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Welcome to Yale Cancer Answers with your host, Doctor Anees Chagpar. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it’s a conversation about lung cancer with Doctor Roy Herbst.

Doctor Herbst is Ensign Professor of Medicine and medical Oncology, an professor of pharmacology at the Yale School of Medicine, where Doctor Chagpar is a professor of surgical oncology.

Maybe we can start off by talking a little bit about the Epidemiology of lung cancer, is it still one of the leading cancers and the leading cause of cancer related death? Lung cancer still is unfortunately the number one cause of cancer worldwide with maybe 1.6, 1.7 deaths a year by incidence.
It’s not the number one cancer diagnosed. Breast cancer is diagnosed in women, and prostate cancer in men. But by death, it certainly is the major killer because it tends to present in a metastatic way, already having spread. And we have seen improvements in survival but there is still work to do. I wanted to start off there and get into some of the recent advances in screening and treatment. Smoking cessation is the best way to treat lung cancer, and we saw that breast cancer and prostate cancer kind of pulled ahead several years ago. And in part, I think that that was related to some advances that were made in terms of lung cancer. Primary prevention. In other words, not getting lung cancer to begin with. Do you want to kind of talk about some of that? Particularly where it pertains to smoking cessation? Right, the best way to treat lung cancer still is to prevent it, and certainly even though there
0:02:19.345 –> 0:02:21.83 is a very real group of patients
0:02:21.83 –> 0:02:23.948 with a non smoking lung cancer,
0:02:23.95 –> 0:02:26.93 as many as 15% or more of patients in the
0:02:27.008 –> 0:02:29.92 United States about double that in Asia,
0:02:29.92 –> 0:02:32.504 still smoking is one of the primary
0:02:32.504 –> 0:02:34.837 reasons for causation and lung cancer.
0:02:34.84 –> 0:02:37.094 So major efforts have been underway over
0:02:37.094 –> 0:02:39.977 the last 50-60 years in the United States
0:02:39.977 –> 0:02:42.31 since the initial Surgeon General’s report
0:02:42.31 –> 0:02:45.256 to stem the tide of smoking.
0:02:45.256 –> 0:02:47.826 We’ve gone down from 50% of Americans
0:02:47.826 –> 0:02:50.034 smoking, perhaps to less than 20%,
0:02:50.04 –> 0:02:51.472 maybe 18% or so,
0:02:51.472 –> 0:02:52.904 differing among different groups
0:02:52.904 –> 0:02:54.09 in different states,
0:02:54.09 –> 0:02:56.286 but we still need to do better.
0:02:56.29 –> 0:02:59.323 But smoking clearly is a cause and now we
0:02:59.323 –> 0:03:02.18 worry as we’ve really worked on smoking
0:03:02.18 –> 0:03:04.015 both with education and
0:03:04.015 –> 0:03:05.483 with medications, with counseling.
0:03:05.49 –> 0:03:07.898 Now we see this big surge in E-
0:03:07.898 –> 0:03:10.354 cigarette use and we worry and I’m
0:03:10.354 –> 0:03:12.134 very involved with the American
0:03:14.661 –> 0:03:16.978 The task force on tobacco control.
0:03:16.98 –> 0:03:18.73 We’re actually looking very carefully
0:03:18.73 –> 0:03:20.81 at E-cigarettes because we worry
0:03:20.81 –> 0:03:22.994 that these are being used now by
0:03:22.994 –> 0:03:24.747 children and young adults
0:03:24.75 –> 0:03:26.31 and they’re filled with nicotine,
0:03:26.31 –> 0:03:27.865 and nicotine is the addictive
substance in cigarettes,
so people are getting addicted to nicotine.
And then they go to what’s called dual use and start to use combustible cigarettes, the type we’re most familiar with.
And then of course the story is all too familiar, and this is important to tell you here in New Haven where we live. 
the rates are probably a bit higher than the national average and we’re doing a lot of work with community programs.

