

Yale CANCER CENTER *answers*

WNPR Connecticut Public Radio



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Radiation Associated Brain Tumors

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Yale Cancer Center Answers

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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. Chagpar welcomes Dr. Elizabeth Claus. Dr. Claus is Professor of Public Health and Biostatistics and is Director of Medical Research at the Yale School of Public Health. Here is Anees Chagpar.

Chagpar Let's start off by having you tell us about what you do and what you study?

Claus I lead a bit of dual life. I am a Professor at the Yale School Public Health and in that role I teach general epidemiology and that is a part of how some of our recent work has come to be published. We developed the largest study of meningioma, worldwide, and the last one was about 10 years ago and we ended up looking at about 3500 individuals, half of whom had the brain tumor that we studied, which is called meningioma, and half of whom did not. Essentially we are looking to define both genetic and environmental risk factors that might be associated with the development of this tumor.

Chagpar Meningioma, that sounds like a pretty rare cancer, can you tell us a little bit more about what exactly it is and how you got interested in studying it?

Claus Meningioma is actually now the number one primary brain tumor that is diagnosed in the United States and we think, based on some recent data from overseas, that approximately 1% of all adults actually have a meningioma. The interesting thing is that many of these are incidental and will never cause anyone a problem during their life, but a proportion of them will actually be quite serious. Meningioma essentially is a tumor of the lining of the brain or the spinal cord and what make it serious or not serious is essentially where in the system it is and how big it grows to be. Many of the lesions that I see, and usually every Friday I have a clinic where I see two or three people that have this diagnosis, probably about half of them are incidentally located. For example, you might have a head injury in a car accident, get an image done, and incidentally find a small meningioma and usually we do not have to do anything about that, but then we have a whole set of individuals who are symptomatic, or have some change in how they function that is associated with the meningioma. For example, I recently had an individual who was driving his car along the highway and had a seizure. We identified the meningioma and in that case had to perform surgery to take it out. So, there is really quite a wide variation in the size and symptoms and what needs to be done for these lesions.

Chagpar So, 1% of all people have a meningioma, that is pretty scary, because I can imagine that there are people sitting on their couch, listening to us on WNPR thinking I have got 100 friends, one of us is going to have a meningioma, that is pretty scary. What are risk factors that would predispose someone to have a meningioma?

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Claus There are a number of risk factors that we think are fairly well confirmed. The one thing that is interesting, although we have never been able to completely tease out exactly what the mechanism is, there is a concept that hormones are related to risk and so the reason that we think that is that women are almost three times as likely to be diagnosed with meningioma as men. In addition, we know that these tumors frequently can have hormone receptors, just as breast cancer can have estrogen and progesterone receptors, a large number of meningiomas also have this sort of hormone receptor, although it is more likely progesterone versus estrogen. We actually just did a small study where we looked to see our hormonal reproductive factors, or taking oral contraceptives or hormone replacement therapy, to see whether this had an effect on risk and we found some evidence among younger women that being current users of oral contraceptives was associated with risk, but the other big risk factor is ionizing radiation and that is a very long standing, very consistent factor and I think a very well known risk factor and the way that people first started to understand this risk was following children that received radiation as a young child for another cancer. So these individuals were followed over time and found to have a greatly increased risk for a number of cancers, but particularly those of the brain or the spinal cord with meningioma looking to be the highest.

Chagpar So, these kids who had another tumor would get radiation and they would be at higher risk. How do we know that was the radiation and not the fact they already had another cancer?

Claus You do not know 100% because obviously their genetic makeup could be a risk factor for not only the first, but later cancers. However, they have looked at a very large cohort of these children and try as much as they can to control for radiation and not only radiation, but other medications such as chemotherapy, the age of exposure, and some genetic factors. It is fairly preliminary so far, but it does appear that it is a fairly strong relationship between the timing and the dosing of the radiation and the outcomes that these children have, and it is usually 20 or 30 years later.

Chagpar And is it in the same location as the radiation, I mean if I had radiation as a kid in my big toe, would I be at risk for a brain tumor or do I have to have my radiation closer to the brain?

Claus It seems very much related to the location of the original treatment, be it head or chest, face or neck, and there are additional studies beyond these childhood cancer survivors, but there is also data from the Tinea Capitis study. That actually was a very well done study where they looked at children who were immigrants to Israel in the 1940s and 1950s and they received, as treatment for ringworm, radiation therapy to the head, and what the Tinea Capitis study did was they actually estimated the amount of radiation to the scalp, to the brain, to the face, to the head, and although the estimated dose to the brain was probably in the range of what a chest x-ray would be, the children were young and they followed these individuals for thirty or forty years and they have noted a 5 to 10 fold increase in the risk of meningioma.

