

Yale CANCER CENTER *answers*

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Hosts

Anees Chagpar MD

*Associate Professor of
Surgical Oncology*

Susan Higgins MD

*Professor of Therapeutic
Radiology, Obstetrics,
Gynecology, and
Reproductive Sciences*

Steven Gore MD

*Director of Hematologic
Malignancies*

Environmental Causes of Cancer

Guest Expert:

Yawei Zhang, PhD

*Associate Professor, Epidemiology and
Environmental Health, Yale School of
Management*

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Welcome to Yale Cancer Center Answers with your hosts doctors Anees Chagpar, Susan Higgins and Steven Gore. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital. Dr. Higgins is Professor of Therapeutic Radiology and of Obstetrics, Gynecology and Reproductive Sciences and Dr. Gore is Director of Hematological Malignancies at Smilow and an expert on Myelodysplastic Syndromes. 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. Tonight you will hear a conversation about the environmental causes of cancer with Dr. Yawei Zhang. Dr. Zhang is Associate Professor of Epidemiology and Environmental Health at the Yale School of Public Health. Here is Dr. Susan Higgins.

Higgins Maybe we could start off by just talking about something that many people do not know too much about, and that is what do epidemiologists do and what was your training? How did you get into this division of health sciences?

Zhang In general, we consider epidemiology a population science. Epidemiology is a cornerstone for public health, so we are generally using the bal-statistic tools, for example, establishing a registry looking at the disease burden and the temporal trends in the populations and also we try to identify the risk factors or determinants for the disease and their outcomes. We do the population based studies and try to identify potential risk factors and then for the future, provide scientific evidence in terms of disease prevention, so that is pretty much what we do, and in general, for the training, mainly we use very sophisticated statistical tools and we have specifically, software to analyze the large database to find the trends and patterns to guide us in what are the risk factors for certain disease.

Higgins So in a sense, all of these diseases have many factors, many variables and you are like the detective.

Zhang Yes.

Higgins Epidemiologists take these hopefully large data sets, I know as clinicians we use the Medicare database because we are looking for clinical outcomes; in your case, you are looking for factors that in some cases cause different types of cancers and it is actually pretty complex figuring out, out of all the things that could cause that particular cancer, which ones are really the core factors. One of the things that you have been very interested in I know is thyroid cancer and I think a lot of people have heard about thyroid cancer because they probably know someone who has had a thyroid cancer. How did you get interested in that topic?

Zhang Actually thyroid cancer is a very interesting topic right now and also it is a very important topic. When I started working in this discipline after I graduated and joined Yale as a faculty member back in 2005, I looked at the SEER database which is a tumor registry database in the United States and we looked at all the different cancer types, their temporal trends during the past 20-30

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years and I observed that in almost every single cancer either decreased or leveled off. They are not increasing that dramatically, but only 2 cancers showed very dramatic increase, one is thyroid cancer and the other is liver cancer, so that is what drew my attention to the reasons why thyroid cancer is increasing and we used the international tumor registry database to look at the temporal trends about thyroid cancer among different countries and pretty much, thyroid cancer incidence risk has been increasing all over the world, not just in the United States, which is really fascinating as to what the reason is for this. Currently there is a lot of debate regarding what the reasons are that cause increasing trends. Many of them consider it purely over diagnosis because there is wide availability of ultrasonography. People can detect those very small thyroid cancers, which we call micro carcinoma which is less than 1 cm, but also when you are carefully looking at the database, it is not just those micro carcinoma increasing. The bigger tumor size thyroid cancer is also increasing, so we really wanted to know what the exact reason is to cause those and we first tried to identify whether those over diagnoses could explain all those increasing trends. We looked at the incidence rates in the United States among the different states and we found there is huge variability, actually, the highest incidence rates we see mainly occurred in the Northeastern area like Massachusetts, Connecticut, we have higher incidence rates and in the South, it was the lowest, so the difference could be 2.5 times difference, almost 3 times difference, so we tried to figure out what the reason is for this huge variability and we look at the density in terms of the endocrinologist and also the general surgeon, so we thought maybe more physicians are available for thyroid cancer, and more disease is being diagnosed and we also used the large health insurance database looking at the cervical ultrasonography, the performance, and then we tried putting all those data together and using the regression model and we do find that there is about half of the variability that could be explained by those variability.

Higgins I am just going to back track a little bit, this is part of your being a detective right, it is basically three categories we think about, patient factors, is it something in our genetic makeup, is it some sort of over diagnosis factor where we are just finding them early and the numbers go up, and I know in prostate cancer we have some of this because some of those prostate cancers we are finding now were not screened for many years ago, so you have the patient factor, the diagnosis factor that could account for numbers going up and then there is the environmental factor.

