“Cardio-Oncology: A New Clinical Frontier” (Javid Moslehi, MD) [#129]

Brad Power
January 28, 2025

“The fact that people are living longer with cancer means that heart disease has become more prominent.” – Javid Moslehi, MD

“There are common risk factors that predispose to both cancer and heart disease. For example, everybody knows if you smoke, you have a high risk of having lung cancer and other cancers and a high risk of having heart disease. Now we appreciate that things like obesity, hyperlipidemia, and diabetes are also important risers of not only cardiac disease, but also cancers.” – Javid Moslehi, MD

Meeting Summary

Cancer patients can suffer many side effects on their healthy tissues or organs from their cancer treatment, such as pain, fatigue, anemia, mouth problems, nausea, weight change, dietary issues, and hair, skin, and nail problems, and there can be heart-related side effects and complications. You should monitor your symptoms and speak up about any problems you have to your doctor, and ideally to a cardio-oncologist, to rule out problems and prevent more serious disease. Your health care team can work with you to reduce these side effects.

Dr. Javid Moslehi is uniquely qualified to discuss the intersection of cardiology and cancer care. He is a cardiologist who specializes in the cardiovascular health of cancer patients, cancer survivors and patients with immunological or metabolic problems that affect cardiovascular health. He is the William Grossman Distinguished Professor in Cardiology, Professor in Residence and Founding Chief of a new section focused on Cardio-Oncology and Immunology at UCSF. His research focuses on how diseases of the cardiovascular system impact cancer patients and survivors. He is also interested in inflammatory heart conditions, such as myocarditis. He earned his medical degree from the University of Connecticut School of Medicine. He completed a residency in internal medicine at the Johns Hopkins Hospital. At Brigham and Women's Hospital, he completed a fellowship in cardiology and a postdoctoral research fellowship in oncology. His career includes directing cardio-oncology programs at the Dana-Farber Cancer Institute and Vanderbilt University Medical Center.

Why do you need to know about cardiac issues in cancer?

- **Increasing prevalence of heart diseases in cancer survivors**: Improved cancer treatments mean that more cancer survivors are living with side effects from their treatments, including heart-related issues.
- **Unexpected cardiac side effects**: Many new cancer treatments, even targeted therapies, can have unexpected cardiac side effects like heart failure, hypertension, and vascular issues. Examples of drugs that cause cardiac side effects include Herceptin, angiogenesis inhibitors, and tyrosine kinase inhibitors.
- **Delayed side effects**: Older chemotherapies can have delayed heart effects, leading to heart disease years after treatment.

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- **Hormone therapy side effects**: Hormone deprivation therapy (a standard treatment for breast cancer and prostate cancer) has been shown to increase the risk of diabetes, heart attacks, and sudden cardiac death, especially in observational studies.
- **Monitoring for side effects:** Given the increasing prevalence of heart issues, you need to be tracking your symptoms.
- **Dose dependency**: The risk of cardiac complications is often dose-dependent, so minimizing the effective dose of chemotherapy is important. Radiation therapy to the chest area can also increase the risk of heart disease, with each gray of radiation directly to the heart increasing the risk.
- **Drugs for cardiac health also for cancer.** Metformin and statins are proven to manage cardiac disease and seem to also provide anti-cancer effects.

What are symptoms that may indicate you have heart-related side effects from your cancer treatment that you should pay attention to?

- Shortness of breath
- Chest pain or discomfort
- Irregular heartbeat or palpitations
- Swelling in the legs or feet
- Fatigue or weakness
- Dizziness or lightheadedness
- Decreased heart function
- High blood pressure
- Blood clots
- Artery disease
- Dizziness, lightheadedness, passing out

How can you leverage this knowledge to improve your outcomes?

- **Monitor**: Get cardiac monitoring and management during and after cancer treatment, including echocardiograms, EKGs, and management of risk factors like hypertension and diabetes.
- **Consider some drugs**: Explore the potential benefits of medications like metformin, statins, and beta-blockers to mitigate cardiac risks in cancer patients.
- **Follow the research**: Better understand the common risk factors and genetic predispositions that contribute to both cancer and heart disease.
- **Get multidisciplinary advice**: Be proactive in seeking out specialists in different disciplines to manage your cardiac health.

What are potential heart-protective measures, including possible adjustments to your treatment plan?

- **Exercise**: Incorporate a mix of cardiovascular exercise, strength training, and flexibility activities.
- **Diet**: Choose healthy foods.

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- **Healthy weight**: Achieve and maintain a body mass index (BMI) within the recommended range.
- **Quit smoking**: Seek support from healthcare providers or smoking cessation programs to help you quit.
- **Consider metformin**: It can control diabetes and may have a beneficial effect on prostate cancer.
- **Consider statins**: Helps manage cholesterol and may also have a beneficial effect on prostate cancer recurrence.
- **Adjust your treatment plan**: Such as minimizing the effective dose of your chemotherapy to reduce cardiac toxicity.

What should you do if you have heart-related side effects from your cancer treatment or you want to proactively protect yourself?

- **Follow the "ABCDE" approach**: A: assessment of risk, aspirin; B: blood pressure management; C: cholesterol management, cigarette/tobacco cessation; D: diet and weight management, diabetes prevention and treatment; and E: exercise, echocardiogram.
- **Speak up**: Be diligent about attending your appointments and your cardiac monitoring. Communicate any symptoms or concerns you have to your doctors.
- **Follow recommendations**: To manage your cardiac side effects, you may have adjustments to your cancer treatment plan, medications, or additional monitoring and testing.
- **Consider preventive drugs**: If recommended by your healthcare team, take medications like metformin or statins, which may help mitigate cardiac risks.

How can you learn more?

- Contact Dr. Moslehi at Javid.moslehi@ucsf.edu

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Meeting Notes

KEYWORDS

Cancer patient lab, cardiac issues, cardio oncology, cancer treatments, heart disease, anthracyclines, doxorubicin, cardiac monitoring, androgen deprivation therapy, immunotherapy, cardiovascular risk factors, metformin, statins, accelerated aging, NCCN guidelines.

SPEAKERS

Javid Moslehi (85%), Rick Davis (7%), Brad Power (7%), David Plunkett (0%)

CHAT CONTRIBUTORS

Hilary Elkin, Helene, Rick Davis, Roger Royse, Brad Power, Ari Akerstein, Jack Baruch, John Antonucci, David Plunkett, Jeff Dwyer, Alane Watkins

SUMMARY

Dr. Javid Moslehi from UCSF discussed the intersection of cancer and cardiac management. He highlighted the increasing prevalence of heart disease in cancer survivors due to improved cancer treatments, noting that heart disease now accounts for 700,000 deaths annually in the U.S. Dr. Moslehi emphasized the importance of monitoring cardiac health during and after cancer treatment, particularly with anthracyclines like doxorubicin, which can cause cardiomyopathy. He also discussed the impact of androgen deprivation therapy on cardiac risk factors and the potential benefits of metformin and statins in reducing both cardiac and cancer risks. The discussion included the need for personalized treatment approaches to manage these comorbidities.

OUTLINE

Introductions

- Dr. Moslehi from UCSF will discuss the intersection between cancer and cardiac issues.
- He is a cardiologist trained on the East Coast, with experience at Johns Hopkins and Brigham and Women's.
- His background is in cardiology and research, including work on kidney cancer and heart disease.
- He transitioned to cardio-oncology and established programs at Vanderbilt and UCSF.

Expansion of Cardio-Oncology Program

- The UCSF cardio-oncology program focuses on cancer patients, with five cardiologists seeing patients and a research group advancing the program's mission.
- Cardio-oncology is important in the context of improved cancer treatments and longer patient survival.
- The program has established a fellowship to train specialists in cardio-oncology and immunology.

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Cancer Statistics and Trends

- Cancer statistics from the American Cancer Society compare new cases and deaths for various cancers.
- Lung cancer is the leading cause of cancer deaths for both males and females.
- The trend in cancer deaths over the past few decades is decreasing due to improved treatments.

Discussion on Prostate Cancer Statistics

- Rick Davis questions the accuracy of prostate cancer statistics, citing an increase in de novo metastatic diagnoses.
- Dr. Moslehi acknowledges the controversy surrounding prostate cancer screening and the potential impact of USPSTF guidelines.
- He agrees that the discussion on prostate cancer screening and treatment is complex and contentious.

