into mp3 file https://cdn1.medicine.yale.edu/cancer/2019-YCA-0113-Podcast-Risch_349501_5_v1.mp3 both generates an immune response that is measurable in the blood and it sits there in the stomach, kind of quietly doing its own thing and not affecting very much. Gore So, even in the normal controls you were able to get blood samples? Risch Yes, that's correct. Gore Interesting. And was there in fact a relationship between the Helicobacter exposure and incidence of pancreas cancer? Risch There is an association and that was my original hypothesis – Helicobacter pylori comes in 2 varieties, and one is a more aggressive version called CagA positive. CagA is a protein on the surface of the bacterium that helps the bacterium to invade the cells lining the stomach and those bacteria, that version of Helicobacter, reduces, shuts off stomach acid. Its cousin, the CagA negative, the bacteria that do not have that particular protein on the surface are less aggressive and do not do that and they allow stomach acids to be normal or even raised, and the hypothesis that we developed was that it was the effect of Helicobacter on gastric acid and stomach acid that the pancreas sees when the stomach acid gets into the duodenum after it leaves the stomach, the pancreas senses that indirectly through gastrointestinal hormones and turns on a hormone and produces bicarbonate that neutralizes the stomach acidity so that that acid does not harm the rest of the intestines. And so, the people who have extra acidity have to make more bicarbonates to neutralize it. People who have less acidity end up making less, and the pancreas is responsible for making this and the same machinery in the pancreas that makes the fluid that comes out of the pancreas and the bicarbonate that neutralizes the stomach acidity also affects how the cells of the pancreas reproduce, and so that mechanism allows the pancreas to feel a response so to speak to what the stomach is doing in terms of the acidity. And what we found is the Helicobacter that increases stomach acidity, increases the risk of pancreatic cancer and the Helicobacter that shuts off stomach acidity reduces the risk of pancreatic cancer. So, this was the mechanism we had proposed that it was actions on gastric acidity in the stomach that affected how the pancreas responded to it, and since Helicobacter came in 2 versions that did opposite things, the theory would predict that opposite risks would occur for pancreatic cancer and that is exactly what we saw and exactly what we saw in the 2 studies both in Connecticut and Shanghai. Gore That's fascinating. I am still trying to get my head around how this response in these cells in the pancreas in terms of trying to generate more bicarbonate is associated

with the cancer risks, so are there stem cells in the pancreas that are reproducing?11:41 into mp3 file https://cdn1.medicine.yale.edu/cancer/2019-YCA-0113-Podcast-Risch_349501_5_v1.mp3Risch The great majority of the pancreas, not all, but the great majority of the pancreas is comprised of ducts. The ducts carry the pancreatic enzymes and fluid that is made in the cells lining the ducts and bicarbonates made in the cells lining the ducts into the intestine to do their functions in the intestine. And the pancreas makes more than 2 L of fluid a day. It is quite a large amount of fluid. So, it is a very active organ for making fluid and bicarbonate. Now, it is correct to think that well, what's the matter with bicarbonate, it does not cause cancer and making fluid shouldn't cause cancer, but the interesting thing is from back in the 1980s, there were experiments in animals on risk of pancreatic cancer where they would give a carcinogen under the skin and some weeks or months later, these were done in hamsters, the hamsters would get cancer of their pancreas. And what they found is, if they gave those animals a pancreatic hormone that stimulated them to produce more fluid and bicarbonate, it tripled the number of pancreatic tumors for the same dose of the carcinogen. So, it is not that this mechanism of the stomach acidity is causing cancers, what it is doing is it is making the pancreas more sensitive to cancers that are being caused from other carcinogens like from smoking, things that get into the blood stream and reach the pancreas.Gore Now that you have learned this about the Helicobacter and the acid in the aspirin through the epidemiologic data that you have developed, has anybody actually modeled this particular thing in animals where you give the animals Helicobacter some equivalent?Risch That's an experiment I would love to do, but because I am not an animal scientist, I do not have the resources and so far I have not been able to convince anybody to do this study.Gore I was going to say there are a lot of good scientists at Yale, you should be able to find somebody who is interested I would think?Risch I would like to.Gore