Zhang Yes.

Higgins And when you look at regions, obviously in the United Stage, where some people in the Northeast are having an incidence per capita or per thousand that is 2.5 to 3 times other regions, which probably drew you towards some environmental factors.

Zhang Exactly. After this detection, we considered that only half the variability could be explained by this over diagnosis theory, but in another half, it definitely could be due to some environmental or lifestyle differences between those states, so that is what we needed to identify, what exact

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environmental lifestyle factors are contributing to those increasing trends? We all know the thyroid gland, which is the most radiosensitive organ in the body, and this has already been demonstrated during the nuclear accident in Chernobyl, for example.

Higgins I think we also have data from Hiroshima, Nagasaki, those are unfortunate events where we are following these patients and victims in that case, for the long term, which gives us a lot of that exposure information, which is really fascinating.

Zhang Yes, but that is very high dose one time exposure, but in the current situation, nobody is exposed really to those large radiation doses. We were naturally considering what if radiation exposure has been increasing, and that has drawn our attention to looking at the diagnostic x-ray. I would say since the 1980s the CT scan, nuclear medicine tests, have started increasing and a lot of people are getting those diagnostic x-ray exposures and there is a report set in the US general population, the per capita dose of the diagnosed radiation exposure, since the 1980s through 2006 has increased 6 times, which is kind of parallel with the thyroid cancer increase in the incidence, so we would consider maybe this diagnostic x-ray exposure plays a role, so that is why we proposed this study hypothesis to the American Cancer Society and we got funding to look at it. It is a population based case control study. We are including all thyroid cancer patients diagnosed in Connecticut from 2010 to 2011. We also use the random digital methods to recruit healthy general population from Connecticut as a control, so we are having everyone recall their previous exposure about their diagnostic x-rays, all the different procedures and when the first time was that they got these procedures and then we look at those data and we do find this increased diagnostic x-ray exposure is associated with thyroid cancer, but particularly with thyroid micro carcinoma, it is not a big tumor size, so that is another fascinating discovery when we are looking at our data, why this association is only observed for micro carcinoma but not for the big tumor sized thyroid cancer.

Higgins I want to divert for one minute to talk about the clinical aspect, because as a radiation oncologist and doing work in safety, the clinicians are already having some concerns about the very things that you are talking about and what is going to be so interesting is that your work will really solidify what a lot of people are already suspecting, for instance in diagnostic radiology, there is a very large nationwide, and I think now worldwide, campaign to decrease exposure to diagnostic x-rays especially through CT scan because the use of CT scans has sky rocketed over the past decade and the Image Gently Campaign has been started by diagnostic radiologists with the efforts to take care of what we know are potential exposures that could cause cancers. But you are already on to that, so this is great because it gives, I think, more impotence and credence to all these nationwide efforts to decrease exposure because the implementation of CT scanners and their use has really been a huge movement in radiology, so I think this part of it is great and one other thing we know from a radiobiology perspective is that these low exposures, as radiation oncologists, we think a lot about radiobiology and the problem with low energy exposure is that the cells can be mutated but not killed. Sometimes we feel that is why that curve that shows basically incidence of cancer, there is no 0 because even the smallest amount of exposure may cause those one or two

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mutations that interact perhaps with some other environmental factor that cause cancer, so what is great is that you are sifting through all these factors and the diagnostic radiology groups can really use this stuff to alter their practice. It will actually alter practice.

Zhang Yes.

Higgins Maybe you could talk about this diagnostic radiography exposure, I know you have some recent publications about this with our colleagues including Dr. Udelsman who runs our thyroid surgery program.

Zhang Actually, from this finding, it is really fascinating and I think in just recent years, another publication came out and they were looking at the CT scan whether it is related to the different cancer types and they do find other people who received the CT scan during childhood have increased risk of adulthood thyroid cancer. It is about a 40% increased risk, but that study is purely based on the medical records and they do not really collect information after 19 years old which means they only have the information during the childhood without the information about adulthood, so one of, I think, the major stresses from our study is we have lifetime radiation exposure, diagnosed x-ray exposure which is a little bit different. We can give a more comprehensive picture, and after this finding, our study group, especially Dr. Udelsman, we discussed a lot about how we explain those results. I think it is very important and we might take the next half to continue to discuss that.

Higgins We will come back to that in the next half. That is really fascinating how your study is picking up these important factors. We are going to break now for a medical minute. Please stay tuned to learn more information about epidemiology and environmental causes of cancer with Dr. Yawei Zhang.

