Yale CANCER CENTER answers

WNPR Connecticut Public Radio

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What's New in Cancer Epidemiology?

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Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss and Anees Chagpar. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at the Yale Cancer Center and she is an internationally recognized clinician and clinical researcher. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven. Yale Cancer Center Answers features weekly conversations about the most recent advances in 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 cancer epidemiology with Dr. Yawei Zhang. Dr. Zhang is Associate Professor of Epidemiology in Environmental Health at the Yale School of Public Health. Here is Dr. Anees Chagpar.

Chagpar Yawei, let's start off by talking about what exactly cancer epidemiology is? What is it that you do?

Zhang In general, epidemiology is a kind of scientific study of the distribution and determinants of the disease in the human population and cancer epidemiology actually is pretty new in the epidemiology field, before we may have focused on the infectious disease and starting from the mid 20th century, a lot of epidemiology study was shifting to cancer. We would need to identify what the risk factors are that cause increased incidence of cancer. So that is how we start. I think the biggest breakthrough study of cancer epidemiology is we identified the modifiable risk factor of tobacco smoking and lung cancer.

Chagpar That is interesting, because I think a lot of people do not really know exactly how we figure that out. How we figure out what the risks of cancer are, and all of us love to read the newspaper or journals or whatever and figure out, why do people get cancer? What can they do about it? Could they have prevented it? So what you are telling us is that this is essentially what an epidemiologist does? How do you uncover that? What are the modifiable or even non-modifiable risk factors for cancer?

Zhang Those are the principles of all epidemiology study design. In general, we are recruiting people from a certain population to identify people who have disease and the people without disease, but they all come from the same population, and then we can compare their lifestyle and their environmental exposures and currently, using the new technology to figure out their genetic susceptibility, and using very sophisticated statistical tools to figure out whether those exposures are associated with the disease and then we can confirm this association from the different population and different studies and then finally make this connection between the environmental exposures and the disease outcome.

Chagpar Is that how they figured out that lung cancer was caused by tobacco smoke? They took a bunch of lung cancer people and a bunch of non-lung cancer people and said, the lung cancer people smoke more?

Zhang Yes, that is sort of right, generally we have a lot of different study designs, for example, we identify lung cancer patients and non-lung cancer, healthy control people, and then we can ask

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them their past lifestyle factors, their exposure information and then we can compare whether the diseased people are more smokers compared to the non-diseased people. That is how we find this association. On the other hand, we could use a prospective follow-up study like a cohort study. We can identify people who are smokers and nonsmokers and we follow those two groups and then we can identify, in the smoker group of people they have more lung cancer cases compared to the nonsmoker group of people and that is how we compare them and then we find out this connection.

Chagpar It seems to me that doing it the first way, taking lung cancer people and non-lung cancer people and saying which group smokes more, would give you a more immediate answer?

Zhang Exactly.

Chagpar Because otherwise it would take forever to figure out that doing x causes y.

Zhang You are totally right. The first way is what we generally call a case control study, so we identify a case and then we compare their exposure and then we find this association, but one drawback of this case control study is the people that come to the study already have the disease and if they believe smoking is associated with their cancer they might over report their exposure. They have what we call a bias or maybe they already have the disease, but we do not know when the disease started. There was a long latency period before they are diagnosed. They already have had the disease for many years, and maybe they have those symptoms and they stopped smoking. They do not feel comfortable smoking and then they stop, and after we identify the case and when they recall their exposure, there could be possible what we call inverse association. Maybe this is not exposure cause of disease, so the disease causes the exposure. This is kind of like inverse association. This way, even though we can identify this association, we cannot really address those causal relationships. But on the other hand, if we identify people who were exposed and not exposed and at the beginning none of them have disease and then we follow up and then they got the disease, we could address they had the exposure and then they got the disease, that is a causal relationship. That is why all epidemiology studies, if we study the rare diseases like you said, the disease is pretty rare, if we follow people, when they get disease, we have to have a huge population base and follow-up for a long-time period and then we can get enough cases and that way takes much longer and a lot of resources, but for the case control study which is shorter and more cost effective, we can quickly establish this association but then we could use other study designs to really confirm the association.

