

Dr. Yawei Zhang, Researching Ways to Prevent Cancer February 7, 2010 Welcome to Yale Cancer Center Answers with Drs. Ed Chu and Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Foss is a Professor of Medical Oncology and Dermatology specializing in the treatment of lymphomas. 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 1888-234-4YCC. This evening, Francine welcomes Dr. Yawei Zhang. Dr. Yawei Zhang is an Assistant Professor of Epidemiology and Public Health at the Yale School of Medicine.

Foss Yawei, could you start off by telling our audience what epidemiology is? Zhang Epidemiology is a study of the factors that are affecting the health and illness of the population. Epidemiology can actually serve as a foundation for identifying risk factors, which can be used to develop a strategy of intervention in the population level. On the other hand, epidemiology can also be used to identify the optimum treatment used for the clinical practice.

Foss So epidemiology stretches across all different areas of health, not only illness, but health as well? Zhang Yes, exactly.

Foss And the Yale School of Public Health and Epidemiology is a school that is involved in the study of epidemiology in all different areas. Zhang Yes, the school of Public Health has several different divisions. Across almost all the divisions, we have the discipline for the epidemiology part, and we do all the different kind of diseases and what's the cause and what factors can affect in prognosis and etiology.

Foss Yawei, you are specifically interested in the epidemiology of cancer. Zhang Yes.

Foss Can you tell us what got you interested in these kinds of studies? Zhang I had medical training in China back in 1993. My major was preventive medicine. So I had the opportunity to be exposed to both the clinical practice and epidemiology side. After I graduated, I worked in the Health Department in China for about six years, and during that time period I was involved in the nutrition and immunization program for children. I worked there for about six years and there is a program that sends people overseas to learn more about new methodology regarding epidemiology. So that's why I came to the United States and started the M.P.H. and PhD program at Yale University. My advisor was a PI for a population-based case-control study.

3:17 into mp3 file <http://www.yalecancercenter.org/podcast/feb0710-cancer-answers-zhang.mp3> of non-Hodgkin lymphoma and breast cancer. I was involved in both studies to help him run the study and we collected the data and I used that data as my dissertation topic. Since then I've liked epidemiology and felt that especially the non-Hodgkin lymphoma is a very important, but understudied, disease in terms of the etiology and what the causes of the disease are. Foss In fact, the Yale Cancer Center Epidemiology Department has done a lot of the pivotal studies in the epidemiology of non-Hodgkin lymphoma. Particularly there was a study that was done a number of years ago that showed an association between hair dye and lymphoma, could you talk to us a little bit about that study? Zhang Yes, I would love to. In about 1991, the National Cancer Institute sponsored a workshop called The Epidemic of non-Hodgkin Lymphoma because the incidence of non-Hodgkin lymphoma risk has been

increasing during the past several decades with unknown reason. All the experts from different disciplines raised one speculative hypothesis for the increasing trends. They said it might be a personal use of hair dye, and this is based on findings from an epidemiology study, the National Cancer Institute investigator, conducted in Iowa and Nebraska. In order to test this hypothesis and confirm the findings, we conducted a population-based case-control study in Connecticut women. We recruited about 601 non-Hodgkin lymphoma cases and about 719 population controls. We did a case control study and we asked all the information about their lifetime hair dye use. From the study we did find increased risk for women who started using hair dye before 1980, and during that time period hair dye actually contained carcinogens in their ingredients. We did not find any increased risk for women who started using hair dye in 1980 or after. So during that time period all the hair dye companies changed their formulation for the hair dye products. This is only from the Connecticut population. We wanted to see whether this finding could replicate in other populations. So, we collaborated with the International Lymphoma Consortium and used populations from six European countries, and also other parts of the United States. We came up with more than 4000 cases and more than 5000 controls, and we did confirm our finding. We found that a woman who started using hair dye before 1980 had an increased risk for follicular lymphoma and CLL and SLL, two major subtypes of non-Hodgkin lymphoma. But an interesting thing from this analysis is we also found woman who started using in 1980 or after had an increased risk for follicular lymphoma, especially for those women who used dark color hair dyes.Foss So based on your initial study that was done in Connecticut, the hair dye companies actually had to switch their formulation to get rid of the carcinogenic element.Zhang Yes, during the 1980s.7:00 into mp3 file <http://www.yalecancercenter.org/podcast/feb0710-cancer-answers-zhang.mp3>Foss But what are you saying is that in your subsequent study with the different hair dyes, for the ones that we are using today, there is still an increased incidence of lymphoma?Zhang Yes, that's true.Foss Do we understand again why that is?Zhang During the 1980s there were a couple of animal studies that demonstrated certain carcinogens in hair dye formulation, so they changed it, but they also added some new products in the hair dye formulation, a new formulation. Right now we really don't know whether those new formulations have potential carcinogens in the products or not. Right now there is no new evidence to really demonstrate that, but from the consequent studies we included women from all over the world and also more recent cases and women using the hair dye for more than 20 years. It may be the long term, and we cannot exactly say that current hair dye is safe or not safe. I think that more studies are needed.Foss You mentioned dark hair dye, does this pertain to all hair dyes or just the dark colors?Zhang It's dark color hair dye including both permanent, non-permanent, and semi-permanent hair dye.Foss And your study only focused on women, so we don't have any information on men and hair dye use?Zhang Yes, from our study we only included women. But for the large study we also included men in the study population, but we did not find