We tried to use new methods to help them stop smoking, new messaging tools, so that’s still such an important part of this field to not smoke also we have to worry about other risk factors.

Asbestos,
radon gas is something we all think about here.
living in Connecticut, all these things can be a risk factor for future development of this disease. So I want to pick up on a couple
of things that you said just quickly. So the first was your study looking at new messaging techniques. Roughly 20% of the population smoke and for many of them it is very difficult to quit. There are all kinds of things out there. There’s quitlines, there’s patches, there’s gum, there’s behavioral modification. Some people even advocate paying people to quit smoking, and some people are even suggesting that E cigarettes can be used as a bridge to help people to quit smoking. So for our listeners out there, the 20% who may be smoking as they listen to this, what’s the best way to quit and where can they get help? Well, first of all, I would definitely ask for help. That could be your physician. That could be a nurse practitioner. Just whoever you see for your regular health checks. Some of these quit lines can be extremely helpful, and there are a number of ways to work on quitting, and now this is an addiction.
and it is hard to quit, especially if you’ve been using cigarettes for a long time. The nicotine is really hard to beat, so there are a couple of ways to do it here in our smoking cessation clinic, they will assess each person on an individual basis. There are certainly ways to substitute for the nicotine other than a combustible cigarette that you smoke. There are certain medications that can help, but then of course, behavioral modification and counseling, which I think is so important here at Yale, where we have an amazing center of emotional intelligence and there have been studies done to show that different types of messaging can be more effective than others. For example, many of you have seen cigarette cartoons. Not so much in the United States, but around the world where there are these horrible images of people and the consequences of smoking. Those are very negative type messages, but they’re intended to scare people from not smoking. There’s been some thought that more
gain framed messaging where you might show well if you don’t smoke, you’ll feel better if you don’t smoke, your skin will look better. That could be another way of doing it. We’re testing some of those new methods here at Yale. The other thing we’ve done is a biofeedback approach, so we actually have an infrared device that can measure carotenoids in the skin and the health of the skin which we know actually can get somewhat destroyed with tobacco use and we actually are using that sort of biofeedback with patients to try to maintain them from using tobacco. So we’ve been working very hard on this. Lisa Fucito leads this effort now in our clinic and we’re trying to serve as many patients as possible. And by the way, it’s not just lung cancer. About 20 different cancers that all can trace their origin back to smoking and we are really trying to work on this. It’s something that’s now as part of our medical record. Everyone’s asked the question about tobacco use.
And primary prevention is just so important, but even if someone has smoked and many people have and they stopped they are still at risk of developing lung cancer and this is where screening comes in and the idea that you can do a low dose CAT scan to screen for lung cancer. And I’m very proud to say that even during this very difficult year with covid and clinics closed or moved, we’ve actually had a very strong year number wise in the number of patients in the area that we’ve screened. So screening patients and finding cancers early in people at high risk is also a very important tool that we’re using. I think the last question before we move on from smoking cessation is I wanted to get your thoughts on taxation. So certainly in some parts of the world they’ve found that making it hurt in people’s pocketbooks is often a deterrent to smoking.
Do you advocate that governments should put stiff taxes on cigarette purchases to make that less appealing?

Well, that a tough one. You know, different states do different things.

I still remember once being in a drug store in New York City and someone came in for a pack of cigarettes. And it could cost up to $15-20 with some of the different taxes and I think people will find the cigarettes elsewhere.

I think it’s a useful technique but it would have to be a universal sort of technique. Otherwise people will find ways of getting cigarettes.

I’m much more in favor of some of the approaches I mentioned, whether it be counseling, medications.

I think that the E cigarettes as a substitute for someone who’s tried everything else could work in that way, but it has to be studied in a regulated way.