That's super-interesting. So, now, these data are all based on patients who had cancer, so I think after the break, I would like to hear what your thoughts are about how one validates or could validate that moving forward in people who do not have cancer, but before we can get started on that, which is a big question, I need to take a short break for a medical minute.Support of Yale Cancer Answers comes from AstraZeneca, a biopharmaceutical business that is pushing the boundaries of science to deliver new cancer medicines. More information at astrazeneca-us.com.14:15 into mp3 file https://cdn1.medicine.yale.edu/cancer/2019-YCA-0113-Podcast-Risch_349501_5_v1.mp3This is a medical minute about genetic testing, which can be useful for people with certain types of cancer that seem to run in their families. Patients that are considered at risk receive genetic counseling and testing so informed medical decisions can be based on their own personal risk assessment. Resources for genetic counseling and testing are available at federally designated comprehensive cancer centers. Interdisciplinary teams include geneticists, genetic counselors, physicians and nurses who work together to provide risks assessment and steps to prevent the development of cancer. More information is available at YaleCancerCenter.org. You are listening to Connecticut Public Radio.Gore Welcome back to Yale Cancer Answers. This is

Dr. Steven Gore, and I am joined tonight by my guest, Dr. Harvey Risch and we have been having a very interesting discussion about pancreas cancer and whether you can prevent it by taking a baby aspirin. I know that you did not actually imply that yet, but what I was starting to ask you about before I realized that we had to take a break was you seem to have this very strong association or causation that you have proven. Oftentimes we want to validate these kinds of observations in a population that does not yet have cancer. Moving forward, is that something that gets underway or that can be envisioned or is pancreas cancer so rare that you cannot really do a study where people take aspirin or don't take aspirin and have *Helicobacter* or don't? Risch Not to say that pancreatic cancer is rare, it might be infrequent, but if you say the disease is rare, then nobody cares about it, and unfortunately, it is a terrible disease and there are 40,000 plus Americans dying from it every year, as much as we might think of it as infrequent, by the time you turn 40 or so, you will have some family member or friend or acquaintance who will have died of it, so it is not that uncommon unfortunately. Gore Okay. So, is anybody studying sort of intervention in high-risk population or can we identify high-risk population? Risch This is a very pressing question. We know that people who have been diagnosed with adult-onset diabetes have about a 50% increased risk. That's if they have had it for a long time. On the other hand, a certain fraction of people with pancreatic cancer, their first manifestation is a new diagnosis of diabetes, the disease itself causes a kind of blanket function over the whole pancreas to reduce the ability to make insulin and for the insulin to function properly. So, they are diagnosed with diabetes, and within say 2 or 3 years, their pancreatic cancer becomes more manifest and they get that diagnosed. So, diabetes and pancreatic cancer goes both ways. If one is diagnosed with diabetes in their 50s or 60s, they have approximately a 6- to 8-fold risk of being diagnosed with pancreatic cancer in that year. That goes down to 3 the next year and 17:27 into mp3 file https://cdn1.medicine.yale.edu/cancer/2019-YCA-0113-Podcast-Risch_349501_5_v1.mp3 down to 1-1/2 or 2 the year after that and stays about 1-1/2 for the rest of their life. So, there is reciprocal relationship between diabetes and pancreatic cancer, and the first year of increased risk would suggest that newly diagnosed people with diabetes comprise a higher risk group that can be looked at to see if any of them are indeed carrying pancreatic cancers that haven't been diagnosed yet. The problem with that is that pancreatic cancer is an infrequent disease and requires a marker, say a blood marker for identifying it that is what we call specific, that means that it does not show positivity for people who don't have it. Well more than 99% of the time you find somebody with a positive marker, the great majority of them will actually be negative anyway because the disease is infrequent. So, we haven't got good markers yet and this is a very active area of study, people looking at markers for identifying people with pancreatic cancer. People with new-onset diabetes might comprise a higher risk group to study, but the risks even at 4-fold or 6-fold for the first year are still actually not high enough for the markers that we have available at present to be able to use them without generating lots of people who are falsely identified as having pancreatic cancer when they don't,