any association for men. It could be because in men, the prevalence of use of hair dye is pretty low. Maybe for our study we do not have enough power to detect this association, and also another possibility is that maybe the hair dye has nothing to do with men.

Foss Yawei, can you let our audience know, when you do these epidemiologic studies they are population based studies, and how many people are we talking about? What are the numbers of patients that you need to get a significant difference, and can you talk about the role of the controls?

Zhang For the epidemiology study it's hard to see the exact numbers. It could vary from less than a hundred to a couple of thousand. That totally depends on many-many different factors based on the study design you are doing; is it a case control study or a perspective follow-up study? And it's also based on how strong the association is. You are looking at how strong the association will be, a stronger association you don't need that much of a sample size, if it's moderate association, you might need a large sample size, but in general when we do a cancer epidemiology study, we would like to find certain environmental exposures or certain genetic susceptibility in relation to the disease and we need at least a couple hundred cancer patients and probably a similar number of healthy controls.

Foss And in your original study you mainly administered a questionnaire to patients?

Zhang Yes, we administered a questionnaire, and we also collected their blood samples.

Foss That's the point I wanted to get to is now-a-days, in epidemiologic studies, a lot of what you do is based on the DNA?

Zhang Yes.

Foss Can you talk a little bit about that?

Zhang For epidemiology studies in the earlier years, we mainly used the questionnaire to get all the exposure information. Since then we all know that everyone is exposed to certain carcinogens, but it is not everyone that gets cancer, it's only certain people that get cancer. So this involves genetic susceptibility. Some people have a certain genetic mutation, certain alleles or certain polymorphisms that make them susceptible to certain environmental carcinogens. That's kind of the point we needed to really look at, the gene environment to interaction to really identify who is susceptible to certain environmental carcinogens.

Foss When you do these genetic studies you look at these things called SNPs?

Zhang Yes.

Foss Can you tell us what a SNP is?

Zhang SNP is a Single Nucleotide Polymorphism, it's more like a point to mutations in the DNA. As we know, every single person has inherited from mom and dad two alleles for each gene, and for those genes they all have single nucleotide polymorphism, it is along the base pair.

Foss It is basically the code of the DNA.

Zhang Yes, the code of the DNA, and for those codes of the DNA they had the variation in the general population. The single nucleotide polymorphism represents all those different variations and certain people carry those variations and other people carry another variation, but some of the SNPs are in the coding region and can change your DNA products, and some of the SNPs in the non-coding region might not change your DNA, but they can affect other factors like transcription factors binding ability.