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In addition, risk of glioma, which is a malignant brain tumor, and acoustic neuroma, so it is a nice study in the sense that there were very stringent measurements made and very good followup. In addition, not only were the children looked at, but their family members who may or may not have also received radiation, so they have a very controlled cohort to compare these children to.

Chagpar What about radiation from other sources? Has anybody looked at patients who may have been exposed say to Chernobyl or massive radiation toxicities from nuclear power plants and so on?

Claus They do have data on that, it is primarily at this point from the bombings in Japan. Part of the relationship between radiation exposure and meningioma development is that there is a long lag time, so the average time from exposure to development is about 20-30 years, or even longer. There are cohorts set up to look at more recent exposures such as Chernobyl, but the time span is really not long enough for us to know fully in terms of meningioma and other brain tumors what the outcomes will be.

Chagpar The other thing that you had mentioned that I found interesting was the exposure that people get with x-rays, so if you are a child and you are getting a chest x-ray, should we be telling kids not to get chest x-rays or dental x-rays? How do x-rays play into this whole story?

Claus Part of our interest is looking specifically at dental x-rays and I will say that our study included only adults, so our particular study does not have any data on children, but outside of high dose therapeutic radiation, that is radiation being used to treat benign or malignant tumors, at least within the United States, the most common form of exposure to ionizing radiation is dental x-rays. So that was our interest in looking at that particular x-ray imaging, and that may change over time because CTs are being more commonly used. What we did was we looked at general frequency in the individuals that had meningioma and compared it to people that did not have meningioma. So we were not able to measure specifically the number of x-rays that you had since you were 2 years old, but we did ask people, and you can kind of think about whether this seems reasonable or not, but are you someone that never goes to the dentist and hence never gets x-rays? Are you someone that is a pretty regular visitor to your dentist and every sixth months you get an x-ray? Are you someone who goes once a year, or are you someone that is kind of in between the never and the once a year? So, we basically ask people to classify themselves as a child, as a young adult and then within the past 10 or 20 years into one of these groups and then we just compare what the cases say. What the controls say and we did find that the cases were more likely to report being a frequent user of dental x-rays than the controls. It was fairly consistent across the age groups and the types. We did also find increased risk when people had a panoramic, which is a little more extensive dental x-ray that tends to rest on your chin and then the x-ray machine revolves around your face. We found that individuals that had high rates of that sort of dental x-ray were at increased risk, but I will have to say that the number of people that reported that sort of exposure was pretty small, so it is a fairly limited group.

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Chagpar We have talked on the show about screening tests for a variety of malignancies and certainly have talked about mammography for breast cancer, but now talking more about CT scans for lung cancer and granted these are not particularly close to the brain but reasonably close to the spine, please tell me that there is not an association between mammography and CT scans for screening for lung cancer and meningioma?

Claus At present, we have no data on that at all, but it is interesting in that for a very long number of years it has been presumed, or at least postulated, that there is an association between breast cancer and meningioma, and it is unclear whether the risk factors are common that many of the hormonal risk factors might be associated with breast cancer and might also be associated with meningioma. There is a supposition that perhaps some of the treatments for breast cancer, including radiation to the breast or the chest, could potentially be one mechanism for meningioma causation, but we do not know that. We really have no data on that at all. In the study that we ran it was adult patients, so the average age was about 57 to 58, although we asked people about their exposure and prior head CTs, because of the age of these patients they really would not have had an extensive history of head CTs because they were born before the time that these things were used very frequently.

Chagpar We are going to pick up on that discussion and learn more about radiation and cancer right after we take a short break for a medical minute.

*Medical
Minute*

This year over 200,000 Americans will be diagnosed with lung cancer and in Connecticut alone there will be over 2,000 new cases. More than 85% of lung cancer diagnoses are related to smoking, and quitting, even after decades of use can significantly reduce your risk of developing lung cancer. Each day patients with lung cancer are surviving, thanks to increased access to advanced therapies and specialized care, new treatment options and surgical techniques are giving lung cancer survivors more hope than they ever had before. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale to test innovative new treatments for lung cancer. An option for lung cancer patients in need of surgery is a video-assisted thoracoscopic surgery also known as VATS procedure, which is a minimally invasive technique. 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 Public Broadcasting Network.