Impact of New Cancer Treatments on Cardiac Health

- Dr. Moslehi discusses the impact of new cancer treatments on cardiac health, using Herceptin as an example.
- He explains that specific treatments like Herceptin can cause heart failure, despite being targeted therapies.
- He highlights the importance of monitoring cardiac health during and after cancer treatment.
- He mentions the role of the NCCN in introducing guidelines for cardiac monitoring following cancer treatment.

Cardiac Risks of Cancer Treatments

- Dr. Moslehi explains the cardiac risks associated with anthracyclines, such as doxorubicin, and the importance of cumulative dose.
- He discusses the risk factors for cardiac issues, including age and underlying cardiac disease.
- He mentions the need for minimizing the effective dose of chemotherapy to reduce cardiac toxicity.
- He highlights the importance of understanding the cumulative dose and its impact on cardiac health.

Cardiac Risks of Radiation Therapy

- Dr. Moslehi discusses the cardiac risks associated with radiation therapy, particularly in breast cancer patients.
- He references a study that calculated the risk of heart disease with each gray of radiation directly to the heart.
- He explains the interventions by radiation oncologists to minimize the exposure of the heart to radiation.

Androgen Deprivation Therapy and Cardiac Risks

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- There are cardiac risks associated with androgen deprivation therapy (ADT) for prostate cancer.
- A study by Nancy Keating found a significant increased risk of diabetes and heart disease with ADT.
- There is a discrepancy between clinical trial data and observational data on ADT's cardiac risks.
- Monitoring cardiac health in patients on ADT is important.
- There are potential benefits to lifestyle interventions.

Immunotherapy and Cardiac Risks

- Dr. Moslehi discussed the cardiac risks associated with immunotherapy, particularly immune checkpoint inhibitors.
- He explained the revolutionary impact of immunotherapy on cancer treatment, particularly in melanoma.
- He highlighted the cardiac risks of immunotherapy, including myocarditis (inflammation of the heart muscle), and the importance of monitoring cardiac health.
- He mentioned the growing appreciation of common risk factors for both cancer and heart disease.

Cardiovascular Wellness in Cancer Survivors

- Dr. Moslehi introduced the ABCDE approach to cardiovascular wellness in cancer survivors.
- He emphasized the importance of monitoring and treating common risk factors for both cancer and heart disease.
- He discussed the potential benefits of lifestyle interventions, such as metformin and statins, on both cardiac health and cancer recurrence.
- He highlighted the need for ongoing research to better understand the interplay between cancer treatment and cardiac health.

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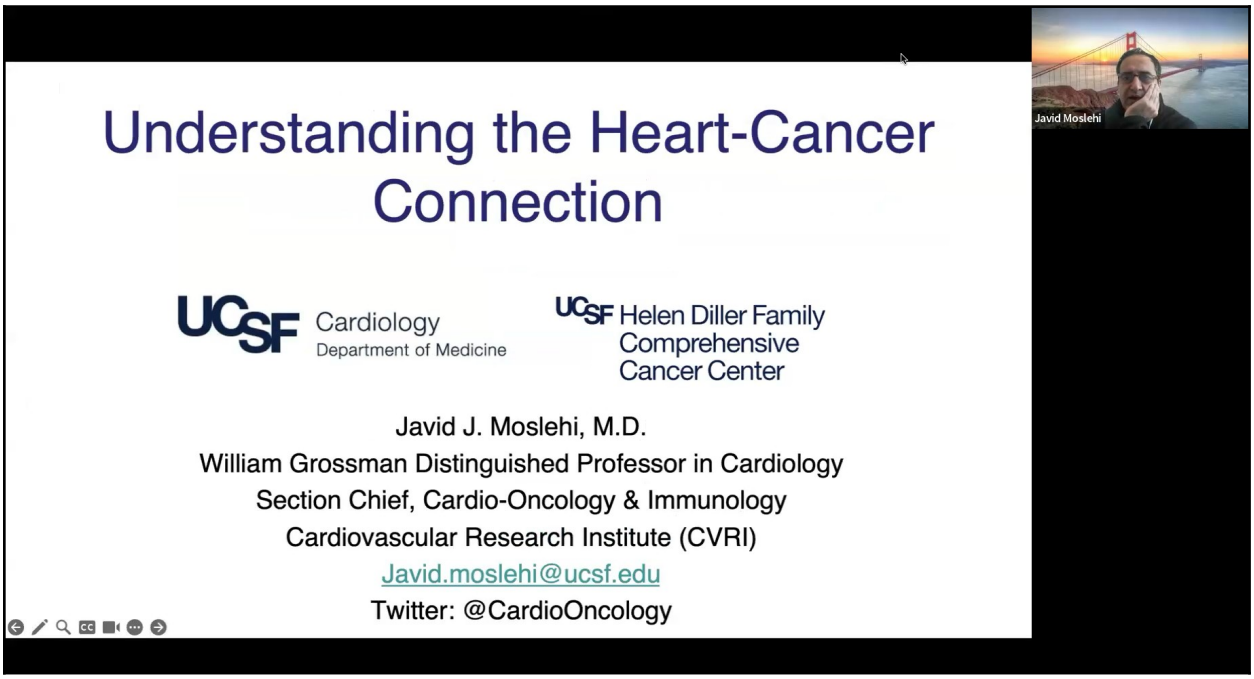
TRANSCRIPT

Brad Power
This is the Cancer Patient Lab and our weekly webinar series.

We're honored today to have with us Dr. Javid Moslehi of UCSF, who will be talking about the intersection between cancer and cardiac issues.

A couple of housekeeping things before we get started:

- This is medical information only. It is not medical advice. We like to arm our patients with information they can take to their medical team.
- We are a patient-led nonprofit organization, so we welcome donations, which you can do through our website, where we have a Donate button.



Javid Moslehi 2:09
My name is Javid Moslehi. I'm a cardiologist by training, and I also run a research lab. I did most of my training on the East Coast. I was a resident at Johns Hopkins, and then went to Boston and trained at Brigham and Women's, which is one of the Harvard programs for cardiology. I became a cardiologist, did my fellowship, and then I went to Dana Farber. I trained with Bill Kalin, working mostly on kidney cancer, but the machinery that leads to kidney cancer. It turns out it had a fundamental role in our biology, including heart disease. I worked on that for a number of years.

It was a long postdoc after I'd become a cardiologist. Somebody gave me the idea of having a clinic at Dana Farber seeing cancer patients, and I thought it would be a side job where I would

just show up and maybe two patients show up, because I had always been told that if you got cancer, you're probably going to die from the cancer, and certainly you don't have to worry about heart disease. But it turned out to be the opposite. This is now more than 15 years ago. What was amazing to me was the number of therapies that were coming in place for cancer, many of which help patients. People either got cured of their cancer or lived with their cancer being on therapies. For that reason alone, the fact that people were living longer with cancer, heart disease became more prominent. This was an important, eye-opening experience for me.

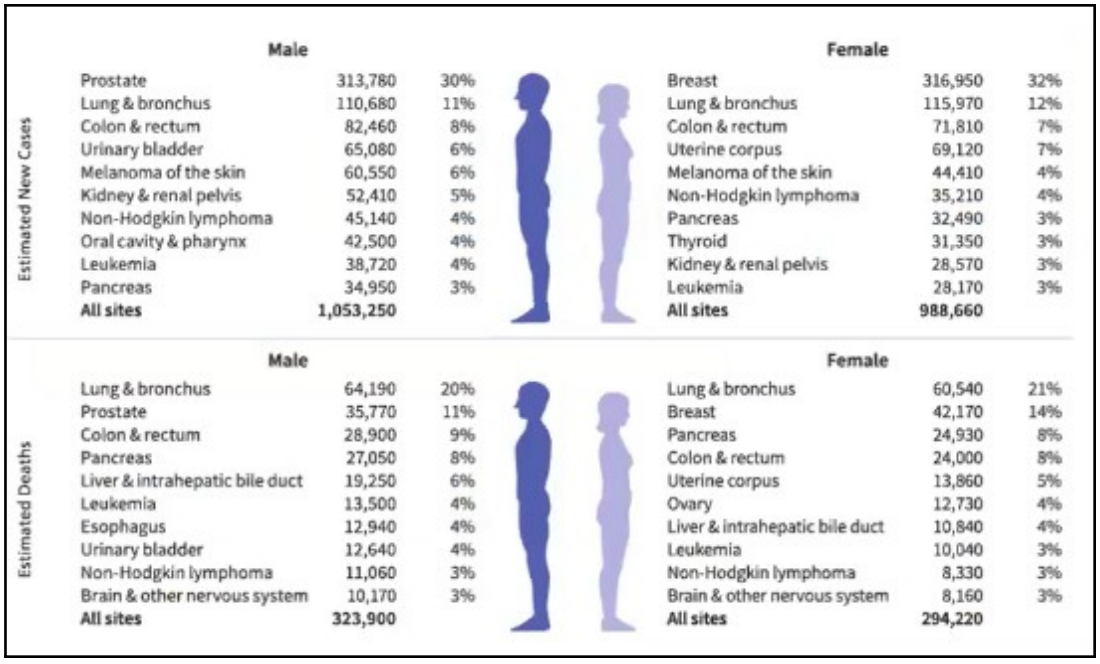
The other interesting thing was the number of therapies that were coming in the space for various cancers, which had definitely an impact, but which can have direct cardiovascular effects. This intersection between cardiac disease and cancer expands beyond that as what our group and others have defined.

