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**The Role of Epidemiology in
Cancer**

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Yale Cancer Center Answers

is a weekly broadcast on

WNPR Connecticut Public Radio

Sunday Evenings at 6:00 PM

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Welcome to Yale Cancer Center Answers with doctors Francine Foss and Anees Chagpar. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1-888-234-4YCC. This week, Dr. Foss is joined by Harvey Risch. Dr. Risch is Professor of Epidemiology at the Yale School of Medicine and he joins Dr. Foss this evening for a conversation about epidemiologic research. Here is Francine Foss.

Foss Let's start off by having you give our audience some general information about the field of epidemiology and how it relates to cancer?

Risch Epidemiology, in defining what it is about, at the risk of annoying my colleagues, epidemiology as a science is the use of representative samples of individuals to study a disease. For example, when we sample people with diseases, we call them cases, and people who are normal individuals from the general population that we use for comparison purposes we would call controls. The importance of that is that those individuals represent everybody, either with the disease or everybody in the general population who would be at risk to get the disease. Once we know that our sample of people is representative, then the rest of the study is any kind of basic science, so we do genetic analysis, we do laboratory tests, we ask people questions about their histories, about their backgrounds, and so on. We do more or less the same kinds of studies that are done in clinical circumstances, except that we do it based on sampling from populations.

Foss Can you tell us how large a population you study when you study epidemiology?

Risch Our studies can be anywhere from a few dozen cases and controls, up to thousands or tens of thousands of individuals. Because we study associations with disease factors that are not so strong that it would be obvious if somebody has them, that they were going to get the disease, then we need a large number of individuals in order to have enough what we call statistical power in order to be able to see a real association. And in order to do that, we typically get 500 or 1000 cases in our study and an equal number of population controls and then after we do our studies for the main things that we are interested in, we typically now-a-days have consortiums which are groups of investigators at different universities across the United States and across the world where we pool our data together and study the same questions, but across everyone, and so we can easily end up with 20,000 or 30,000 subjects in a study that way.

Foss This is a good example in science of how people are getting together to share their data. Is that the way things are moving now in most areas of cancer as well?

Risch Yes, this has become a very popular and very powerful method for observing and deriving associations with cancer.

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- Foss Let's back track a little bit and have you tell us a little bit about yourself and how you got interested in this area of epidemiology. It does not seem like the most common area in the cancer arena, we have had a few epidemiologists on the program, but why did you get interested in this area?
- Risch When I was in medical school at the University of California in San Diego, we had a thesis requirement. It is one of two schools, the other being Yale, which has a thesis requirement for medical training and it really turned me on to medical research. So much so that after medical school I went and pursued a PhD in mathematical epidemiology and a post-doctoral fellowship that was in cancer epidemiology and after that I started doing research on mathematical kinds of questions in epidemiology, but over a few decades of work, I have come to realize that the biological questions are both more interesting and harder, and that is really what I have been trying to deal with, more basic biology and medical questions in epidemiology and cancer epidemiology.
- Foss Can you tell us a little bit about what some of those medical and scientific questions are that you are investigating?
- Risch There are two cancer sites that really intrigue me. I have had the luxury of being able to do scientific research that gives me pleasure and at the same time it has a social benefit because of what we are able to find and how we are able to help people, and in general to prevent them from getting cancer, but those cancer sites are ovarian cancer and pancreatic cancer. For ovarian cancer, which is of the sites that I started with when I started my career, we know that there are two major risk factors for the disease and both of them prevent ovarian cancer. One of them is having pregnancies and the other is using the birth control pill, what we call oral contraceptives. Both of them are protective. They seem to be protective in almost every study that has examined them and we do not quite know why, but because the finding is so consistent across every study, we know that there has to be some biological mechanism going on and it is an exciting thing to try to understand, but at the same time it is frustrating not being able to come up with the definitive answer yet, but we have a number of theories related to how those factors might be working.
- Foss Basically what you are saying when you say protective effect that does not mean that you won't get ovarian cancer. It just means that you have a lower chance of developing ovarian cancer.
- Risch Yes, they reduce the risk of developing ovarian cancer and it is not just a subtle amount. Having had two or three children, full term pregnancies, or live children, can reduce the risk perhaps 50%, or half, and the same with five to seven years of usage of oral contraceptives. Oral contraceptive use can cut the risk of developing ovarian cancer in half. So those are sizable amounts of prevention.

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Foss Can you talk about some of the pitfalls with that kind of analysis and how we apply that say to the individual patient? That is obviously over a wide population with other variables, so how do you put that in context for the individual patient?