Chagpar Welcome back to Yale Cancer Center Answers. We are discussing radiation and cancer and specifically talking about one of the most frequent types of brain cancers called meningioma and the association that this has with various types of x-rays. Elizabeth, right before the break we were talking about dental x-rays, and other kinds of x-rays. Tell us a little bit more about that association and the time lag that is required between getting an x-ray and developing a

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meningioma and the dose relationship of that? If we go to the dentist and they never do an x-ray, but just this one time they say “You know, I really need an x-ray,” do we say, “No I might get a meningioma?” How does that work?

Claus We do want to make it clear that obviously good dental care is important and this is not an effort to stop people from going to the dentist, obviously you need to go to the dentist and you need to take care of your teeth, but as with any ionizing radiation source, you need to think about why you are having this x-ray, and that is medical dental, whatever the trip is for, and let us have a conversation about the purpose of it and feel comfortable with your conversation with your physician or your dentist about why it is being done. That was one of the interesting things that we noted when we looked at the dental x-ray history and meningioma risk, is we simply ask people over the past few years how frequently they received a dental x-ray and the majority of people were receiving some sort of dental x-ray every six months, or every 12 months, so what we did was we then looked at the Food and Drug Administration guidelines and the American Dental Association Guidelines, which if you go to their website they have a very nice listing with the guidelines and go through all the details of how they come to these guidelines which are certainly very reasonable, and on that we noted that the guidelines for an adult who is not at increased risk of having dental problems, the suggested frequency was every two to three years. I think that was interesting that what people were reporting on average was a bit more than what we saw the guidelines suggest. Now, obviously the decision has to be made between each dentist and their patient, but I think it would be of interest to individuals to take a look at the guidelines and next time they go to the dentist or their doctor, maybe think about what sort of screening schedule is right for them.

Chagpar I guess the other thing too that we were talking about was other forms of radiation outside of the dentist’s office and certainly getting radiation therapy if you have a cancer, for example, a breast cancer, one would think that you would still recommend carrying on with your radiation therapy after your breast cancer rather than worrying about the effect that this could cause in terms of potentially increasing your risk of meningioma.

Claus Absolutely, this is not to change anyone’s treatment plan for any sort of malignancy that they may be undergoing, this is more in line with if you are receiving something that is a screening form of ionizing radiation to just think it can add up over the years, particularly now with the increasing use of CT be it for the head or another body part, just thinking over time these things can add up. There was actually a very nice paper in The New England Journal about two or three years ago from a group here at Yale looking at cumulative exposure to low dose ionizing radiation and really showing that as the years increase, the number of people that have somewhat significant amounts of exposure to ionizing radiation through PET scans or CTs or whatever they might be using is increasing quite a bit, so just think about what the goal of the imaging is.

Chagpar One other question that comes to mind, just a few weeks ago, or perhaps a little longer, we were talking to some of our colleagues in endocrine surgery, and endocrine cancers and they were talking about radioactive iodine and how this was kind of like a silver bullet in the sense that the

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thyroid is one of the few organs that actually can harbor iodine and incorporate this into thyroid hormones and when you attach a radiation dose to that iodine we can really target thyroid cancers. Has that been looked at as a potential risk factor for meningioma?

Claus We did ask individuals in our study about that and we found that as noted here that people that had previous therapeutic radiation including for treatment of the thyroid were at increased risk but we had so few individuals that had had previous treatment to the thyroid to say something specifically about that, at least in our study.

Chagpar And then it gets back to a similar kind of conversation that we were having with regards to childhood malignancies and whether there is something perhaps genetic that links multiple cancers together. Tell us a little bit about some of the genetic causes of meningioma, or have people looked at that?

Claus We are just starting to look at that. There is one well known syndrome, neurofibromatosis 2 or NF2 and that is a change on chromosome 22 that is associated with not only meningioma development but development of other tumors as well. Outside of that though very little is known about the genetics of meningioma. We are undertaking a germline study, meaning looking at DNA from blood or saliva now in about 1600 individuals with and without meningioma and we have the data up and running right now. We are just about to start to analyze that. And then two groups, recently one from Brigham and Women's Hospital and one from Yale University looked at the genetics of the actual tumors themselves and did find some very interesting outcomes. They found a number of genes associated with the development of meningioma and what was very exciting is the two groups had some overlap of findings, which is sometimes rare in the world of cancer genetics. So, we are hoping to go forward and look at some of those things. Also to look at the genetics of individuals who develops these radiation associated meningiomas. We think that it is likely a special group because all of this is not only exposure, but the way that your genes are set up and when the exposure meets your genotype some people are more or less likely to develop these tumors.