You know there needs to be a clinical trial and we’re actually trying to do some of those here right now at Yale, especially now with some of the covid regulations.
But it would be nice to see if we can use these cigarettes in a measured way. With a prescribed dose, there are other forms of nicotine replacement, but clearly stopping people from smoking whatever method is used because it’s a National emergency despite the fact that it’s so much better than it was really the only good level of tobacco use is none. And you worry also about the E cigarettes being yet another addictive substance and we don’t really know long term what the health consequences are of that. The other thing that you mentioned was that there are many lung cancers that happen for reasons outside of cigarette smoking. For example, you mentioned in Asia about 50% of lung cancers are not related to cigarette smoking, and I wonder whether you think that there are some environmental issues that we need to consider. I mean is this part of the pollution that we’re seeing in terms of manufacturing and so on that might be greater in some industrialized parts
We're talking about the non-smoking lung cancer which initially was due to the epidermal growth factor receptor mutation that was discovered more than 20 years ago and those levels are much higher in Asia than in the US. About double, 30 to 40% versus 15 to 20%.

I don’t know that it’s environment because if someone is born in Asia and moves to Southern California, it seems like they have the same higher risk. So I think there’s something genetic which amazes me with all the tools we have now to sequence genomes and we can sequence dozens and dozens of patients each day. We still have not found what the link there is. What is the genetic factor? It’s being looked at quite intensively. It’s this cooperation between researchers around the world. But we still don’t know exactly why these mutations in epidermal growth factor receptor are so much more common in Asia than the US, but we’re looking for it and learning how to treat that type of cancer.
0:12:09.563 → 0:12:11.66 cancer with oral agents.
0:12:11.66 → 0:12:13.14 It’s actually been historic.
0:12:13.14 → 0:12:14.892 I think that’s part of the reason we’re seeing a couple percent a year decreases in the death rates from lung cancer because of what we call targeted therapy.
0:12:22.35 → 0:12:24.429 But even when those drugs work, patients will become resistant.
0:12:27.742 → 0:12:29.94 as you know, patients will become resistant.
0:12:33.325 → 0:12:35.505 That’s actually something we’re studying very much here in our group. NOTE Confidence: 0.8304425
0:12:35.505 → 0:12:37.642 Katie Politi and Sarah Goldberg and Mark Lemon actually is one of the projects on our big lung Spore Grant looking at mechanisms of sensitivity and resistance to these drugs so that we can help more patients develop newer and better, more effective and less toxic ways to treat this disease.
0:12:48.79 → 0:12:51.574 Yeah, and as we kind of think about lung cancer and the fact that it no longer is the number one cancer in people thanks to reduction in smoking cessation and other things, it still remains the number one killer in terms of being the number one cause of cancer related morbidity.
and mortality. Has that reduced in recent years thanks to some of the things that we’ll be talking about in terms of understanding the genomics and tailored therapy and so on. Are we seeing the needle move? Oh absolutely, and I’ve seen this myself, so I started working in this field about 20-25 years ago as a young fellow at Dana Farber Cancer Institute actually, and no one even wanted to work in this field. Back then, it was really a death sentence if you had lung cancer, we had surgery and radiation techniques, but if it had spread the chemotherapy was OK, but really didn’t do much. And I think over the years we’ve really taken the five year overall survival for lung cancer, which was in the low teens 10-11%, and now it’s as high as 19% or more. Now that’s all across all stages, Four being the most advanced, but that’s progress. But the real progress that we’re seeing is identifying a more personalized approach to this disease and learning how to treat it with
some of these new targeted therapies.
Learning how to treat it with immunotherapy.
And yeah, I’ve seen patients now in 2021 who now come here to our clinics and they either get standard care or clinical trials.
A smaller proportion increasing every day are doing better, so there is definitely progress visible progress in this field.
And understanding the science, what drives the lung cancer, what’s causing it to grow and how to treat it in more effective ways.
We’re going to talk all about that right after we take a short break for a medical minute.
Please stay tuned to learn more with my guest. Doctor Roy Herbst. Support for Yale Cancer Answers comes from AstraZeneca working to eliminate cancer as a cause of death.
This is a medical minute about genetic testing which can be useful for people with certain types of cancer that seem to run in their families.
Patients that are considered at risk
receive genetic counseling and testing so informed medical decisions can be based on their own personal risk assessment. Resources for genetic counseling and testing are available at federally designated comprehensive cancer centers. Interdisciplinary teams include geneticists, genetic counselors, physicians, and nurses who work together to provide risk assessment and steps to prevent the development of cancer. More information is available at yalecancercenter.org.