So that's why we can look at those SNPs, but in

general, all those SNPs are inherited from the parents. They are not changed during development and it's not changed based on the environment. So even though we have a case, that they got a treatment, we can still look at their SNPs and get a causal relationship. Foss So the SNPs basically tell you about specific genes which tell you about specific proteins in that patient and those proteins may explain why say one patient reacts to a hair dye and the other one doesn't, for instance? Zhang Yes. We just did a paper on the use of hair dye. We looked at the metabolic pathway genes, and the genetic variations metabolic pathway genes, and we did find a certain variation, people carry a certain variation in metabolic pathway genes and they have a higher risk compared to other people when both exposed to the hair dye. Foss Let's talk a little bit more about that after the break, Yawei. You are listening to Yale Cancer Center Answers with Dr. Yawei Zhang discussing cancer risk and epidemiology. Foss This is Dr. Francine Foss and I am here with Dr. Yawei Zhang, Assistant Professor of Epidemiology and Public Health at Yale Cancer Center. Yawei, we talked a little bit about the genetics of lymphoma and how you look at SNPs, or these pieces of DNA that help you to explain a predisposition to cancer. How does that work for a patient? How do these SNPs lead to cancer in some patients but not in others? Zhang For those genetic variations, they inherit it from their parents and in general, the majority of them, from an evolution point, they should be suitable to their surroundings and to the environment, and the rapid economic change and the environment has changed a lot. There are some solvents, new15:59 into mp3 file <http://www.yalecancercenter.org/podcast/feb0710-cancer-answers-zhang.mp3> chemicals every year put into the market and for people it is harder to change their genetic makeup to conquer all those newly emerged chemicals. At the beginning, people have the different genetic makeup or background suitable for all those surroundings. We talked about the SNPs, all those SNPs are like a genetic variation and certain SNPs can cause your DNA to translate to the different products in terms of the protein, and it can change your amount of the protein and changes the structure of the protein. We can go back to look at people's genetic makeup, and we can come up with the fact that some people may be more susceptible to certain carcinogens and some people may not be susceptible to certain carcinogens. We know that in the genetic component of your body, there are so many different pathways, the metabolic pathway, DNA repair pathway, and the immune pathway, and through the different pathways it changes the different structure of the protein and conquers the different environmental stimuli. We can go back to look at people's genetic makeup, and we can also get the information from the environmental exposures, using the statistics model we can figure out which genes, which certain genetic variations are susceptible to certain chemicals. In the future, we can inform people if they carry those genes, genetic variation, they should stay away from certain carcinogen environments. Foss So this would be like identifying your genetic fingerprint? Zhang Yes. Foss And then applying that into your environment? Zhang Yes. Foss You talked a little bit about the role of lymphoma, genes and lymphoma, but I know that your group has also

studied a couple of other types of cancer; breast cancer, testicular, and now thyroid cancer. Can you talk a little bit about that?Zhang In our group we also look at breast cancer and testicular cancer and we mainly focus on the environmental endocrine disruptors. As you know, breast cancer and testicular cancer are more hormone related cancers and a major hypothesis for those two cancer types is environmental endocrine disruptors. We know estrogen is a carcinogen for breast cancer, particularly, and during the early 1980s, there were a couple of studies published that found an increased risk of breast cancer associated with the environmental endocrine disruptors like PBDE. If you have a high body level of PBDEs, you will have a higher risk of breast cancer. But subsequent studies, especially the most recent studies, the majority of them found no association and even the protection factor in certain studies. People will question what happened, is it because of the different population or because of the study design? So, when we look back there are some certain concerns about the study. All the studies look at the environmental endocrine disruptors in relation19:26 into mp3 file <http://www.yalecancercenter.org/podcast/feb0710-cancer-answers-zhang.mp3> to breast cancer, all using the adult blood samples and collecting the blood samples starting from before diagnosis of disease, or just at diagnosis of disease, and people think that maybe you capture the wrong exposure time window. Maybe the early life exposure time is more important, as we know that during pregnancy and early puberty, your mammary gland is developing and during that time period if you encounter some certain environmental endocrine disruptors, it will change your structure, like estrogen receptor expression may be more susceptible to the future development of breast cancer. That's why right now there is a huge effort to look at the early life exposures of the environmental carcinogen to the human breast cancer risk. Another point on this, people also consider maybe the different genetic susceptibility around the different population. So, that's why you do not find similar results. Actually, we do look at the metabolic pathway genes in one family with exposure to the PCBs and in relation to all breast cancer. We do find that there is genetic polymorphism modifying the relationship between the environmental endocrine disruptors and the breast cancer risk.Foss You recently obtained funding from the American Cancer Society to study risk factors for thyroid cancer, which is not a common cancer, but I think last time I looked it was actually the number 5 cancer in the United States.Zhang Yes.Foss Could you talk a little bit about that one?Zhang For thyroid cancer, as you said, it's a rare cancer and also it's a very mild cancer so it has a very good prognosis. Since the 1970s until now, thyroid cancer has increased more than two fold, so, it's a large increase. One of the major arguments for those increases is over diagnosis, and so the increasing majority of thyroid cancer is from small nodules, and they think that because of the current technology available for ultrasound and many subclinical patients have been diagnosed with the thyroid cancer, but also some other considerations are we look at the SEER Data, Surveillance, Epidemiology, End Results Program. It's supported by the National Cancer Institute for the Tumor Registry to collect all the cancer incidence prevalence