I went from the Brigham to Vanderbilt, where I started my own lab and started a program in cardio oncology. Things actually went quite well in terms of both our research program and I'll show you some of the stuff that we did, but also this area was really exploding, and so I got a call from the my current boss, Jeff Olgin, to try to set up this program in cardio-oncology here in the West Coast. I moved for the first time in my life to the West Coast. The day I got in, I'd been here a number of times for meetings, but I feel really at home. It's been two-and-a-half years, three years, that I've been in San Francisco. It’s my first time living on the west coast. I am so happy that I'm here.

I'm hoping to explain to you what our program is. We have grown quite a bit. This is the group that works with me. It includes the clinical faculty that I have recruited. There are five cardiologists that see patients with cardio-oncology and this immunology tidbit. For this whole

section, most of the focus is on cancer patients, 90% or so. In fact, as I'm sitting here, I got a text from Hope Yugo, who runs the breast cancer program, about a patient. It's been really nice to see the program expand to having five people in my group who are attendings. It has been helpful, because we've been able to cover each day in the clinic. That works well. On a Tuesday, when I don't have a clinic, I can do stuff like this, or be in my research lab.

We've also, for the second time ever, I should say, because I did this at Vanderbilt, in this area of cardio-oncology, these cardiologists have focused on cancer and cancer survivors, which has really grown. We established a fellowship. I started this at Vanderbilt, and that's extended here, and these are three of our fellows that are training. Amir is actually now an instructor, so she should go up here. But Evelyn Song and Ricky Bayless are two of the fellows who are getting trained in the subspecialty of cardio-oncology and immunology. We have a whole research group that's helping us in the advanced research missions of our program. So this is our group in a nutshell.



Estimated New Cases	Male				Female		
	Prostate	313,780	30%		Breast	316,950	32%
	Lung & bronchus	110,680	11%		Lung & bronchus	115,970	12%
	Colon & rectum	82,460	8%		Colon & rectum	71,810	7%
	Urinary bladder	65,080	6%		Uterine corpus	69,120	7%
	Melanoma of the skin	60,550	6%		Melanoma of the skin	44,410	4%
	Kidney & renal pelvis	52,410	5%		Non-Hodgkin lymphoma	35,210	4%
	Non-Hodgkin lymphoma	45,140	4%		Pancreas	32,490	3%
	Oral cavity & pharynx	42,500	4%		Thyroid	31,350	3%
	Leukemia	38,720	4%		Kidney & renal pelvis	28,570	3%
	Pancreas	34,950	3%		Leukemia	28,170	3%
	All sites	**1,053,250**			**All sites**	**988,660**	

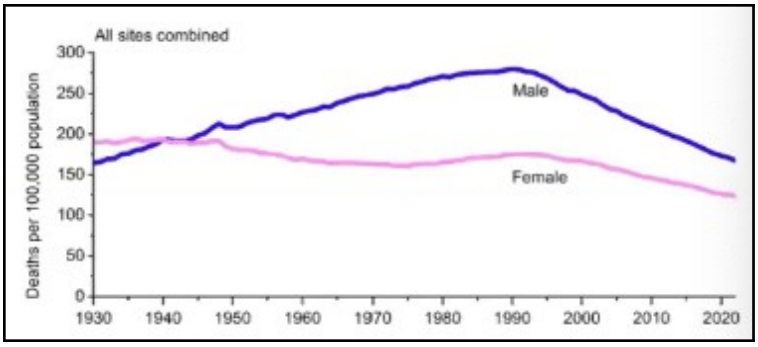
Estimated Deaths	Male				Female		
	Lung & bronchus	64,190	20%		Lung & bronchus	60,540	21%
	Prostate	35,770	11%		Breast	42,170	14%
	Colon & rectum	28,900	9%		Pancreas	24,930	8%
	Pancreas	27,050	8%		Colon & rectum	24,000	8%
	Liver & intrahepatic bile duct	19,250	6%		Uterine corpus	13,860	5%
	Leukemia	13,500	4%		Ovary	12,730	4%
	Esophagus	12,940	4%		Liver & intrahepatic bile duct	10,840	4%
	Urinary bladder	12,640	4%		Leukemia	10,040	3%
	Non-Hodgkin lymphoma	11,060	3%		Non-Hodgkin lymphoma	8,330	3%
	Brain & other nervous system	10,170	3%		Brain & other nervous system	8,160	3%
	All sites	**323,900**			**All sites**	**294,220**	

But to really appreciate where we are and why this area of cardio-oncology is exploding, it's important to take a step back to understand what's happening in cancer. I realized, especially when I went to Dana Farber more than 15 years ago to do my postdoc, that there was this whole revolution that was happening with cancer treatments and cancer in general.

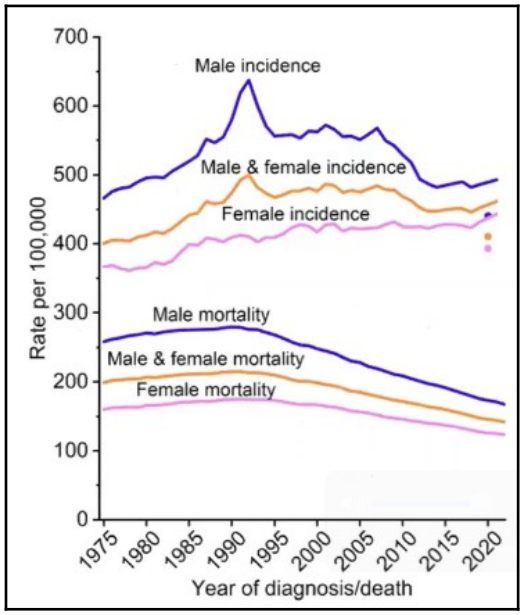
There's a journal that's very famous. It's called *CA: A Cancer Journal for Clinicians* (from the American Cancer Society). Every year in January – so this was just published last week – there's a six- or seven-page document that explains all the cancer statistics in the U.S. When you think of cancer, it divides it up into male and female. On the left are the new cases each year that occurred. This is last year. I think the statistics are from 2024 or 2023. I'm not sure, but

these are the number of new cancers that were diagnosed, and at the bottom are the number of deaths from the cancer.

