

Yale CANCER CENTER *answers*

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Detecting Lung Cancer Early

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Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss, Anees Chagpar and Steven Gore. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at Yale Cancer Center. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital and Dr. Gore is Director of Hematological Malignancies at Smilow. 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. This week you will hear a conversation about lung cancer with Dr. Dan Boffa. Dr. Boffa is Associate Professor of Surgery in the section of Thoracic Surgery at Yale School of Medicine. Here is Dr. Anees Chagpar.

Chagpar Dan, we hear a lot about lung cancer, but tell us a little bit more about how many people get lung cancer and how many people die of it in this country.

Boffa Lung cancer affects about 200,000 people each year in the United States, and it is one of those cancers that is one of the most dangerous cancers, meaning that at every stage, stage I, II, III and IV, the lung cancer is more likely to shorten your life than a lot of other cancers that you commonly think of such as breast or colon. With 200,000 new cases of lung cancer a year, there are about 150,000 deaths, so it is a major healthcare problem in the United States. It is the nation's number one cancer killer.

Chagpar In fact, as a breast cancer doctor, lung cancer is the number one cancer killer of women as well, it overtook breast cancer which is the number one cancer that affects women, but as you say, lung cancer is far more lethal, and one of the reasons for that I think might be that it is harder to detect. I mean, when women come in, they get a mammogram, and we find cancer early, how do we detect lung cancer?

Boffa Historically, lung cancer has not been one of the cancers that we had a good screening test for, so most patients would come to the attention of their doctor when they had a symptom and unfortunately, once the symptom develops, a fair number of patients go beyond the point in which we are able to cure the lung cancer. That all changed with a recent study that was done that looked at the ability of CT scanning to screen patients felt to be at risk for lung cancer and that study, which examined patients between the ages of 55 and 75 that had smoked within the past 15 years and had smoked an average of a pack a day for 30 years, found that it reduced the chances of dying of lung cancer by 20%.

Chagpar Wow!

Boffa That is very likely going to be the most significant research to improve the outcome of lung cancer probably in my lifetime, it is truly an enormous advance in the treatment of lung cancer.

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- Chagpar Does that mean that everybody should get a CT scan whether or not they smoke, should it just be routine like how every woman gets a mammogram over the age of 40, should every person get a CT scan over the age of 50 or is it really for those high risk people?
- Boffa One of the interesting things about the National Screening Trial was that it really is not just a scan. It is picking the people at greatest risk to have lung cancer, but also patients that we can do something about. For instance, it does not help to screen somebody who has a whole bunch of medical problems in which if you diagnose lung cancer, they are not going to be able to tolerate the treatment and benefit from the early detection, and CT scans, because they do have a fair bit of radiation with them. We are now doing low dose CT scans which just means we are able to reduce the amount of radiation, but the fact is, if you are not in a population at a reasonable risk to develop lung cancer, you probably should not be exposing yourself to that radiation. So if you have smoked a pack a day for 30 years on average, or half a pack a day for 60 years, so at Yale, if you have a 30-pack-year average and are between the ages of 55 and actually 80, and you have smoked within the past 15 years and you are otherwise relatively healthy, then we will evaluate you with a CT scan, but one of the real keys to this is it cannot just be a CT scan, screening is a process, and what I mean by that is a scan will find an abnormality in up to 28% of people and the vast majority of these are actually not cancerous and for the balance to work out, the clinicians that are evaluating you must be able to balance the risk of a cancer with the risk of having harm from unnecessary biopsies, unnecessary x-rays, and so on. In order for a lung cancer screening to work, you really need to be evaluated by a program not just get a CT scan in isolation.
- Chagpar Are these things being offered throughout the country where people who are heavy smokers can go and get evaluated by a team of people and get a CT scan that can be appropriately done?
- Boffa Right now Medicare is not covering these CT scans. We have reason to believe that ultimately this will change. Yale, as well as a number of other institutions, are very active in trying to persuade the Federal Government to include this in coverage, but presently, patients are either funding these out of pocket or are participating in free events. Yale has actually sponsored a couple of these in which it is not just the CT scan, but the Yale Nodule Program will offer a free CT scan as well as the entire nodule program or screening program which includes an evaluation by somebody who can help you stop smoking if you are a smoker currently, and a breathing evaluation and so we are really trying to maximize the benefits of the screening process. We actually have an event on November 8th and I am told there are still a few slots available and if any of your listeners are interested, they could certainly contact the Yale Nodule Program; I believe the number is 203-200-LUNG which I think comes out to 5864.
- Chagpar It sounds like a phenomenal kind of program, especially for people who cannot afford to undergo such a process but even for those who can, it seems pretty comprehensive in terms of working up all of the potential issues for smokers, but lung cancer can happen in nonsmokers too right, so what happens with them?