You're listening to Connecticut Public Radio. Welcome back to Yale Cancer Answers. This is doctor Anees Chagpar and I'm joined tonight by my guest Doctor Roy Herbst. We're talking about recent advances in the management of lung cancer patients and Roy, right before the break you were telling us that you have seen visible progress in terms of reducing lung cancer mortality. This remains the number one cancer killer of Americans, both men and women, but we’re seeing progress. So there are so many different avenues that we’ve seen in terms of lung cancer management that have contributed to this. What do you think is the greatest driver?
The ACS announced earlier this year a 2% decrease in deaths from lung cancer since 2013.
So clearly something’s happening.
I think part of it is the prevention,
either primary prevention by avoiding smoking and other toxins, or the screening.
But I have to believe a lot of it’s been the therapies that we’ve seen in the last several years.
Understanding the molecular basis of this disease.
Everyone’s cancer is a little bit different,
caused by a different mechanism,
a different genetic background.
So now what we’re doing is we’re taking the patients cancer and we’re performing molecular techniques for sequencing.
We’re looking at what makes it tick now.
What is driving that cancer?
And now there are about seven or eight different different mutations,
different markers that we can then pair with a specific drug.
So we’re personalizing the therapy,
and that’s nice because these are oral therapies,
that you take by mouth and are much less toxic than the chemotherapy we used to use,
0:17:46.17 -> 0:17:48.186 and we see the tumors shrink in
0:17:48.186 -> 0:17:49.799 a large percentage of patients.
0:17:49.8 -> 0:17:51.31 So many of these started
0:17:51.31 -> 0:17:52.518 out as clinical trials,
0:17:52.52 -> 0:17:53.724 and now they’re moving
0:17:53.724 -> 0:17:55.229 forward to standard of care.
0:17:55.23 -> 0:17:57.646 So I think that’s having a great benefit.
0:17:57.65 -> 0:17:58.866 I’ve seen it myself.
0:17:58.866 -> 0:18:00.386 Over the last 15-20 years,
0:18:00.39 -> 0:18:01.81 certainly within the last decade,
0:18:01.81 -> 0:18:03.508 many approved drugs in this space,
0:18:03.51 -> 0:18:05.526 so you really want to make sure
0:18:05.526 -> 0:18:07.3 that your cancer is analyzed in
0:18:07.3 -> 0:18:09.274 this way so that you have access
0:18:09.338 -> 0:18:10.898 to these drugs now.
0:18:10.9 -> 0:18:11.755 Like everything else,
0:18:11.755 -> 0:18:13.465 nothing is perfect with time
0:18:13.465 -> 0:18:15.319 the tumor will get smart and learn
0:18:15.319 -> 0:18:16.86 how to override these blockages.
0:18:16.86 -> 0:18:18.57 But that’s why we’re doing research.
0:18:18.57 -> 0:18:20.565 All of us that are at different
0:18:20.565 -> 0:18:22.307 centers to try to figure out
0:18:22.307 -> 0:18:23.957 one of the next steps and,
0:18:23.96 -> 0:18:25.948 and we’re continuing to raise the bar,
0:18:25.95 -> 0:18:27.294 but that’s certainly been
0:18:27.294 -> 0:18:28.974 one of the major advances.
0:18:28.98 -> 0:18:30.56 The second has been immunotherapy,
0:18:30.56 -> 0:18:32.536 and the idea that we can
0:18:32.536 -> 0:18:34.489 use the body’s own immune system
0:18:34.489 -> 0:18:36.583 to attack the cancer really began
0:18:36.651 -> 0:18:38.456 in Melanoma and kidney cancer.
But lung cancer being so common, we’re seeing just amazing results that we can now actually take a cancer that’s already spread throughout the body and we can treat with one of these immunotherapy drugs. And we’re doing that now.