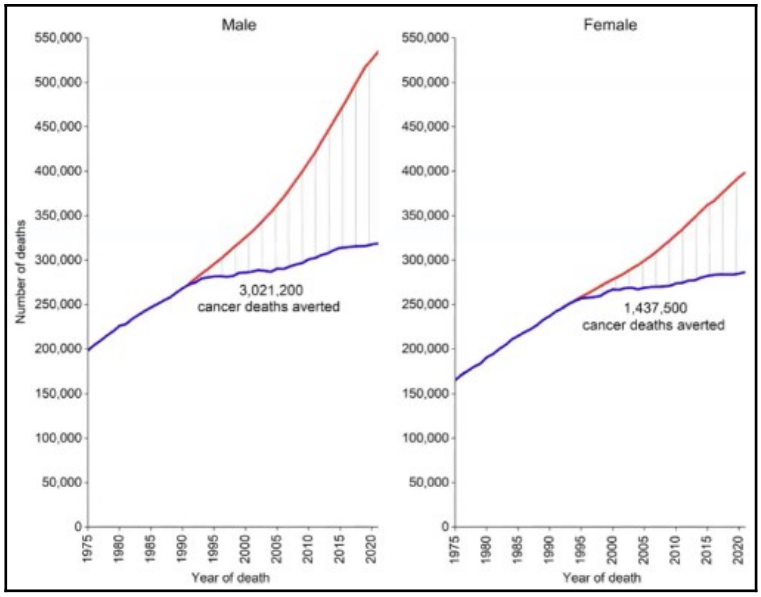
To break this down among the males, the most common new type of cancer is prostate cancer, and with females it is breast cancer. But when you look down here, the number one cause of death is lung cancer. It still remains to this day, where we have 64,000 deaths from lung cancer. Even though there are 313,000 incidents of new cases of prostate cancer, the number of deaths is almost 1/10 of that – 35,000 or so. The same goes with breast cancer where there are over 300,000 new cases of breast cancer each year, but the death rate is about 40,000, so slightly less. This is interesting, because you can look at the different types of cancers that exist. You can get an idea of the incidence of new cases, and which cancer tissue it affects.



The more telling thing is the number of deaths and the trends we're seeing between cancers. This is per 100,000 population, so you can see the data both in males and females. The number of deaths we're seeing each year from either cancer type is decreasing significantly, and that's a trend that we have seen probably since 1990, but you can see this really picking up in the last decade or so in terms of decreased risk of death from the cancers that people invariably get.



Another thing that's helpful here is this statistics on incidents again between male and female. You see the death rate going down. This is a little bit similar to the previous version.



What's interesting is that if you follow the number of deaths, and the number of cases each year in both male and female. What one would expect, given the fact that we detect cancer more, so the incidence is in some ways stable, one would expect the deaths to be significantly more than what we see. Because of the number of interventions in the last 30 years, the number of deaths has actually become stable at least, or trending down, when you compare it to the number of new cases that we see. This is really important. One of the things to appreciate here is just that the number of cases, which is about 600,000 deaths in America each year, has remained fairly stable in the past decade or so.

Rick Davis 13:36
I don't think this is true for prostate cancer. I don't want to make this a prostate cancer webinar, because I know there are other people, but I wrote about this last week. These numbers are very, very deceptive for prostate cancer, because as a result of the USPSTF (United States Preventive Services Task Force) rulings, what we're seeing in prostate cancer now is a very, very significant increase in de novo metastatic diagnoses. (The U.S. Preventive Services Task Force recommends that men ages 55 to 69 years discuss the possible benefits and harms of prostate-specific antigen screening with their health care provider and make an individualized decision about whether to get screened.) What we expect to see, because it's lagged, is a really huge increase, like maybe 10% to 15% or more, maybe even 20%, in deaths from prostate cancer over the next two to three years. I don't agree with these ACS (American Cancer Society) statistics. They're saying that prostate cancer deaths are going to go up by 500 this year, and they're predicting that breast cancer will go down by 100 people. If you look at the breast cancer deaths, for example, they're 42,000 and change. That's 100 people lower than they predicted for 2024. Of course, these are predictions. This is a model, so we have to understand that you never see this compared to actuals, which is a great concern, but they say

we predict 100 less. They're predicting 500 more prostate cancer cases. We are seeing so many men diagnosed as de novo metastatic, and we know that 43% of men diagnosed de novo metastatic are not getting treatment intensification. They're only getting a single drug. What we are going to see, and we've started to see, is a huge increase in the number of deaths from prostate cancer.

Javid Moslehi 16:25
I appreciate this. There's another part of this, if I understand it correctly, is some of the disparities in treatment and that people are getting single treatment rather than combination treatment. Is that where you're going with this, Rick? I just want to appreciate and understand your comments.

Rick Davis 16:46
Where I'm going more is that there's no accounting for de novo metastatic prostate cancer. There's no accounting for the huge increase in de novo metastatic that we've seen over the last 12 years as a result of the USPSTF. What's happened is men did not get tested. They didn't get diagnosed. When they did get diagnosed, they were already metastatic, and their life expectancy is a lot shorter than what we're used to in these statistics, and the statistics have not been adjusted to reflect the huge increase in de novo metastasis.

Javid Moslehi 17:23
I don't want to belabor it either, but what you're saying is – and half of my friends are urologists, it turns out, from my Hopkins years – the U.S. Preventive Task Force’s lack of recommendation for a testing for prostate cancer. I hope you recognize that's a very controversial thing, and there are people on both sides of it. There were data that were amplified, and there are many things with the U.S. Preventive Task Force that I don't agree with. What Rick is referring to is whether we should do testing for prostate cancer, either with digital rectal exam or PSA testing. In general, the U.S. Preventive Task Force has not supported this fully.

Rick Davis 18:29
Correct, but I don't want to go down that rabbit hole.
We now see one in five men – this is Chuck Ryan's statistic, not mine, from a couple of years ago – is diagnosed metastatic. It's somewhere between one in five and one in seven. But if that is the case, we are going to see a huge increase in deaths. I'm just saying these numbers are not reliable, as far as we see. Talk to Rahul Aggarwal. Talk to Matt Cooperberg. (UCSF oncologists). They're going to tell you.

Javid Moslehi 19:11
I'm fully in sync with the prostate group, and I appreciate it. I wasn't going to make this a prostate-specific thing, but we'll keep that in mind. Because of the need to screen, which we didn't do, frankly, 50 years ago, we did hit a good number of people who would get diagnosed early. That’s where, what you're saying, Rick, is that's now potentially fallen off a little bit based on the U.S. Preventive Task Force. I don't know how much that would be increased, but it's important to keep this in mind. Point taken. I'm completely on board.