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Boffa One out of seven lung cancers will happen in somebody who is a lifetime nonsmoker. There are other established risk factors for lung cancer, some of them are environmental, such as radon or arsenic or even asbestos. Some of them were exposed to secondhand smoke and there certainly is a genetic component. Patients with a family history, for instance, are at an increased risk of developing lung cancer. Right now, the screening guidelines have not addressed that population as far as the risk. Ultimately, I suspect that people with a family history will be included in screening protocols, but at present, they are not.

Chagpar What proportion of people who get lung cancer are smokers versus nonsmokers?

Boffa A smoking history can be elucidated in about somewhere around 85% of people who are diagnosed with lung cancer. What is unclear is whether or not all of those are directly linked to the smoking. The vast majority we believe are smoking associated cancers; however, if you think about it, if one out of seven is destined to happen in somebody without a smoking history, some of them may have happened to have smoked at one point in their life and certainly the nonsmoking associated cancers appear to have a different biology and come about through a different mechanism and present their own set of treatment and outcome issues.

Chagpar I want to get into the treatment issues and the nuances of smoking versus nonsmoking related cancers, but just to kind of wrap up something that you said when we were talking about screening, you had mentioned that many of the screening protocols allowed for CT scans if you had smoked more than a 30-pack-year history within the past 15 years, so that means that even if you quit 14 years and 364 out of 365 days ago, you would still be offered screening? Is there ever a time when your risk actually disappears, like you can be forgiven for the mistake of smoking years ago?

Boffa The consequences of smoking on a person's health are multifactorial and if we just think about the cancer consequences, specifically lung cancer consequences, lung cancer in smokers is actually not the most common cause of smoking associated death. Only 6% of smokers will be diagnosed with lung cancer. Smokers are much more likely to have their lifespan affected by emphysema and cardiovascular diseases. Both of those respond very predictably to quitting smoking, so people that quit smoking, pretty much right after they quit, will have a benefit in their long-term survival. Now there are a number of studies that have examined the impact of ongoing smoking once you have been diagnosed with lung cancer, and the outcomes appear to be better in people that quit smoking as opposed to people who continue to smoke, so without question, if somebody is to quit smoking really at any stage of their life, they do a tremendous amount of benefit to prolonging their life and that is why we think this is an integral part of the screening process. Now, why it would take 15 years to develop a lung cancer or why that window is tailored the way it is, the study that has led us to support screening, the investigators had to design the population they felt to be at highest risk. There certainly is a dropping off of your risk the longer you go without smoking. It never returns to that of a nonsmoker but there is a predictable decline in your smoking

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associated cancer risk the further you get out from quitting, so if you are thinking about quitting, the sooner the better, but there really is never a point in time where quitting does not have very real pay off as far as your overall outcome.

Chagpar We are going to pick up on smoking and lung cancer right after we take a short break for medical minute. Please stay tuned to learn more information about lung cancer with my guest, Dr. Dan Boffa.

Medical Minute

The American Cancer Society estimates that in 2014 over 45,000 new cases of pancreatic cancer will be diagnosed in the United States. Pancreatic cancer is the fourth most frequent cause of cancer death. Clinical trials are currently underway at federally designated comprehensive cancer centers, such as Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven to make innovative new treatments available to patients. Clinical trial participation is offered for treatment of advanced stage and metastatic pancreatic cancer using chemotherapy and other novel therapies for the disease. FOLFIRINOX, a combination of five different chemotherapies is the latest advancement in the treatment of metastatic pancreatic cancer. There is continued research being done at centers like Yale and around the world looking into targeted therapy and a recently discovered marker hENT1. 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 the WNPR, Connecticut's public media source for news and ideas.