Risch I think for ovarian cancer it is difficult because people make their choices about their reproductive behaviors not thinking about what kinds of cancer they might be liable for later in life. Their family planning is based on their desires for a family, children, or not having children and whether they want to make further choices related to risk is a very small component of that calculation. There are other considerations with regard to using a medication like oral contraceptive, birth control pills, because ovarian cancer is a relatively rare cancer. By the time most people are over age 40 they know or knew somebody who has had ovarian cancer in their family, friends or acquaintances. Nevertheless, it is a relatively uncommon cancer and is not something that most people plan their life around and therefore the considerations of about what other things those medications do, and what the risks are, have to take priority. For example, if they increase the risk of breast cancer, which they may, breast cancer is much more common than ovarian cancer and so one has to take that factor into consideration as well as heart disease and other diseases which are more common, but not as strongly affected.

Foss So, once you identify the risk factors the next step would be to have the clinicians figure out how to implement that in some preventive strategy?

Risch I think as part of an overall preventive strategy that would be fine. It is just that these are intellectually challenging because if we can figure out how they work, we can try to get into the mechanisms and somehow interrupt the mechanisms through some other processes. Their keys to understanding the mechanism if we can do that, but they themselves are not necessarily factors that we would use for controlling these mechanisms.

Foss Can you talk a little bit about pancreatic cancer now, is there a similar paradigm in that you have identified risk factors there?

Risch Pancreatic cancer is probably easier to prevent. It has about the same life time risks as ovarian cancer. It is about one and a half percent lifetime risk and it is related to a number of risk factors, for example, smoking, obesity, and diabetes are risk factors. Non-ABO blood group is a risk factor and Helicobacter pylori colonization which is a bacterium that colonizes the stomach is also a somewhat complicated risk factor, but a risk factor as well. These are things that largely we can modify. So therefore, there is a chance that we can do something about lowering the risk of pancreatic cancer.

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- Foss The only intervention I heard is looking for the H. pylori. I guess the others are really more lifestyle interventions.
- Risch Yes, Helicobacter pylori is a current topic of vigorous research. Helicobacter itself comes in two major varieties, the more virulent aggressive strain of Helicobacter, which is the most common form in Asian populations, in China, Japan, and Korea and so on, and in the United States and western countries a less virulent form that is about 50-50 spread, in other words about equal to the more virulent form, and these two kinds of the same organism do opposite things in colonizing the stomach. They both increase risks of gastric cancer and stomach ulcers to a small degree, but we now understand that the more virulent form of Helicobacter pylori reduces the risks of pancreatic cancer and reduces the risk of esophageal cancer whereas a less virulent form does not do that and so depending upon which kind you are carrying, you may have a higher or lower risk of the disease and one has to think about the possible eradication of the organism as a way of preventing pancreatic cancer, esophageal cancer or gastric cancer.
- Foss Is this something that we should be screening for at this point?
- Risch It is a good question. In Asia, it is a major-major plan now in the last 20 years, especially in Japan. They have been screening for Helicobacter and eradication, but they are much more aggressive there. They do endoscopy which is looking at the stomach directly in order to screen for gastric cancer in its earlier state when it could be surgically removed to preserve the life of the individual. Helicobacter pylori can be tested using blood tests and it is much easier to find. Nevertheless, there is a certain reluctance to do that because people are concerned, some people believe that the removal of Helicobacter from colonization increases risks of heartburn and that is controversial. There are studies that show that is true and there are a number of studies that show that it is not true. There is no increased risk of heartburn. So, it is not clear, and in fact, I have had scientists come to me and discuss with me that they have carried Helicobacter and did not really want to have it removed, did not want to treat it because they were afraid of getting heartburn in spite of the evidence now in the scientific literature that people who carry Helicobacter should probably have it treated unless it is the lesser virulent kind in which case they could wait and have screening done in another fashion at a later date.
- Foss If you look at all patients that are carrying Helicobacter, what percentage of those patients develops pancreatic cancer?
- Risch Approximately, 2% to 2.5% over the lifetime.
- Foss So it is still a low enough number that you would not necessarily want to screen the whole population.