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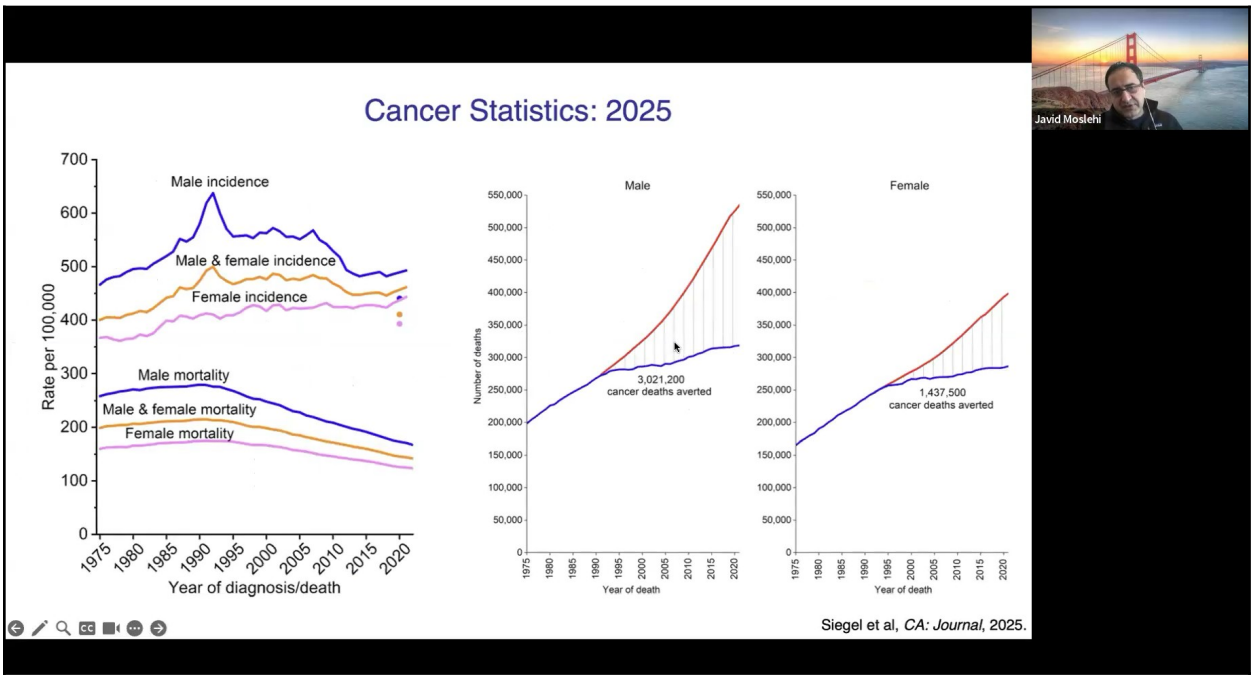
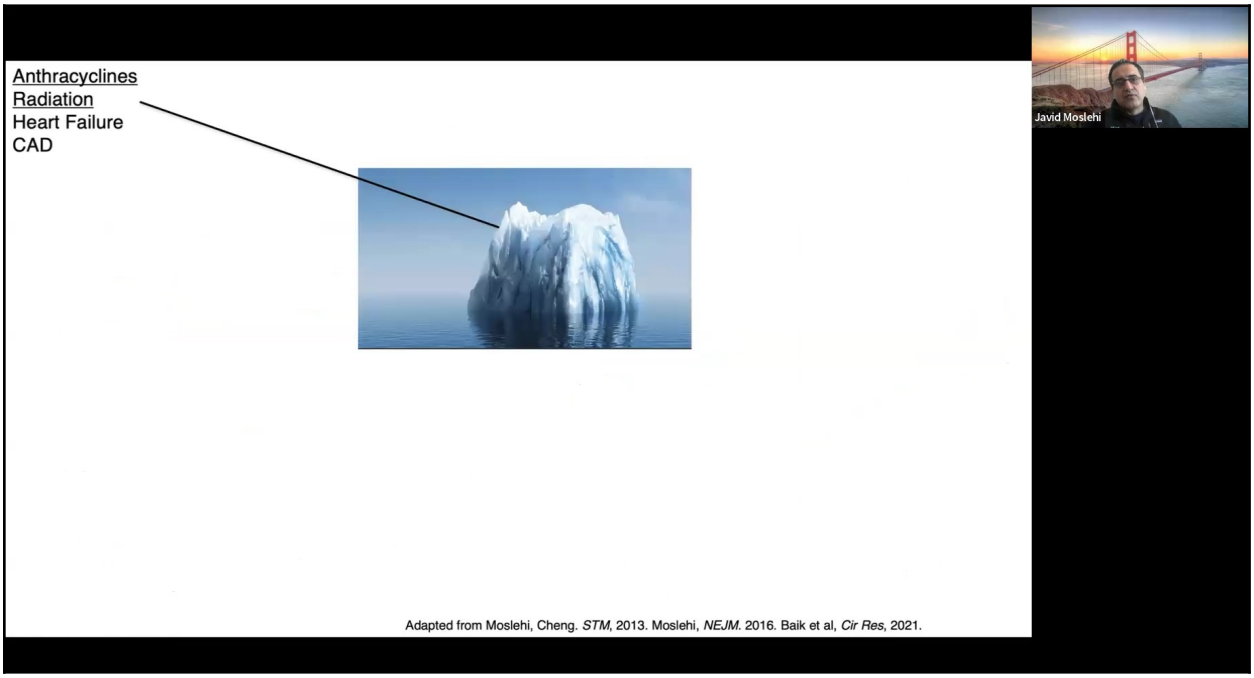


What I was trying to say here was more about the general incidence of cancer. Each year the total number of cancers has been fairly stable in the past few years, 600,000 or so. The number of deaths from cardiac disease is actually 700,000. Switching gears a little bit, appreciating that there is better treatment of all cancers. You can get into the minutia with prostate, or not, and other things. But in general, the mortality from all cancers between male and female has gone down. Specific cancers may be different, but this is what we have right now.



The question then comes: “Why is it?” A great part of it is the introduction of new treatments. I'm the first to admit that hasn't necessarily translated to prostate cancer, for reasons we'll talk about, but we're fairly good with kids at least, diagnosing and treating cancer, going back 50 years ago. That's in part because a lot of our pediatric oncology colleagues got into the research and started doing trials on children using old drugs. For that reason we have better treatment for different types of cancers in kids.

This is where a lot of the data about this intersection of cardiac disease and cancer comes from. We know for many pediatric cancers, if you give anthracyclines, an old, old drug, which was a drug that was taken out of the red soil in Italy. A company there made it. It becomes red when you give it. It's the backbone of treatments for many different cancers, not prostate cancer, but certainly pediatric cancers. People do quite well, and it's a backbone of treatment, I would still say for sarcoma in the adult population, lymphoma, Hodgkin's lymphoma, and at least a subset of breast cancers.

We also know radiation could be an effective treatment for a subset of cancers. This pertains to some extent to prostate cancer. These are old drugs. We still don't understand how they exactly work at a molecular basis, but they're a kind of poisonous drug. These are old drugs you would throw at patients, and people did well with their cancer. But what was interesting with at least the anthracyclines, which is still a backbone, including for some of the adult cancers. The observation was made back in the 1970s in kids, who got old anthracyclines, that they would do well. They would grow up to be 20 or 25, and get heart disease. This was very unusual because with anthracycline, for example, you expect some toxicities early on. You lose your hair. You get nauseous. You lose your red blood cells. “Myelosuppression” is the term. That's partly why we typically associate cancers and cancer treatment with people losing their hair and being nauseous. It's because of these older drugs, including anthracyclines. That was expected. What was unexpected is that years later, people will have heart problems, including heart failure.

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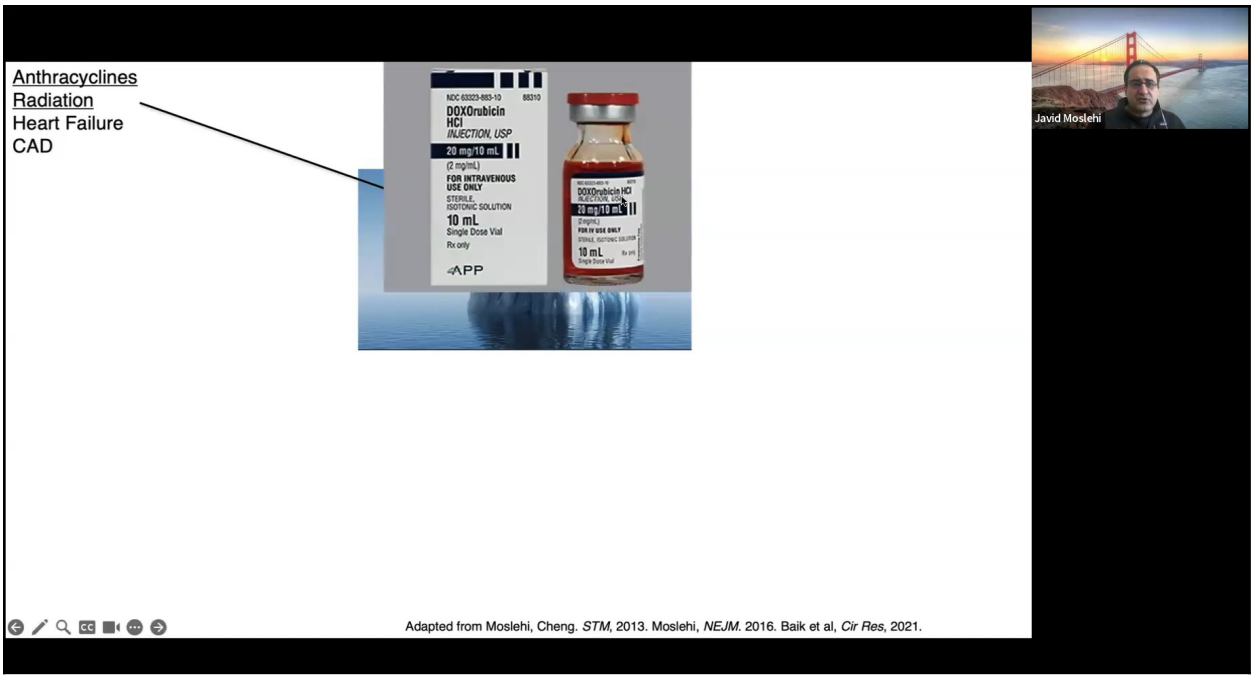
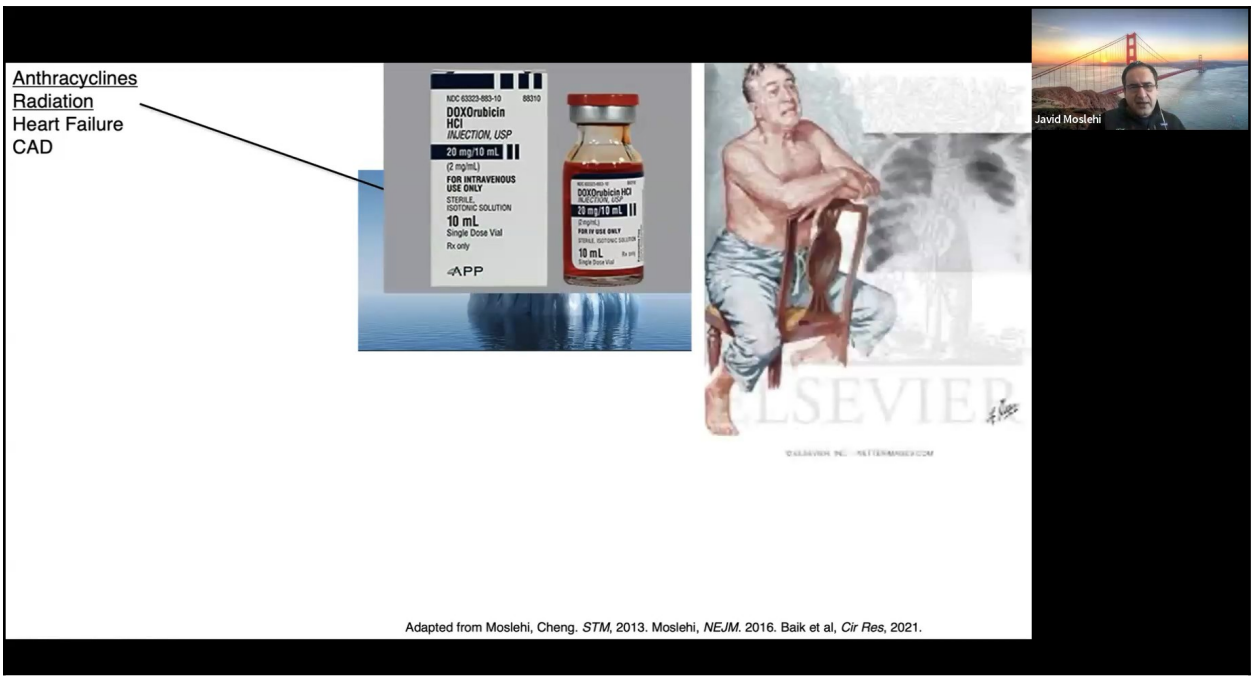