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined tonight by my guest, Dr. Dan Boffa. We are talking about lung cancer, and before the break, we were talking about the screening which is a protocol that is offered in this really great multidisciplinary fashion with smoking cessation and all kinds of risk assessment for smokers with CT scans, but what we discovered in our conversation is that nonsmokers can also get lung cancer but more interestingly, the two are very different, cancers that arise as smoking-related cancers versus nonsmoking-related cancers. Dan I wanted to pick up on our conversation there. Tell us a little bit about how the two are biologically different, genetically different; can you tell that these are different just at a molecular level?

Boffa There are differences that trend across pretty much all of the aspects that you mentioned. The population statistics are very different. We see these classic nonsmoking-associated cancers more often in Asian populations, and they are more common in females. The types of cancers as they look under the microscope are much more weighed towards the adenocarcinomas, lung cancers. There are two big umbrellas of types of lung cancer; there are small cell and nonsmall cell which are about 13% of all lung cancer, is highly associated with smoking. Of the nonsmall cell, there is adenocarcinoma and squamous cell carcinoma. The nonsmokers tend to be much more heavily weighted to adenocarcinoma, and from a molecular standpoint, there are certain mutations that are much more common in the nonsmoking population and mutations or abnormalities in the DNA

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and the ones that we are really interested in are the ones that allow us to use what we call targeted chemotherapy that is specific to the cancer cells, that is different from most chemotherapy which happens to kill cancer cells but also affects the entire body. Targeted therapy certainly can have effects throughout the body but is much more targeted towards the cancer cells that have these mutations.

Chagpar So wait a minute, you are telling me that somebody who does not smoke who gets lung cancer can get these genetic abnormalities that you can target with certain targeted therapies, whereas people who get lung cancer due to smoking, either do not have the same genes or have different genes?

Boffa There are different frequencies in the two populations. There are certainly patients with smoking-associated cancers that have mutations and it is seemingly every month that a new mutation is discovered that allows us to apply a new form of targeted therapy. The pattern is distinct though. We see certain EGFR mutation frequencies that are much different and much higher in the nonsmoking patient populations than we seen in the smoking patient population, but both smoking-associated cancers and nonsmoking-associated cancers are the focus of a great deal of study to identify these targetable mutations, and we have a number of clinical trials both in smokers and nonsmokers looking to take advantage of these mutations, so certainly if somebody were to be diagnosed with a cancer and had a smoking history, there are certainly a number of mutations and targeted therapies that are being explored to treat those patients as well as the nonsmokers.

Chagpar You used a term which many of our listeners may not be familiar with, EGFR. Tell us a little bit more about EGFR and what it is and why it is important in lung cancer.

Boffa Under normal conditions within the body, there cells react to signals from their environment and EGFR is one of those proteins on a cell whose responsibility is to transmit the signal from the environment into the cell, and of the many reactions that signal can have, one is to stimulate growth, and you can imagine, if you had a fire alarm that was malfunctioning and was constantly giving the signals to react, there would be great consequences within the building in which that fire alarm is going off. Well, if the EGFR pathway is abnormal, the response to divide can be abnormally affected by this abnormal signaling through this pathway and so there are a class of compounds or medications that target this pathway to blunt the effect of this signaling and it turns out that a certain number of cancers become addicted to this signal and blocking this signal actually greatly reduces the cancers ability to grow and potentially spread. We have a whole range of medications that are coming out to target not just EGFR but a number of signaling pathways that cancer cells appear to be functioning abnormally and the cancer cells become somewhat addicted to.

Chagpar Dan, you are a surgeon, are all lung cancers treated with targeted therapies or chemotherapies or are some treated with surgery as well? How does that work?