Medical Minute
Smoking can be a very strong habit that involves the potent drug nicotine and there are many obstacles to face when quitting smoking, but smoking cessation is a very important lifestyle change especially for patients undergoing cancer treatment. Quitting smoking has been shown to positively impact response to treatments and decrease the likelihood the patients will develop second malignancy. Smoking cessation programs are currently being offered at federally designated comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven. The smoking cessation service at Smilow operates on the principles of the US Public Health Service clinical practice guidelines. All treatment components are evidence based and therefore all patients are treated with FDA approved first-line medications and smoking cessation counseling. 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. For more information, go to yalecancercenter.org. You are listening to WNPR, Connecticut's Public Media Source for news and ideas.

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Higgins Welcome back to Yale Cancer Center Answers. This is Dr. Susan Higgins and I am talking with my guest, Dr. Yawei Zhang about epidemiology and environmental causes of cancer, particularly thyroid cancer. During our first half, we talked about diagnostic imaging and exposure that could cause thyroid carcinomas, in particular these micro carcinoma, and we were focusing on your study. Maybe you could tell us a little bit more about your study and how you came upon this connection.

Zhang After we observed those only associated with micro carcinoma and not the big tumor size, we look at the explanation. There are a couple of things that we could explain in our results, first of all, maybe this diagnostic x-ray promoted the diagnosis of thyroid cancer and make those micro carcinoma diagnosis early before they progress but on the other hand, we also find when we are looking at the lag time period, no matter if you are exposed to the diagnostic x-ray 5 years ago, 5-10 years, more than 10 years ago, 20 years ago, the association did not change that much, which means that those micro carcinomas may be a very slow growing tumor. They are not going to grow very quickly. Actually, from the earlier study from Japan, observing those micro carcinomas of the thyroid cancer, they did not do any intervention, they just followed those people, observed them and then after 10 years, less than 16% of the people had the tumor enlarged, which means a lot of micro carcinoma patients actually stay in the micro carcinoma stage, maybe forever. We really want to know whether we should treat them, whether the medical intervention benefits those people, so that is one concern, the suggestion from our study indicating this and on the other hand, we were also considering those radiation related micro carcinomas as a total different cancer type compared to the conventional thyroid cancers. They might have a very different etiology profile. Actually during follow up of this was a very interesting finding, we looked at the genetic background and genetic susceptibility, whether those 2 tumors have very distinctive biology mechanisms, so from our population based case control study, we collected the people's blood samples and we tried looking at the genotyping SNPs which could be post susceptibility for the different cancer type.

Higgins I have to interrupt when you say the word SNP, I think that most people would need a little background on that, but as a clinician we understand that you are getting at these genetic factors because again we talked about, there could be patient factors, environmental factors and one of the patient factors could be their actual DNA make-up and it sounds like now you are talking about the molecular level, maybe you can tell us how the word SNP gets into this conversation as a way of looking at the genetic makeup of any person and how they might be susceptible to one cancer versus another?

Zhang The SNP we are talking about is single nucleotide polymorphism which is kind of a DNA makeup, different people carry different SNPs which might translate into different proteins in your body, for example, people have better enzymes in the liver, they can detoxify a lot of toxic substance, but for certain people they cannot. For example, we all know that smoking causes lung cancer, but it is not every single smoker that will get lung cancer, so they have the different genetic makeup in the body, they can detoxify those toxins in a very different way, so some people get cancer and other people don't, so this is something we wanted to further explore. Actually, from our very

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preliminary study, this has not been confirmed yet, but there is some signal showing the small micro carcinomas of the thyroid cancer are different from those bigger size thyroid cancers that will be our future direction, we would really like to identify which micro carcinomas that will eventually progress to the more aggressive tumors, those people might not really get the benefit from treatment, but for those people who never progress, maybe they do not need additional treatment for that.

Higgins I was just going to say, that this is sort of the trend now right, as clinicians we have always, especially historically and I think it has been a revolution in the past 10 years, looking at a disease like thyroid cancer and saying, well this is not one disease, this is really many diseases and then looking at how each individual type of thyroid cancer is different and even within one person and of course, we are now getting towards personalized medicine, so again you as the detective you are in the background of this whole trend and all these efforts towards really getting at for each person what is going to be the best treatment for their particular cancer, even on an individual level, so that is really fascinating. As you were saying, looking at the finger print of a person's DNA and saying, well this is the kind of person for this. And we spoke to Dr. Gettinger about this a few weeks ago for lung cancer, there are a group of people who get lung cancer that are what we call never smokers, and now we are finding out that is a different cancer than the cancers that smokers have because it has obviously huge implications for how we as clinicians are going to use targeted therapies for these people, so as a clinician what is really great for me, is seeing all of this come along at a time in my career where it was something we could have really never dreamed of 20 years ago, and it is great to hear about how you are a part of this especially the diagnostic exposures and looking at these particular cancers. What other things are you looking at aside from the thyroid, do you have some other interests in other research projects including adverse outcomes after pregnancy and so on, could you briefly touch upon some of that?