This is the drug. It's called doxorubicin. This is because the French company also made it. The “rubicin” refers to the red color.



People would come in with heart failure. From where I sit, this was an old observation that was made with these older drugs that were non-specific, where you have cardiac effects that occur sometime later.

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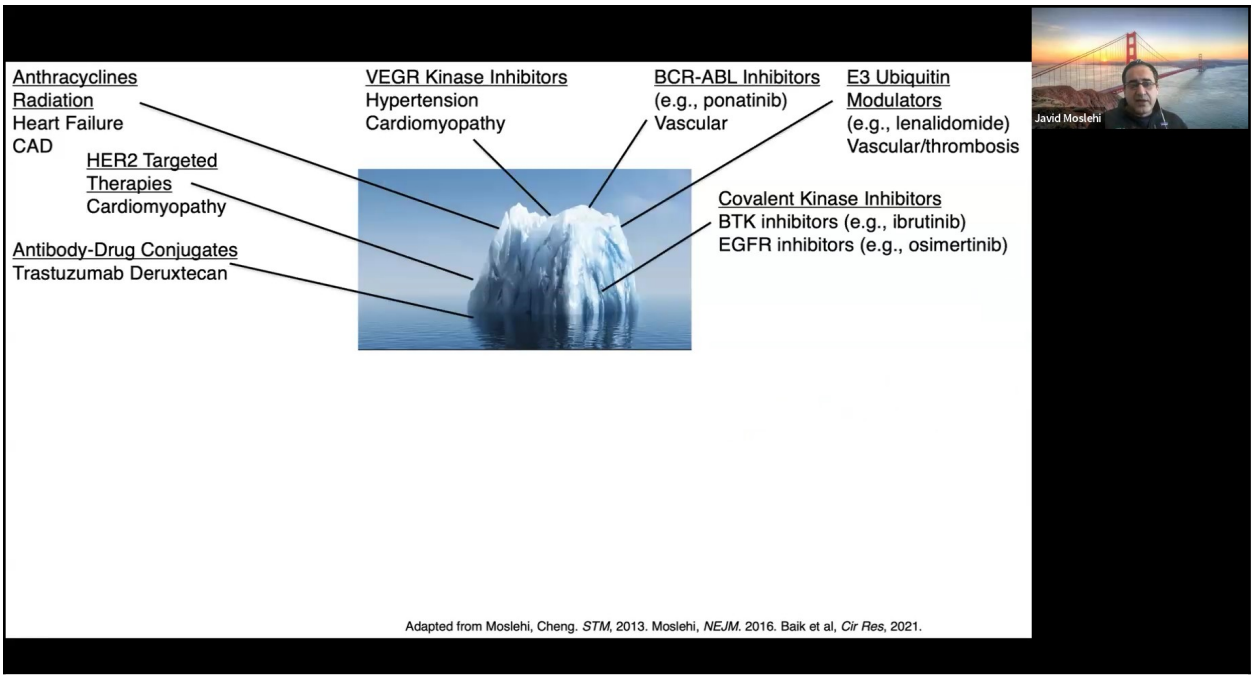


That's interesting, but we have a revolution in treatment for many cancer types, and that's not because of these old drugs, but that is due to these very specific treatments that exist for different cancer types. I'm the first to admit that hasn't necessarily translated as much to prostate cancer. Let's take a step back. For example, a company called Genentech is right south of where I live. My clinic and my lab is in Mission Bay. It makes a drug called Herceptin, which is an antibody that targets 20% to 30% of breast cancers where HER2 ligands are over-expressed. Herceptin, or trastuzumab, has revolutionized treatment for this subset of breast cancer patients. The problem is it causes heart failure, much like anthracyclines. When the drug was approved, this is now 20 plus years ago, they actually make sure every patient who gets Herceptin gets Echocardiogram monitoring of the heart during the course of treatment. This was, frankly, unexpected, because you would expect these poisons to cause heart problems, but not these more specific treatments. Specifically, with this HER2-targeted therapy, trastuzumab, we were not expecting to see heart failure.

I worked in a lab that worked on angiogenesis (the process of forming new blood vessels from existing ones). This was during my time at Dana Farber. A lot of new treatments that come, including a drug called the avastin that targets angiogenesis, or formation in new blood vessels that's important to feed the cancer. All these patients get hypertension, the blood pressure shoots up, and they can get cardiomyopathy (a group of heart muscle diseases that weaken or thicken the heart muscle, making it difficult for the heart to pump blood effectively) and other vascular diseases.

We saw some revolutionary drugs up in Oregon. A guy named Brian Drucker, who, until recently, was head of the cancer group there in Oregon, discovered Gleevec, or Imatinib, a drug that has been very successful for a subtype of leukemias called CML. But as newer drugs in this class have been introduced, we realized that they can cause both cardiac and vascular issues,

and this sort of list goes on again. I'll be the first to admit these new treatments haven't quite translated to prostate cancer, because we use some of the older drugs. They all have specific cardiac issues that can arise both during and after treatment, in a class where people actually do much better.

Brad Power 27:59
I had doxorubicin. I had to look it up, because I had R-CHOP, and there's no D in R-CHOP, but there it is, and I don't recall hearing anything about heart disease side effects. (R-CHOP is an acronym for a combination chemotherapy regimen used to treat certain types of non-Hodgkin's lymphoma including: Rituximab: A monoclonal antibody that targets and destroys B-lymphoma cells; Cyclophosphamide: An alkylating agent that damages cancer cell DNA; Hydroxydaunorubicin, or Doxorubicin: An anthracycline chemotherapy drug; Vincristine: An alkaloid chemotherapy drug; and Prednisone: A corticosteroid that helps suppress the immune system and reduce inflammation.)

What percentage of people who get doxorubicin are at risk of heart disease from that or any other of these ones that you've listed here?