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- Boffa Whenever we meet a patient, we must first decide where the patient's cancer is presently and often patients will have something abnormal on an x-ray or a CT scan that may or may not reflect what is going on throughout their entire body. If a cancer is contained within the lung and the lymph nodes in that area, then they are potentially curable with surgery, possibly the use of chemotherapy or radiation in combination, sort of multi-modality or single-modality plan. There are patients in which the cancer has either spread already, and we can see that on the scans, to other vital organs or whose tumor has other features that lead us to believe they are very likely to have microscopic spread. And while surgery gets safer and safer every year, it does not make sense to go down that pathway if the cancer has already spread. I give the analogy to patients that if your house catches on fire because of the furnace, if the whole house is on fire, you do not risk your life to go remove the furnace, so most of my patients are patients where their cancer remains contained where it started within the lung and we have a number of advances to minimize the impact of surgery on the patient's health and probably on their ability to receive additional treatment, so we specialize in minimally invasive surgery which is doing the traditional lung cancer operation, but through smaller incisions without traumatizing the chest wall, so we usually do not crack, break or spread any ribs. We just go through small incisions using a camera to conduct the cancer operation.
- Chagpar Is that similar to how people take out gallbladders these days instead of making a big cut like they used to?
- Boffa That is exactly right. The key, much like with the gallbladder, is that doing surgery through small incisions has to follow the same principles, and because it is a cancer operation while small incisions are nice, you have to follow the principles, meaning you have to completely remove the tumor, you have to ensure it is surrounded by a rim a normal tissue, you have to evaluate the lymph nodes and we do that with a minimally invasive approach; however, if it seems that the tumor is more extensive, then we use traditional approaches but with modifications, in that we do not cut any other big muscles of the chest wall, we just sort of spread them out of our way.
- Chagpar We have talked a little bit about targeted therapy which is a form of chemotherapy and a bit about surgery, but you mentioned in passing radiation, where does radiation fall into the whole paradigm of how we treat lung cancer?
- Boffa If you had to take therapy and separate it into two broad categories, chemotherapy being through the bloodstream addresses the whole body, whereas local therapy is targeting areas in which you see tumor on the CT scans. Radiation is like surgery in that it is a form of local therapy and we use radiation in combination with surgery in patients who are at risk to have the tumor recur or show up again in tissues that are not able to be removed at the time of surgery. One example would be if a tumor came close to a part of the heart and we remove the tumor completely but there were lymph nodes near the heart and main windpipe, we know that despite removing every visible lymph node, there is a chance that it can come back in the microscopic lymph nodes and so we will add radiation to those patients. There is also a form of radiation which is called stereotactic body radiosurgery, sometimes called CyberKnife at some places, that is a much more aggressive form of

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radiation and that is a treatment we use in patients in place of surgery if they are either too sick to have surgery or if we feel that the consequences of surgery would leave them with an unacceptable quality of life. A lot of our patients do not have normal lungs and at the end of the day, we want our patients to live as long as they can, as well as they can, and we do not help anybody by curing them of cancer and leaving them unable to do the things they want to do to enjoy their life and so we certainly have some patients where we will treat them with radiation because we are concerned that a surgical intervention would leave them incapacitated.

Chagpar I love that line that you used, which was, we want our patients to live as long as they can, as well as they can, and I want to come back to a couple of points that I heard you say just to get some clarification. One is that you used the term cure a few times, is this really a disease that you cure and people can live a long time without getting their cancer back? How much hope can you give patients with lung cancer?

Boffa We cure patients that are stage I. We cure the majority of patients. As the stage goes up, the cure rate certainly goes down. We used to think of cancer like a broken arm, you either fix it or you do not. Now in many cases we treat cancer more like a chronic disease, more like diabetes, so that when it is a problem, we treat you and when you respond and you go into remission, we back off and we follow you. So again the equation remains the same. We want everybody to live as long as they can, as well as they can and we have to balance the benefits of treatment with the risks of treatment.

Dr. Dan Boffa is Associate Professor of Surgery in the section of Thoracic Surgery at Yale School of Medicine. We invite you to share your questions and comments, and 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 format at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another addition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.