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Risch No, and in fact screening for pancreatic cancer or ovarian cancer in the general population is a very difficult problem and the difficulty is because their lifetime risks are so low and the error in screening, screening is not perfect, and because of that if you have a factor that you can screen and with 99% accuracy can tell whether the person carries that factor or not, the error in that will be larger than the number of individuals you predict who will get ovarian cancer or pancreatic cancer who turned out not to. So what that means is that by doing the screening test, you will be doing more aggressive testing in people, the majority of whom turn out not to have the disease and because of that those people are put through the trauma of the testing, the psychological trauma, thinking that they are likely to be a carrier of the disease when in fact they don't because of the error in the screening test. Even a screening test that looks good with 99% accuracy, is still not good enough for rare diseases like ovarian or pancreatic cancer.

Foss We have to stop and take a break for a medical minute at this point, but please stay tuned to learn more information about epidemiologic research with Dr. Harvey Risch.

*Medical
Minute*

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

Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined tonight by my guest, Dr. Harvey Risch. We are here discussing epidemiologic research in cancer. We talked a little bit prior to the break about the effects of some of the epidemiologic studies that you have done on certain cancers such as ovarian cancer and pancreatic cancer and I wonder if you could just tell us in general, is that a paradigm that is applied to other cancers as well? Can you give us other examples of how epidemiology has really helped us to learn about the etiology of other kinds of cancers?

Risch I think epidemiology, without necessarily using that term, goes back quite a long way. We know about, for example, the utility of pregnancies in reducing the risk of ovarian cancer from realizations starting in the 1920s that countries where women who had larger families had lower

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average rates of ovarian cancer, and over the succeeding decades, as average family sizes went down, the rates of ovarian cancer went up. So that was a very crude kind of epidemiology to look at pregnancies and risks of ovarian cancer. Perhaps the best scientific study epidemiology-wise was carried out in the late 1940s on the British doctorate study looking at smoking, tobacco smoking, and risk of lung cancer, and that study very clearly showed, and provided the first evidence of the harm that cigarette smoking did in causing lung cancer. Those were definitive studies, a kind of smoking gun, no pun intended, but the point is that those studies had very obvious risks factors to evaluate for the association and the associations of interest for the disease we are interested in and so early on epidemiology studies used simple questionnaires with ideas that clinicians typically had about their patients led to good ideas about risk factors that panned out into larger scale organized epidemiologic studies. That is the paradigm for epidemiologic studies, using as I have said before, representative samples, people with disease and normal people in the population to study associations, factors of those people, their backgrounds, their genetic history, the family history, and their other laboratory measurements, their diets and other behaviors, in association with risk of getting the disease, the cancer that we are studying.

Foss Can you talk a little bit more about some other molecular tests that are being done? You were talking a lot about questionnaires and surveys, but we have gone to the next level now where we are actually studying the genomics and individualized therapies, so to speak. Can you talk about how you are actually doing that in the context of the epidemiologic studies?

Risch We have used genetic testing to study disease for decades and decades. What has become new in the last 10 or 15 years is the organized way of studying genetic heritability in a major scale. We now have the technology not to study 1 or 2, or a handful of genetic alterations, but all possible genetic alterations that occur across the genome and the technology has led to using 500,000, a million, 2 million or more genetic places to look for genetic alterations in the DNA. And then the question is, what do you do when you find changes, because we do not know whether those changes are innocent or whether they are associated with disease, with causation of disease and because we typically do such large scale studies with thousands of individuals, we are able to find alterations and risks that are very, very small, in the order of 10% or 20% changes in risk associated with the particular genetic alteration and then we have to look for meaning. The search is not a technological one, but one of interpretation of trying to understand whether the changes that we see are true precursors, real risk factors for the cancer, or just happened by chance. And because we are looking at such a large number we can tell the chance ones from real ones and we have a lot of advanced statistical technology to help with that and nevertheless nature is really what controls the underlying ability to do this and sometimes we are lucky and sometimes we are not.

Foss Basically what you are saying is that if you ran 100,000 genes and you found a certain number of mutations you wouldn't necessarily be able to associate those with the disease itself.