Javid Moslehi 28:23
In R-CHOP there is doxorubicin. The “H” is actually, for whatever reason, doxorubicin hydrochloride. So the “H”, believe it or not, stands for doxorubicin or the anthracycline.

It all depends. Extremes of age are a major risk factor. If you have underlying cardiac disease already, that is a major risk factor with doxorubicin or anthracyclines. But the number one risk by far is the total dose that you receive. With R-CHOP, what you normally get is about 300 milligrams over meter squared. You really see the increase come after 400 milligrams over meter squared of total doxorubicin that you would receive. It increases precipitously. That's not to say you don't see effects. The best study that looked at this came initially with breast cancer trials in breast cancer patients, where about 7% to 10% of the patients with anthracyclines for breast cancer, which is slightly lower dose, get heart failure or cardiomyopathy, where the heart doesn't squeeze as well with the best overall treatment. It looked at a single Italian study group. They looked at 2500 patients who got anthracyclines for whatever reasons. It was all comers. In that study, the number of patients who had cardiomyopathy, as defined by the heart squeeze being slightly abnormal following completion of treatment, was again around 7% to 10%.

This is important, because I sit on this committee called the NCCN (National Comprehensive Cancer Network, which sets cancer treatment guidelines). I'm the only cardiologist there, and for the first time, we introduced language for doing an echo cardiac monitoring following completion of treatment. But the numbers are somewhere in 1 in 10 or so of patients who develop cardiomyopathy, as defined by the squeeze of the heart being abnormal.

Brad Power 30:49
What that argues for is since toxicity is dependent with chemotherapies dosing, what's the minimum effective dose, not what's the maximum tolerated dose? Can you speak to that?

Javid Moslehi 31:13
To bring this home with anthracyclines, the first studies with anthracyclines were done in the 1960s and 1970s. A lot of that was done at the NIH, and they were giving up to 1000 milligrams over meter squared cumulative total of doxorubicin. Doxorubicin is a little unusual in that you're giving the risk factor that's become apparent for cardiac disease is really the cumulative dose. The toxicities for other things like losing your hair and nausea go down if you decrease the amount that you give them at once for that reason. For example, I'm willing to bet when you got your R-CHOP treatment, that you got six cycles. You didn't get it all at once. You got breaks of three weeks or so. That number has gone down from 1000 or whatever they were giving to 300 to address the cardiac issues.

For Herceptin, there doesn't seem to be a dose effect that we see, although to be fair, when Herceptin came, there was one dose that was given. The people weren't doing titration. With the antibodies it's a little harder to do titration. With small molecule inhibitors you can do the titration, and you can see the effect depending on the dose.

You also bring up a very good point with respect to the total dose that people should get to see an effect. This is a hot area because it's unclear whether people should get everything that they're supposed to with respect to treatment. There are many cases where you can go lower on the dose for more effect and get just as equal treatment efficacy without the side effects.

Brad Power 33:07
Ari had a follow up question: Does it matter at what age you get the drugs? For example, talking about R-CHOP early in life, in my 30s or something, versus in my 60s?

Javid Moslehi 33:30
This is not the kind of study that can be done as well, but you can do observational studies. It does seem like extremes of age – when you're older or you're younger – are risk factors, and that's one of the reasons we saw this in kids. Why that is, is an area we're very interested in and we're studying. It seems like when the younger hearts are more susceptible to death than older hearts when your heart cells mature. You don't get as much susceptibility to death that you see in younger people, at least in preclinical models. The extremes of age with doxorubicin specifically is a risk factor as you get older because your heart is not as good at 65 as it is at 20, mostly because of accumulation of other risk factors that come over time, such as high blood pressure, cholesterol, so on and so forth.

Brad Power 34:41
Roger Royse has a question: My calcium score went up a lot while I was on chemo. Was that from the chemo or just coincidence?

Javid Moslehi 34:53
That's a really good question that comes up. We just had a think tank with the NIH (National Institutes of Health) and NCI (National Cancer Institute) on this issue. We and others have been

interested in this topic, and it's not so much about calcium, because calcium goes up with age. There's this concept of accelerated aging in our cancer patients and cancer survivors, and this is a hot topic with calcium, because we check that now. It can be helpful in terms of deciding which patient goes on which treatment. But that's an area we are studying in the lab, and clearly the NCI is very interested in accelerated aging.

To bring this home for this think tank we just had: I was the only cardiologist, but they had other experts. For example, a number of our colleagues who are HIV experts, and it sounds like with HIV, they're seeing the same trend with accelerated aging, part of which is this calcium score. Again, the calcium score is normal zero in a 20 year old, but it goes up as you get older. We're seeing more of this, and whether that's an effect of the treatment or the cancer itself tells us an expansion of this field.

Brad Power 36:34
Helen has a question about being on Avastin. She's got ovarian cancer. Can you speak to the side effects of chemo and Avastin?

Javid Moslehi 36:47
Almost everybody who goes on Avastin or any VEGF inhibitor has their blood pressure go up. It's variable. For some people it goes up to five millimeters of mercury. Other people get so high suddenly, like 40 milligrams of mercury, that you have to stop the treatment because your blood pressure shoots up. We've seen a number of patients have bad things happen, like strokes and so forth on VEGF. Everybody's blood pressure goes up. It's just variable how much it goes up, which partly depends on what other treatments they may get.

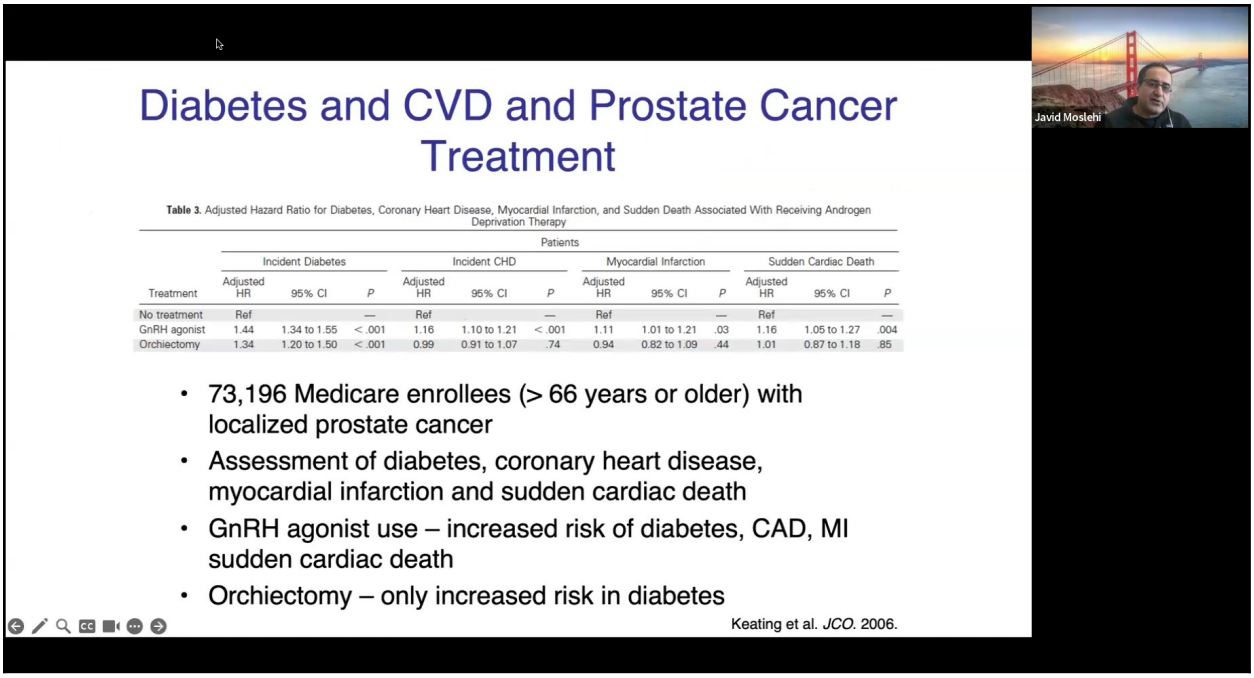
That was one of the areas that we have a major NIH grant to study. What we're finding is it seems like they also lose protein in their urine, so they get proteinuria. One of the things we've instituted clinically is measuring the protein in the urine. We don't know whether that's an effect on the kidney, which has an important role in regulating blood pressure. We're doing a lot of studies on that for almost everybody who is on Avastin or other similar drugs. Avastin is a biologic. Other drugs like sunitinib, sorafenib – there are like 12 drugs in that class – all increase blood pressure. We've instituted being proactive and helping the blood pressure come down as quickly as they get on the study. In some patients we preemptively start them on treatment for blood pressure. We're doing a lot of studies on that. It's very interesting biologically.