and survival data. From the SEER Data, you can look at all the trends for whether the incidence rate is increasing for each different type of cancer. With thyroid cancer, we have another point of view and we do not totally agree with what the majority of clinicians are considering, that this is over diagnosis for thyroid cancer. We go back to look at the SEER Data and also the International Tumor Registry Data, and we found that those increase are not only in folks having small nodules, but the big nodules are also increasing, and also from the International Data, there is a large geographic difference and almost every single country has increased incidence of thyroid cancer. So, we consider there must be some environmental changes that caused thyroid cancer and as we know, radiation is the major environmental risk factor for thyroid cancer. We know that during the 1950s or 1960s there was a23:27 into mp3 file <http://www.yalecancercenter.org/podcast/feb0710-cancer-answers-zhang.mp3> lot of radiation treatment for the head and neck that might explain a little bit of the increase around the early trends, but for the later trends, you cannot use that to explain the increasing trends. So, we proposed two major hypothesis, one is that maybe current diagnostic x-ray use might explain a certain degree of the increasing trends, and also another major hypothesis we proposed is flame retardants. It's a chemical used in the flame retardants called PBDE that may also cause an increased risk of thyroid cancer. This hypothesis is basically based on the findings from an animal model. PBDEs can cause liver toxicity, thyroid toxicity, and kidney toxicity. The PBDE structures are similar to the thyroid hormones and they can interrupt your thyroid hormones and might be affecting the thyroid and may be a potential risk factor for thyroid cancer. So, we fortunately got this grant from the American Cancer Society to look at the radiation exposure, especially the diagnostic x-ray exposure in a DNA repair capacity in relation to the thyroid cancer. We hope to use this population in the future to get more funding to test the PBDE hypothesis.Foss Can you talk a little bit about how you are going to figure out how much radiation exposure folks have, for instance a lot of people get dental x-rays, is that going to count?Zhang Yes. We have the questionnaire. We are collecting their lifetime exposures about the diagnostic x-ray including the dental x-ray exposure.Foss And what about the chemical that you are talking about, will you be measuring levels of that chemical in the blood?Zhang Yes, we are also collecting the blood samples from thyroid cancer cases in the general population controls. We will measure all those PBDEs. We are collaborating with the CDC Lab to do this measurement.Foss Are you also looking at the DNA fingerprint of these patients? Are you looking to see if there are specific SNPs that would predispose them to the development of this kind of cancer?Zhang Yes, that's what we plan to do and we plan to do the first pathway to go to see the DNA repair pathway because the radiation mainly affects your DNA repair capacity and can cause a double strand break, so we first look at the DNA repair pathway fingerprint.Foss Can you talk about areas like say Chernobyl, or other areas where people have been exposed to a lot of radiation. Is there an increased incidence of thyroid cancer compared to other cancers in those areas?Zhang Yes, that's true. That's how people figured

out radiation is a major environmental risk factor for thyroid cancer. After the Chernobyl accident, one of the first cancers to increase from that26:39 into mp3 file <http://www.yalecancercenter.org/podcast/feb0710-cancer-answers-zhang.mp3> population was thyroid cancer. That's one of the major things that people found as to why radiation is the major cause for thyroid cancer.Foss Yawei, you talked about collaborations around the world in your epidemiology studies. Is there a network of academic institutions around the world, or are there international groups that are focused on studying the epidemiology of these cancers?Zhang Yes, in almost every single country they have their universities. They have certain people to do the epidemiology and cancer epidemiology and also almost every single country has their cancer center, their institutions, and a lot of people doing the cancer epidemiology. We get to know each other through the peer review publication and also through all the meetings like the AACR meeting, American Association for Cancer Research, and certain other meetings. So we get to know each other and we are collaborating.Foss Can you leave us with one thought, which is where do you think the future is for cancer epidemiology? Is this going to be something that's going to be a part of all of our lives in terms of looking at our fingerprints and predicting what's going to happen to us in future?Zhang Yeah, I would love to see that and I think so. For every single disease, there is not purely genetic and purely environmental, it must be gene environmental interaction. You have a certain genetic susceptibility and you also encounter certain environmental carcinogens, so that's kind of the way we should go.Foss This has been a very thought provoking discussion and I would like to thank you for being my guest tonight. You have been listening to Yale Cancer Center Answers and I would like to thank Yawei for coming. Yawei is the Associate Professor of Epidemiology and Public Health at Yale Cancer Center.If you have any questions or would like to share your comments, you can go to yalecancercenter.org, where you can also subscribe to our podcast and find written transcripts of past programs. I am Bruce Barber and you are listening to the WNPR Health Forum from Connecticut Public Radio.