and that of course is a horrible thing to have happen to you, you think you have a fatal disease when in fact you don't, so we don't want to do that and that is what is limiting how far we can go with markers even at high-risk groups for now. Gore I know many people are studying the ability to detect cancer genes in the blood from DNA that is released from tumor cells. I don't know if any of that is being investigated in this context, I imagine probably some people are? Risch Yes, people are investigating every possible marker of every kind that you can measure from almost anywhere, especially from the blood. So, there is quite a wide repertoire of different kinds of genetic and hormonal and other markers that just get into the blood from tumors, from the immune system that are responding to the tumors, from the DNA and RNA that are reflective about things going on in the tumors or that are secreted by tumors for some other reason, everything that is out there that might reflect what possible tumors are going on is being studied. But of course, the problem is that biology is an approximate and inexact science and measurements are always not exact and there will always be errors in those measurements, and when you have the statistical problem of having an infrequent disease, if you have even a small amount of error, then you make too many false positives, too many people who are labeled as having the disease when they don't. Gore My mother unfortunately died of pancreas cancer at age 76 and her sister at an older age, so according to some definitions, I would be considered at a high risk based on family history and when I was at Johns Hopkins, there were people who were enrolling people in studies where people like me could be getting all sorts of screening with 21:07 into mp3 file https://cdn1.medicine.yale.edu/cancer/2019-YCA-0113-Podcast-Risch_349501_5_v1.mp3 ultrasounds done through an endoscope and stuff, and I never really felt strongly about it, so I never did anything about it, but I eventually did have my DNA screened for cancer susceptibility genes. Risch Are you speaking about BRCA-1 and BRCA-2? Gore Yeah. Well, what happened was, those I guess are common from what I have learned, but they actually went ahead and screened for a whole variety of things, any familial syndromes that might be associated with pancreatic cancer and I fortunately don't have any of them. Risch They are uncommon. Even among pancreatic cancer patients, they still account for less than 10% of cases of the disease. What is interesting is that there is almost double risk in Ashkenazi Jews. Gore So, I qualify for that. Risch So do I, and my grandfather died of pancreatic cancer although he was 94 at that time. We have a very active study on that going on now, a doctoral student of mine who finished her dissertation last summer, is working on a publication where we did a genome wide association study in Ashkenazi Jews in the United States and we were able to do this because there are large databases of studies that have pancreatic cancer cases in controls and from those, from the genetic data, we can identify who is Jewish and who is not; in fact, we can tell how many Jewish grandparents a person has from that. Gore Just like 23andMe? Risch Even better. I think that our precision is quite accurate about identifying Jewish ancestry by genetic means, and so when we restricted it to Jews, we indeed found 2 variants that are not commonly observed in non-Jews, and account for about 1-1/2 or 2-fold increased risk together and could explain why Jews who

should otherwise have lower risk in spite of a higher frequency of BRCA-1 and BRCA-2 mutations, that does not explain their increased risk. There are other factors like education and socioeconomic status that should actually explain a lower risk, not a higher risk, and so we think that these genetic changes that are common and not high risk particularly but are enough to explain the 2-fold risk.23:26 into mp3 file https://cdn1.medicine.yale.edu/cancer/2019-YCA-0113-Podcast-Risch_349501_5_v1.mp3Gore And those were changes in the BRCA genes or any different genes?Risch Different genes. Innocuous genes, we are still exploring.Gore How interesting. Maybe I should get myself re-screened, but that's fascinating. Baby aspirin is a pretty benign treatment for many people and as you well pointed out, many internists will recommend baby aspirin to people of a certain age with certain risk factors for cardiovascular disease, so for people who are kind of worried about pancreas cancer, and thinking about taking baby aspirin, what is your thought about that?Risch The problem again is, pancreatic cancer is infrequent. So, people knew for some reason that they really were at elevated risk, it might be indicated. But on the other hand, colorectal cancer is frequent