Chagpar Even if you have a disease that is common, lung cancer is really common, breast cancer is really common, even then it seems me to that if you were going to follow people forward, which it make senses that that would be a more robust way to look for a causal link, you have x exposure, do you get the disease or not. The issue that I would see there is number one, you would already have to have an idea of what the exposure is going to be and so you may guess wrong, and the second is

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you would still need a lot of people followed for a long time because of this latency period you were talking about. How do we get around those things, are those issues for epidemiologists?

Zhang Yeah, that is a big challenge when we do epidemiology studies, and that is why at the beginning many studies, you can say most of the associates came from the case control study. It is a lot easier and quicker, but recently you probably saw a lot of results came from cohort studies. There are a lot of different study populations and study groups, they establish this cohort and they are recruiting people, they are either general people like a Harvard nurses' health study and also in the Shanghai Women's Cohort Study and the famous Framingham Heart Disease cohort and also there are a couple other occupational cohorts from the National Cancer Institute and all those cohorts were established 20 years ago, some 10 years ago. Right now, it has already been 20 and some of them even 50 years. They already accumulated a lot of cases, which give us opportunity to really look at those causal relationships in a cohort study design. So that is how the epidemiologist do the study and actually right now we consider the cohort studies more robust but we need more resources to do that, but we can use those already established, especially the longer follow-up time, the cohort is more valuable.

Chagpar So it is a good thing that the epidemiologies 10, 20, 30 years ago established these cohorts. Let me ask you this, for many of these cohort studies they ask a whole bunch of questions and in part I think it may have been related to the fact that you kind of have to guess what your exposures are going to be in order to see whether or not your exposure results in your outcome, but aren't there cases where two exposures may be linked, so for example, we often talk about people who smoke and drink, or people who smoke, drink and gamble, how do you know that it is the smoking that causes lung cancer and not the other things?

Zhang You are totally right. When we establish the study population we try to ask as much information as possible. So you never know which one really caused the disease and maybe you have a prior hypothesis but sometimes the hypothesis is not really true, probably it is the wrong hypothesis after your study. So, when we design a study we generally ask a lot a lot of questions. In general, our questionnaire is like 20-30 pages. It takes about an hour to really answer all the questions, but afterwards, for the epidemiology study, I think the beauty is that we have such sophisticated statistical tools, so we can really control those confounding factors like what you said, people smoking may also be drinking and then if you are looking at smoking associated disease and control the drinking factor, you might find the association is confounded by drinking. So, that is why our model already contained a multivariable model. So we put a lot of potential confounding variables into the model to control those factors and then we can find those independent risk factors.

Chagpar That is using fancy statistics to take out the fact that you could smoke and drink, but looking at just smokers, controlling for whether or not they drink.

Zhang Yes.

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Chagpar What about all of the factors that you might not have asked about in that 20 or 30-page questionnaire? What if it is actually not smoking, what if it is carrying a lighter in your pocket and you never asked whether they carried a lighter in their pocket or a box of matches, you asked whether or not they smoke, and you find that smoking is related to the cancer, but what if that is not the answer, what if it is something that was not in your questionnaire, how do you get around that?

Zhang Many times, after the study is finished we have some regrets, "Oh I forgot to ask this one or I forgot to ask that one" and that happens, but I think during the past 20 years we have already accumulated a lot of experience and right now most of the studies try to ask all the possible potential risk factors related to the disease. For example, for the environmental factors, if we are looking at one environmental factor, sometimes we are talking about a confounding factor. There are also some effective modifications we caught, maybe under these circumstances the disease associations is like this, but for example, for overweight people the disease exposure association could be significant, but for the lean people, it may not be. So this BMI could be effective modification for the exposure and disease association. So, that is another epidemiology study we have been looking for, and also the genetic susceptibility as well. That is why in the current study we are also collecting those samples, for example a urine sample, a blood sample were stored there. In the future if we have some new idea we could measure those as a biomarker in the serum samples to discover those factors we never thought about before and when we are talking about the confounding factors, sometimes the factors must be related to both the exposure and disease and if they do not relate to both, they are not a confounded study looking at certain exposure and disease association.

Chagpar We are going to pick up on that conversation about how epidemiology is also linked to some of the biomarker research that has been going on, but first we have to take a short break for a medical minute. Please stay tuned to learn more information about cancer epidemiology with our guest Dr. Yawei Zhang.