And when we do that, actually in about 20% of the patients we see amazing results and the rest sometimes we see some activity and others we don’t, so we have to do a little bit more, but these are patients who never before would have had any hope of doing well on some of these therapies. And then if that all was not enough, we’re taking all these therapies that work in the most advanced stages and we’re moving them earlier and earlier in disease.

I can tell you one thing that I’ve seen over my career is the best drugs work best when they are used in the earliest possible stage after surgery, when the burden of lung cancer is the lowest. So now we’re doing what’s called adjuvant therapy, and I was very fortunate to actually
present last year

some data where an EGFR inhibitor used

after surgery had really high impact

on how patients did after that surgery,

so the sky is the limit.

Research in this area is paying off.

We’re seeing tangible benefits,

but when I could also say and tell you,

I’m sure many listening to this

notice from their own experience,

we still have to do even better,

and that’s why research, science,

operative work working together

is going to be so important,

and that’s the type of programs that

we lead here at our center.

Roy, let’s dig into a few things

that you talked about.

So the first was targeted

therapy and Genomics,

and we’ve talked a lot on this show

about kind of unpacking that concept

in a variety of different cancers.

and really trying to figure out what

are the main drivers in lung cancer,

so are all lung cancers kind

of profiled in this way?

And are there particular mutations that

have druggable targets that you look for?

Well, certainly all lung cancers

when they’ve already spread
From the lungs are what we call non squamous lung cancers, which the majority should be profiled in this way. And actually it’s my belief we actually should probably profile all of them to understand one of the determinants that are causing that cancer to grow because that will allow us to match with the best therapy. Now I’m concerned you know one of the big issues we have is access to care and making sure all patients get this screening done. One thing we’re doing a lot of work on is to try to get navigators out to all the different areas of the city to build trust. Within Connecticut we want every patient to have access to coming to a center where they can have their tumor profiled. But yes, if you profile the tumor, there’s probably as much as a 20% chance you’ll find something that will allow you to match that patient with an oral drug, which in my opinion is certainly preferable to giving a nonspecific chemotherapy, so that’s a huge advance. And we’re continuing to find more of
these and new combinations that can be used.

So yes, that’s what we call precision guided therapy and for the patients who don’t have one of these mutations, do they get standard chemotherapy and have there been any advances in terms of standard chemotherapy for those people who either don’t have a druggable target or who have a druggable target, and who recur? Well, incredibly, the answer is yes.

So I mentioned immunotherapy already. So if someone does not have one of those targets, we actually can look for another target, something called PDL1, now PDL1 actually was in part discovered by Lieping Chen, a professor here at Yale, and he’s one of our collaborators, but we actually can measure PDL one and tumors. And if the level is very high, that tells us that the immunotherapy might work alone. So we give those patients immunotherapy, assuming they don’t have some reason we can’t.
Sometimes you can’t reactivate the immune system because someone might already have some bad arthritis or know what we call an autoimmune disease that precludes that. But for the rest of these, again, unless they have a contraindication, we’re giving immunotherapy in combination with chemotherapy. Would have been what I would have guessed would have been such an active therapy, but for whatever reason, when you give chemotherapy and immunotherapy together, you at least have an additive effect, meaning the chemotherapy kills some of the tumor cells, releases some of the proteins that activate the immune system, and then use these drugs that we call a checkpoint inhibitor that unleash the power of the immune system and that’s become a standard of therapy. Now I’ll tell you that those results are really good and much better than what we’ve had in the past. But in my opinion we still have to raise the bar, so that’s where clinical trials come in,
and it would be my big hope that in that room when a patient and a physician or nurse practitioner or whoever is there are meeting, someone brings up, is there a clinical trial? Is there something new that’s looking at a new agent? A new drug, something that might even be more active? And of course, that’s investigation, but that’s really how we continue to do better and better, and we’re inching up the benefits from therapy in lung cancer. So certainly clinical trials.