enough and cardiovascular disease is frequent enough that perhaps half the population would have indication for taking baby aspirin anyway and they will get the side benefit for reducing risk of pancreatic cancer. The other half of the population has to weigh the pluses and minuses of taking aspirin against an outcome that would be horrible but infrequent. And so, it is hard to quantify something with big damage that does not occur very often. It is like what chances would you take of not getting hit by lightning, would you stay indoors the rest of your life, probably not. I wouldn't personally.Gore Right. What about screening for Helicobacter? Should people be screened for Helicobacter who don't have stomach symptoms?Risch I think this is a totally open question at the moment. Helicobacter does not make the risk very different. Gore It causes lymphoma also.Risch Yes and stomach cancer and ulcers, and the same diseases that Helicobacter affects, the ABO blood group affects. And what that connection is, it will be fascinating for somebody to discover. I would love to know what it is, but we have not been able to work that out.Gore Is it a particular one-of-the-blood types?Risch In western populations, the A, B and AB – the non-O blood types are associated with increased risk of pancreatic cancer. A is associated with increased risk of gastric cancer, and in Asian populations, it seems to be non-A blood types that are associated 26:00 into mp3 file https://cdn1.medicine.yale.edu/cancer/2019-YCA-0113-Podcast-Risch_349501_5_v1.mp3with pancreatic cancer. So, there is a little bit of variation from region to region and disease to disease, but ABO blood group is involved in all these things in the same way that Helicobacter pylori is, and just to add one little interesting detail to this, the ABO blood group is expressed on the surface of the stomach, lining of the stomach, and the little molecules where it is expressed are right next to the place where the Helicobacter pylori actually sticks to the stomach lining. So, the ABO blood group, the little molecule of it banks into the Helicobacter pylori where it is sitting there. And I do not think that is a coincidence. It is too much of a coincidence.Gore True. It makes sense, that's certainly interesting. It is easier to take aspirin

or antibiotics for *Helicobacter* than it is to change blood type, because that would require a stem cell transplant, I don't think we want anybody to have that. Risch No, I don't think it is indicated to worry about *Helicobacter pylori* unless one is symptomatic from it. There are people who are symptomatic, who have reflux and heartburn that is attributable to the *Helicobacter* that is worth dealing with. Gore Gotcha. What about other potentially causative exposures that people can do something about, I mean is tobacco associated for example with pancreas cancer? Risch Yes. Gore That is something people really can potentially control. Risch That is something that is a much bigger issue than just pancreatic cancer as we know. The cigarette smoking, manmade epidemic, is a horrendous aspect of our society that we are so inured to the damage caused by tobacco that we hardly even think about it anymore. We make our campuses smoke free and pat ourselves on the back but meanwhile the government is saving 100 billion dollars a year in social security payments that aren't being paid out to people who die 10 years earlier from their smoking. That is the real warning that should be on the sides of the cigarette packages, that you will die 10 years earlier and you will not collect your social security. Gore Cynical there, Dr. Risch? Risch Unfortunately, the money is much more important at the political level in what you can do with it to the benefit of your country than the lives of people who are viewed as choosing by their own free will to addict themselves or not. 28:23 into mp3 file https://cdn1.medicine.yale.edu/cancer/2019-YCA-0113-Podcast-Risch_349501_5_v1.mp3 Gore Actually it is fascinating because so many people look to nutritional supplements and the lifestyle things, which are well associated but not so easy to change including obesity, which is a problem that I struggle with and smoking which I do not, but many people do, and these are measurable causative factors people do potentially have control over and is such a societal problem. Risch I agree with you. I think it gets harder and harder as people get older to change these things and they are very difficult, whatever scientific methods we can find to ameliorate these behaviors is going to be very helpful in the long run. Dr. Harvey Risch is a Professor of Epidemiology and Chronic Diseases at the Yale School of Public Health. 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. I am Bruce Barber, reminding you to tune in each week to learn more about the fight against cancer here on Connecticut Public Radio.