Medical Minute *The American Cancer Society estimates that in 2014 over 1500 people will be diagnosed with colorectal cancer in Connecticut and nearly 150,000, nationwide. When detected early colorectal cancer is easily treated and highly curable and as a result it is recommended that men and women over the age of 50 have regular colonoscopies to screen for the disease. The patients with colorectal cancer have more hope than ever before due to increased access to advanced therapies and specialized care. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale and at Smilow Cancer Hospital to test innovative new treatment for colorectal cancer. Tumor gene analysis has helped improve management of the disease by identifying the patients most likely to benefit from chemotherapy and newer targeted agents resulting in more patient specific treatments. This has been a medical*

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Chagpar Welcome back to Yale Cancer Center Answers, this is Dr. Anees Chagpar and I am joined today by my guest Dr. Zhang. We are talking about cancer epidemiology, and essentially the whole field of science, which tries to figure out what causes cancer, which is the most popular question that I get asked every day in the clinic. Yawei, before the break, you were talking a little bit about looking at all of these factors and we talked about cohort studies, which follow people and case control studies where you take people who have the disease and people who do not have the disease and look backwards to see whether or not they had an exposure, and we were talking about the fact that you can never completely guess exactly right. You can try hard to guess what the exposure might be that gives you the outcome, but often, as you said, you have regrets and you started to tell us a little about grounding some of these hypothesis that you have as a cancer epidemiologist from studies that have been done and kind of linking with biomarker studies. Tell us more about that.

Zhang For the biomarker studies, actually right now it is very popular and I think it is also a major breakthrough for this area of research. As you know, the biomarker could be a biomarker for exposure, and also it could be the disease outcome, particularly for certain exposures such as a chemical exposure. When you ask people whether they are exposed to certain chemicals nobody would know, right? You cannot remember what chemicals you have been exposed to, you can tell what you eat every day and what I do for my work, but I cannot tell you what kind of chemicals I have been exposed to. With chemicals you never know, they could exist everywhere. For example, one of my studies is looking at flame retardants exposure in relation to thyroid cancer and flame retardants we know exist almost everywhere. All the construction materials and also furniture has to contain those types of chemicals and they could be released into the air and even contaminate food and every day you are exposed to those, but you never know how much you are exposed to. So, we have to rely on those biomarkers to measure from serum samples. You have to rely on those biomarkers and also certain chemicals after they enter into the body they could metabolize, which probably would be more harmful compared to their original form. That is one type of the biomarkers and also we do some early detection and I try to identify high risk populations, so we could identify those people that might benefit more from the cancer prevention program. For example, for thyroid cancers radiation, ionizing radiation exposure, is a risk factor, but not every single person exposed to ionizing radiation will get a thyroid cancer. So that is the genetic susceptibility, maybe some people are more susceptible to radiation exposure than others. So if we could identify those genetic biomarkers we could then distinguish between people, the high risk population and non-high risk population. So for this group of people, we try to give them the least amount of radiation exposure as possible. For another group you could do routine, whatever you could do. So that is kind of how currently what we wanted to do, try to distinguish people, which group is high risk and another group is not high risk population.

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Chagpar I want to get back to the flame retardants. It seems really interesting that flame retardants may actually be associated with thyroid cancer, but as you were telling us about flame retardants, if they are ubiquitous, they have to be on everything, then would not everybody have the same exposure and in that case how would you be able to tell different populations?

Zhang For things like flame retardants exposure, they started to use this chemical in the late 1960s and until recently I would see, starting about 15 years ago, the usage of those types of chemicals increased dramatically and all those materials, you do not know how you are exposed, mainly through ingestion or through breathing, and right now they have the measurement for the CDC, they have a lab from this cancer study, a national nutritional study looking at the general population, their body burden levels of the PPDs, actually they found that kids have the higher levels compared to the adults and also there is a huge variation between the individuals. It is not that all that are sitting there will be exposed to it, some people like to touch things and put them into their mouths but certainly people do not like those things and every time they wash their hands they are exposed less. All those behaviors will associate with your exposure but you never know through a questionnaire, you can measure through the blood samples.

Chagpar How did you come up with this idea that flame retardants may actually be associated with thyroid cancer? I do not know that any of us would come up with that idea?