Chagpar And so as we start to put this story together we have got these genetic factors in play and the ionizing radiation, talk a little bit more about the hormonal factors, the hormone replacing therapy, that has been shown to be as significant or more significant than oral contraceptive use that you were talking about earlier.

Claus It has always been very intriguing, this potential association between hormones and meningioma and as I mentioned, just the fact that this is a diagnosis that occurs three times more frequently in women versus men and when you look at the increase it is most marked before menopause. And although women are always at increased risk relative to men, the difference in risk really drops as women pass through menopause. As I said, there are also hormone receptors on the tumors. We looked and did find a slight increase in risk in young women currently using oral contraceptives.

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But, what is hard to study now is the fact that most meningiomas occur in older woman so they would not be using oral contraceptives and now most woman are not using hormone replacement therapy, so the exposure in the groups have kind of separated and it is hard to look at this. I do have a number of patients that ask me about fertility medication, and if that increases their risk. We had a very small number of people, and we did not find an increased risk, but again, I would say that the number of women we had that had used fertility medications was pretty small. We did interestingly find that the heavier you were, than the higher the circulating estrogen, so the greater your risk of meningioma. We found a decreased risk associated with ever breast feeding and a decreased risk associated with smoking, not to send everybody out to buy a cigarette.

Chagpar Do not smoke.

Claus Do not smoke, but there is a well-known relationship that women who smoke tend to have lower circulating estrogen. So this sort of a reverse association between cigarette smoking and outcome and it has been seen in uterine cancer and other sorts of hormone related cancers.

Chagpar If we have these genetic factors that we now know about, or we are learning about, and we know about the association with ionizing radiation and the association with estrogen, can we screen people who are at high risk for meningioma and are there preventative strategies for preventing meningioma?

Claus At this point in terms of risk benefit, there is no suggestion that screening would be something that would have a high enough benefit, at least in the general population, to undertake. One thing patients do ask me, because we have seen it even among families who we do not believe to have NF2, we so see an increased risk to family members. In our data set we saw about a four fold increased risk to family members of people that had been diagnosed with meningioma. There is always some bias in the sense that if a family member is diagnosed with some sort of tumor you tend to look more closely in other family members. In addition, many meningiomas although individuals may have a diagnosis of this tumor, they are clinically silent and you might not need to ever have any intervention. So there is no plan for any screening at this point in time and it is not clear if they are not significantly significant whether you for many of them need to do anything anyway.

Chagpar So even things like if you have a family who was not NF2 family and you had in that NF2 family a child who went to the dentist every six months and got dental x-rays and then as a young female was using oral contraceptives, who presumably would be at high risk you would simply tell them, you know, you are at the high risk but there really is not preventative strategies as there are, for example, in breast cancer where we may say, you know, we can reduce your risk by giving you an estrogen blocker or whatever.

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- Claus Exactly, so the NF2 patients are one of the category and they actually are screened and followed separately and there are specific guidelines for those individuals for a variety of organ systems but presuming that someone is not an NF2 patient there are no set guidelines for screening or prevention, you know, other than sort of the general guidelines of try to keep your weight down and try to stay healthy.
- Chagpar Okay, and do not smoke.
- Claus No there is a reverse association, don't smoke correct.
- Chagpar So then if people are at risk but we are not necessarily doing kind of screening tests which would make sense because we want to reduce ionizing radiation. How do the patients present, I mean I remember the story that you told of the guy driving down the highway and having a seizure, hopefully, there are other ways that meningioma is present if they occur in 1% of the population.
- Claus So, the majority and actually the one percent was a study in Europe where they looked at about 3000 healthy adults and they got an MR of the brain and then look to see what they found. In those individuals about 1% had meningiomas but they were all asymptomatic and likely the majority would never have had an issue that would have come to clinical attention. We see all sorts of presentation so it depends a little bit on where you are in the brain, frontal lobe, personality change, motor strip weakness, and some are incidental but in most instances we can follow individuals and if not we take care of them with surgery and radiation.

Dr. Elizabeth Claus is a Professor of Public Health and Biostatistics and is Director of Medical Research at the Yale School of Public Health. If you have questions or would like to add your comments, visit YaleCancerCenter.org where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.