Zhang In addition to thyroid cancer, one major interest area of mine is looking at reproductive health. The reason that drove me into that area is that early life exposures, we call the fetal origin hypothesis for adulthood disease. For example, cardiovascular disease and diabetes, as well as certain forms of cancer, even breast cancer, can be considered perinatal exposure which is very important for those people who in the future are getting those adulthood chronic diseases, so that is a very fascinating research area. I really wanted to look at what the perinatal exposures are that are causing certain epigenetic changes in the baby and then eventually getting chronic diseases.

Higgins Just to go back to this phrase, epigenetic change, people read about this, but could you explain the concept of epigenetics because this is something we are really honing in on as time goes on, that epigenetic changes may be one of the most important changes that precedes a cancer.

Zhang Yes, we call it epigenetic change because we all know that the DNA will have mutations which will cause the base to change, but for the epigenetic change, actually, they do not cause any coding ranging change for those DNA changes, but they are changing the transcription,

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so when they transcript to the protein or RNA, they will make changes but the DNA sequences do not change at all, so that is what we call epigenetic changes which are mainly related to those environmental exposures.

Higgins So if the DNA fingerprint, there is a certain code in the DNA, it doesn't mean that it is going to get translated into the products in our cells, so you are looking at that, which is really sort of a whole cascade of processes.

Zhang Yeah exactly.

Higgins It is very challenging to find the epigenetic causes. What kind of tools do you use to look at epigenetic factors?

Zhang Generally right now we are using the Illumina, and we are looking at the whole genome wide epigenetic change in patterns and then we have the questionnaire to look at the perinatal exposure information and we also collect the maternal and cord blood looking at the certain exposure biomarkers in the blood samples, for example, the different metals in the blood sample and also those chemicals, a variety of different chemicals which are considered as human carcinogenic which can be detected from the blood samples so we will know which people are exposed to this particular chemical or metal by their level and then we can correlate those to the epigenetic change markers, so we will know because of those exposures, it has caused the epigenetic change and then we will refer to the future, the chronic disease, so that is the whole concept, but right now, we started a birth cohort study in China, one in Lanzhou city and another in Taiyuan, and these are two of the air pollution cities in China and we had more than 10,000 mother-baby pairs from Lanzhou sites.

Higgins 10,000?

Zhang Yes.

Higgins And that is part of the beauty of doing these studies in China where you have such huge population density and numbers and so your job is all about the numbers, and more usually means better and more important or more significant data, right?

Zhang Yes, and another beauty is that we all know that air pollution will cause adverse health outcomes, but all those studies came from more developed countries which has much more clear clean air and we really do not know in people who are exposed to really high levels of air pollution, whether it will cause adverse outcomes or maternal complications, we really do not know, so I think this study we conducted in China, can tell us whether the high level exposure will cause impact in terms of the birth outcomes and maternal complications. The Chinese Government right now is paying a lot of attention to try to control that air pollution. Even just for our study sites like

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Lanzhou when we conducted the study back in 2010 and 2012, right now the air is much cleaner. They changed all the heating systems to the central heating system which is using natural gas and also a lot of cars, they changed their oil to natural gas.

Higgins I was wondering about that, there is some evolution in the exposures in the city, you are focusing on some of the smaller regions where it sounds like things are not changing as rapidly, so probably helps you with your study, correct?

Zhang Yes, and within the city, because when we are looking at the air pollution, the exposure and disease association, the exposure levels are at different levels among the population then you can find whether compared to lower exposure, the higher exposure will have the health impact. In Lanzhou City, even though we are in a relatively small city, one of the major things in that city is that we have a huge seasonal variation in terms of the exposure.

Higgins Because of inversions and weather patterns, is that what you mean?

Zhang Actually the heating system during the winter time, they cause much higher air pollution compared to the summer time and the pregnant women, they are only pregnant for 10 months, so their average exposure during pregnancy could be a large variation so that gave us power to look at those lower exposure and higher exposure and what the relationship with them is.

Dr. Yawei Zhang is Associate Professor of Epidemiology and Environmental Health 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 form at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another edition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.