I mean, we’ve talked on this show a lot about clinical trials and the fact that people who participate in clinical trials tend to do better than people who don’t. Are all of the clinical trials in lung cancer now really geared around targeted therapies and immunoncology or are there any clinical trials that are looking at advances in standard chemotherapy for people who may not be eligible for those other therapies? Either because they don’t have a target or because they don’t have a tumor that’s expressing PDL 1.
Well, standard chemotherapy clearly has its place, and certainly in earlier stages of disease before the tumors have spread from the lung we're using chemotherapy with radiation therapy, for example, and that can be curative therapy. We often add immunotherapy in afterwards, but I actually personally think we've pretty much come as far as we can with chemotherapy. It's somewhat nonspecific. It can have a number of side effects. However, we're finding new targets like right now, just in the last several months, there's been data on a new target against something called Kras. Now Kras, which is an oncogene, actually first came from a rat model. The actual variant of this that now has multiple drugs that are out there is what we call G12C. Probably doesn't mean much to a lot of those who are listening, but it's a specific abnormality that occurs in 12% of lung cancer patients. That's a lot of patients. Remember,
I told you it’s 1.6, 1.7 worldwide and there are actually agents now, not approved yet, but that are in clinical trials showing positive results that can make those tumors shrink. So before I pull off some chemotherapy, which by the way we will do and we do need to use and sometimes we even use it as we’re waiting for a clinical trial to become available. We are beginning to study and use these Kras drugs, and I think that’s going to be the next paradigm. So we’ve gone from chemotherapy to targeted therapy, to immunotherapy, and now Kras which is another target. But it’s a broad target and it always was the Holy Grail, there’s been so many approaches and ways to try to target it. It’s a very difficult target for a cancer because I don’t want to get into too much detail here, just to say that the pocket that we have to block with a drug is so narrow that it’s very hard to get a drug in there to block that.
But scientists and chemists have figured that out. Another example of science drives innovation, science brings new agents to the clinic. Then we test them in the clinic and we test them using samples from patients and a series of very careful studies to bring new things to standard of care. So amazing progress but more that needs to happen. And this brings me to the whole area of clinical trials. For many patients historically they always thought that clinical trials were what you tried when there was nothing else left when you had exhausted all other options when the cancer was metastatic and had spread all over the body, but you’re really talking about clinical trials as being state of the art medicine and that might actually be helpful, particularly in patients who are so fortunate as to have detected their cancer early when it’s not metastatic. Can you talk a little bit more about that? Clinical trials really are the best way and in many cases to you know, treating cancer,
especially when you’re dealing with a situation where you know it is incurable and you’re not able to treat with the standard of care, I still remember the example of the patient, has to be about 8 years ago, we were studying a drug in clinical trial, one of these immune checkpoint inhibitors and he came in with advanced lung cancer. He had already been to see several other practitioners around the state and we had one slot left in this trial and you know we went back and forth and he decided to go on this study and he went on this drug that is now approved and did very well. Eight years later, I still get emails from him. He’s a photographer. He sends me pictures from the wild. This is where a clinical trial can really pay off now, because now many years before approval of a drug, someone took a chance on this trial that the alternative would have been standard of care therapy. So we’re not keeping anything but bring that trial to bear
on that patient really helped him and helped him live a quality life. So that’s what we hope for. That’s why clinical trials are so important.

So now what we’re doing is we’re taking these best therapies in lung cancer, the immunotherapy that targeted therapy when using them after surgery even when we see that there’s no disease.

Knowing that these are high risk of recurrence and those data, some of them are already showing positive results so the field of research and clinical care are one and the bottom line is we want to give the best care for patients at the best possible time.

Dr. Roy Herbst is Ensign Professor of Medicine in Medical Oncology and professor of Pharmacology at the Yale School of Medicine. If you have questions,

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We hope you’ll join us next week to learn more about the fight against cancer here on Connecticut Public Radio.