Zhang There are some animal studies that have shown flame retardants could alter thyroid hormone levels and cause thyroid dysfunction. Because of this strong evidence the European Union already has banned those types of chemicals in Europe, but in the United States, in certain states, they are just starting to ban those chemicals and manufacturers right now are voluntarily stopping the production of those types of chemicals, but because of the lack of direct human evidence to show there is a link between the flame retardants and thyroid cancer, that is one of the major research projects I am currently working on. Actually we tried using the DoD serum repository samples. We all know the DoD serum repository has a lot of serum samples from people. Actually they have multiple samples before they have the disease being diagnosed. When you enter the military they have to do HIV testing every two years, and the left over serum is stored in their serum repository, and could be used for future research purposes and identify the more than thousand thyroid cancer cases in this DoD serum repository, so we could use their serum samples before their disease diagnosis, the serum samples, and then measuring those PPD levels and then we can look at their matched controls, whether their PPD level is different from those two groups. So the study started two years ago, fortunately we just got the serum samples shipped back to Yale. So hopefully, during the next two years we will have some exciting results to report.

Chagpar I was hoping that you were going to break news right here on Yale Cancer Center Answers, but one of the other things that I think is interesting and I certainly think that this is going to be incredibly fascinating, is you mentioned that when they looked at flame retardant exposure and these PPDs, it is highest in young kids, but young kids are not the people who necessarily get thyroid cancer, are they?

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Zhang I mentioned that kids are exposed more compared to the adults, but that does not mean kids will get a thyroid cancer. Also, since PPD could alter thyroid hormones it might be related to some kids development, that is another issues a non-cancer risk for the kids, actually right now, currently some studies have shown positive association between PPD levels and IQ for the kids. So that is another total different research area, but for thyroid cancer right now we are just trying to test this hypothesis whether this is true or not and hopefully within the next two years we will have the answer.

Chagpar How would you make sense of it if you looked at these military samples from DoD and you found that you have higher levels of PPDs in the people who ended up getting thyroid cancer, and lower levels of PPDs in their matched controls, but that young kids might have an even higher PPD level than even the people who got thyroid cancer in the military, but they do not get thyroid cancer. Is there a thought that maybe these kids long-term would have a higher risk or does it have something to do with being a kid and being able to metabolize this differently than an adult? How do you make sense that children do not usually get thyroid cancer unless they have a genetic abnormality or is there an intertwining of having a RET proto-oncogene and having PPD exposure?

Zhang Actually, right now, there is another major hypothesis, that we consider many human diseases actually have their origins in fetal life, so we call it the fetal origins hypothesis for certain types of cancer. So the exposure time window is also very important, for example, for those adults we never know when they were exposed to those chemicals. We only can only measure when the bio sample is available and we can measure those, but we definitely do not know for the kids, they are exposed to those PPDs and currently we saw those positive associations related to their neurodevelopment but we do not know yet about their long-term consequences, there might be a link associated with the future, their risk related to thyroid cancer, but this answer I do not know yet and also even though for those linkage between the thyroid cancer and PPDs association we are still in speculation there is no direct evidence that has demonstrated those associations. So that is our study we are currently working on. No matter if it is positive or negative, I think it is all very important.

Chagpar It is certainly very interesting and I suppose we always think about a dose response curve, right? The more of an exposure, the higher the outcome, but is it possible that there is a sweet spot for exposure that is more likely to cause an outcome and that maybe if you have a lot of that, your body kind of says, that is too much, I am not going to develop thyroid cancer, but if you are in that range, you do?

Zhang That is always possible, like we said, generally the cancer development has two stages, right? The initiation stage and promotion stage and you never know when they are initiated and when they are promoted. Maybe certain people already had this initiation a long, long time ago and because they do not have enough their body tricks them into developing cancer so they might be in this stage IV for the rest of their life, but for other people they might have another chemical exposure or some other environmental exposure could trigger that cancer to be promoted into developing as a cancer.

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We never know when the initiation stage was started or the promotion stage. We call those a black box. We are trying to discover what exactly is going on for many cancers, still we cannot answer what this latency period is and when it started, so that is kind of the research area we would like to pursue for the future, we could know when they are initiated and that we can prevent them as early as possible.

Dr. Yawei Zhang is Associate Professor of Epidemiology and Environmental Health at Yale School of Public Health. We invite you to share your questions and comments with Dr. Foss and Chagpar. You can send them to canceranswers@yale.edu or you can leave a message at 1-888-234-4YCC. As an additional resource, archived programs from 2006 through the present are available in both audio and written versions at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6 for another edition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.