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- Risch That is correct. We do not know and we have to do additional studies where we go and interview and collect blood samples and test DNA from another thousand subjects and a thousand controls and see if the changes we see in them mirror the changes that we saw in the initial group to validate the initial findings. And after doing that 2 or 3 times, if we actually come up with a set of small numbers of genetic changes, then we go and do laboratory experiments to show that those changes actually have some functional relationship to some biochemistry or pathology process in people that causes something about the way their biochemical machinery changes and if we know that then we have the evidence that those changes are related to the causation of the particular cancer.
- Foss It must cost a lot of money to do this, these extensive genetic analyses, and I am wondering, as money becomes tighter in the whole health care arena, if it is really worth it to do this and do you feel that we gain enough information this way in order to justify continuing to do these large genomics screening projects?
- Risch The potential is enormous, if we can find genetic changes that are involved in biochemical mechanisms and those mechanisms are indeed related to some process that leads to the transformation of the normal cell into a cancer cell, then it is worth it in the long run because it allows us knowledge of the basic machinery of cancer and how to distinguish that from the normal way that the body works. So, you cannot say is any amount of money worth it, but the amount of money we've spent so far probably is worth it. We have learned a huge amount and not just in cancer, we have learned about genes that are associated with diabetes, genes that are associated with height, genes that are associated with obesity and many other conditions, so it is not just cancer that is associated with genetic changes. Now what we have to do is we have to systematically go through those genetic changes and put the pieces of the biochemical machinery puzzle together to get an idea of what the real processes are and to link one kind of change to another kind of change and see what we can derive as far as the biochemistry is concerned.
- Foss There has been a lot of talk about shifting more funding toward the prevention of cancer and I think that's what the NCI has been doing for the last 9 or 10 years. Can you predict, with this new sequester that is about to hit, how that is going to impact the kind of research that you are doing and the field of epidemiology and cancer prevention?
- Risch I think there are two issues that you raised. The first is the support for active prevention activities. Honestly, I feel that there is a fair amount of hubris today in patients, we have been fighting the war on cancer since the 1970s and how far have we gotten in some respects we have learned a lot, and in others we are still struggling. Nevertheless, we want to translate as much as we can into active prevention effects. While we know what the major causes of cancer are, cigarette smoking

being the major one, diabetes and obesity as well, there are some rare occupational causes and some rare genetic causes, but by in large the big ticket item is tobacco smoking. However, the

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factors underlying why there is still tobacco smoking in our society are not scientific and they are not medical and society as a whole has to decide it wants to address that and putting money into programs to study prevention is not going to address enough for the amount of money that is spent because we don't know the basic biology well enough yet. We have tried, for example, with the beta-carotene supplementation trials with smokers and various other studies, clinical trials, to see if what we have learned in observational epidemiologic studies, pan out when we actually try to use them clinically and sometimes those trials have worked and sometimes they have not. On average, we have not gotten a lot of good mileage out of the prevention trials that we wished we could have. That's because we usually don't know other factors that are related and we tried to use beta-carotene because that was one of the studies that showed beneficial effects of fruits and vegetables that are high in carotenes, but the supplements of the carotene is not the same as eating fruits and vegetables and does not have all the same other ingredients and therefore we don't quite know what we are doing when we do a prevention trial and it is not necessarily the same, and if it works that is great but if it does not work, we do not know why it did not work necessarily. So many prevention efforts in scientific terms may be premature at the moment but putting money into them now, in the face of the sequester budget and what it has been doing to funding of the biomedical research and the individuals who carry out that research I think it could be somewhat destructive. I think it has been a very stressful time for everybody including medical scientists and what we face right now is that the great majority of major medical studies are funded by the NIH. These are studies that are sufficiently large and sufficiently expensive so it would be difficult to fund them through other avenues, through private funders, foundation funders and so on, and the pay lines, meaning the percentiles of quality that these studies are ranked when they are proposed through review by NIH scientist in review, the pay lines have been getting smaller and smaller to the point now where very meritorious studies that have a very good chance of finding out very beneficial results are not getting funded because there is too much competition and the competition extends to the fact and it is not just studies that are not getting funded, but investigators are not getting funded and what we have now are senior investigators who are not able to get their major grants funded and who will not be continuing or likely beginning to drop out of doing the scientific research and removing a whole class of major expertise. At the same time training grants have been cut back and other support, federal support, for cancer research is declining and it has caused the best and the brightest of undergraduate students not to think about going into medical research and I think that is a big problem for us.

Foss Given the state of affairs, do you think that we need to start pushing for money from the private sector to do these kinds of projects?

Risch I think that the private sector has more focused interests in achieving certain definable aims rather than a more open approach to science the way governmental funding has supported science, that

we do science as an abstract kind of activity and the most interesting findings are the ones that get applied but when you do science in a technologically or financially driven way you may not end up with the quality of the science that ultimately you would get if you just let people think most creatively.

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Dr. Harvey Risch is Professor of Epidemiology at Yale School of Medicine. If you have questions or comments, we invite you to visit yalecancercenter.org where you can also get the podcast and find written transcripts of previously broadcast episodes. You are listening to the WNPR Connecticut Public Media Source for news and ideas.