Brad Power 38:33
Question from Rick Davis: “Is there a cardiac risk of getting a couple of radiation treatments to the chest to prevent gynecomastia (a condition where there is an enlargement of the male breast tissue caused by an imbalance in hormones, specifically between estrogen and testosterone)?”

Javid Moslehi 38:42
My introduction to the field was a very nice study by this group at Oxford that was published in the New England Journal of Medicine in 2013 on breast cancer. They calculated that when you

get breast cancer radiation, how much of it goes directly to the heart. Each gray of radiation (measure of the amount of energy deposited by radiation in a kilogram of matter) that they calculated directly to the heart, you get a 7% increased risk of dying from heart disease, having a heart attack, or having a stent placed. But this risk starts sometime later. I wrote the editorial for this paper, and it was a hot topic, covered in the New York Times, the Wall Street Journal. Everyone covered it because for the first time, it was an actual calculation of the treatment. The caveat there is they calculated how much of the treatment goes directly to the heart.

One of the things that's happened in the last decade or so is interventions by my radiation oncology colleagues. For example, in women, they pronate you. They put you on your chest, or they have you take a deep breath so it separates the heart. But the risk is clearly there, but it all depends on how much the heart sat in the field of radiation, and how much the heart received. No question that with each gray it goes up. This was probably the best study that gave us some numbers of what the calculation is.

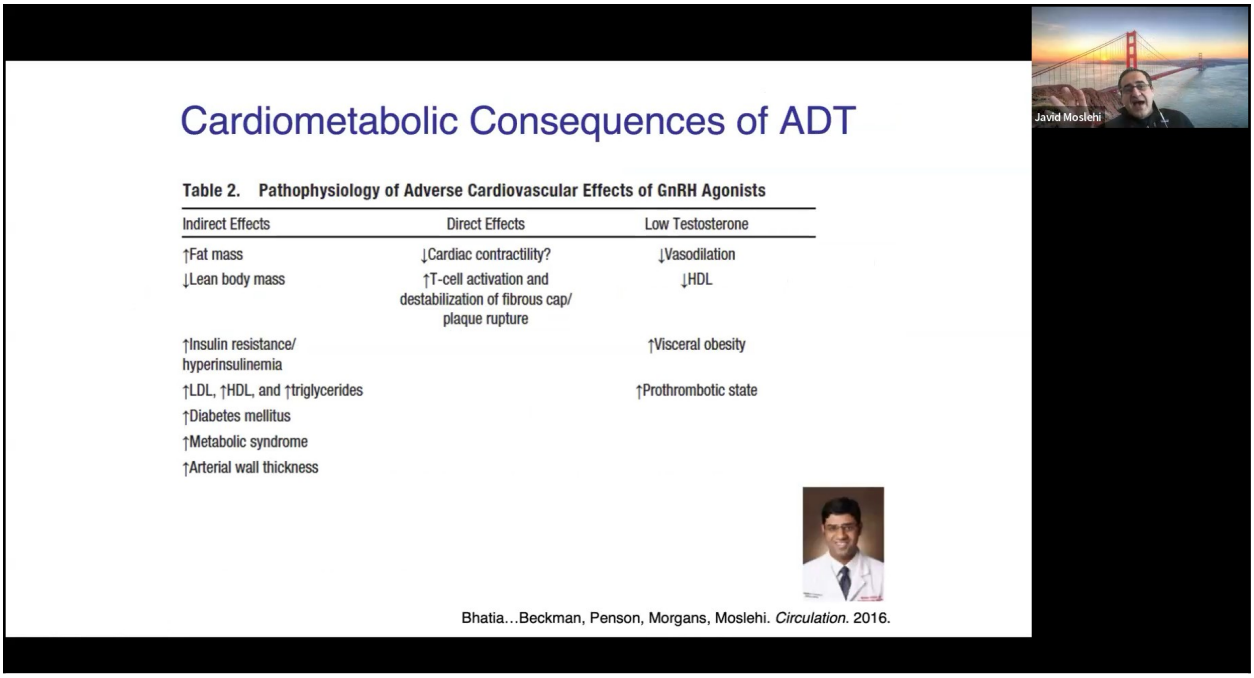


Just a couple of things on prostate cancer. With some of these newer treatments, we'll still have to see whether they make it. I'll talk about immunotherapy next. It hasn't really panned out, for whatever reasons we won't get into.

A mainstay of treatment for prostate cancer is androgen deprivation therapy. We used to give one drug and one drug only. I won't get into the biology of it. It works in the brain. Lupron is what some of the people with prostate cancer may have received. The study that was really interesting back in 2006, Nancy Keating, who was one of my colleagues in Boston, an epidemiologist, looked at patients who get either orchiectomy (a surgical procedure where one or both testicles are removed), which is the old treatment we used to do for getting rid of our hormones, and then this GnRH agonist, which is Lupron, and calculate the risk of developing

either diabetes or heart disease, and for with the GnRH agonist, specifically Lupron, in this large Medicare observational data, there was a significant increased risk of both diabetes, which would be expected, but also heart attacks. This is a heart attack or coronary artery disease, having a heart attack and sudden cardiac death, which is really interesting.

For the most part this panned out, but with a caveat. This work was nicely done by two of my old colleagues at Dana Farber, Phil Kantoff, who went to New York and is now back in Boston. Phil did a nice study. What's interesting is, if you look at the clinical trial population with the newest androgen deprivation therapy, the effect is not as large, but there's a reason for that. But when you look at observational data, the effects on heart disease and sudden death and heart attacks is significantly higher. The reason is the following: with many cancer clinical trials, when a company decides to test a drug, they take the healthiest cancer patient they can find and put them on the trial. That sounds like an oxymoron, but you take somebody who doesn't have a bad heart. You take somebody who doesn't have risk factors. But when the drug is actually approved, everybody gets it, and that includes a lot of patients who have existing heart disease or heart risk factors. That's part of the reason why we see this discrepancy between observational data and clinical trials, where the effect is less. It's still there.



It's something to keep in mind, especially as new treatments are coming that affect the hormones. For example, now you can get both Lupron and other drugs, Abiraterone, that works with adrenals, or Enzalutamide, which affects the receptor, and the effects are still there.

This is work we published out of Vanderbilt. I think this paper is with Dave Penson, who was head of Urology at Vanderbilt, and Alan Partin and Mo Allaf, who's now the head of urology at Johns Hopkins. He took over from Pat Walsh. I happened to be roommates with them in college at Hopkins and then later residency. When you get androgen deprivation therapy, these

hormonal treatments, you clearly see effects on cardiac risk factors. You have a higher risk of diabetes and insulin resistance. As a result, you get higher incidences of heart problems, which could be because of these risk factors.

But one of the risk factors that people don't appreciate as much is when you get on androgen deprivation therapy, hormonal treatments for prostate cancer, your total weight may stay the same, but what's in the weight dramatically changes. You lose muscle mass and you gain fat. You may get a net slight increase in weight, but the composition is very different. This is an area that we are really interested in and studying in the lab, because I think it's been woefully understudied in terms of risk factor profiles that could occur in patients getting androgen deprivation therapy.

Brad Power 45:33
Do you agree with prophylactic use of metformin, statins, beta blockers, while remaining on androgen deprivation therapy?

Javid Moslehi 45:46
Yes. I'll answer that in a minute.

Brad Power 45:55
John Antonucci asked in the chat: A prostate cancer man asked me about changing his losartan (relaxes the blood vessels to lower blood pressure and increase the supply of the blood and oxygen to the heart) for telmisartan (another treatment for high blood pressure). Cell culture work. Any comments?

Javid Moslehi 46:05
No, because it's cell culture work. I will get to this issue of cardiac prevention in a moment. Some of this stuff, especially with prostate cancer, will become more clear in one minute. Because I want to tell you a whole dimension on another side of this field that's exploding: immunotherapies.

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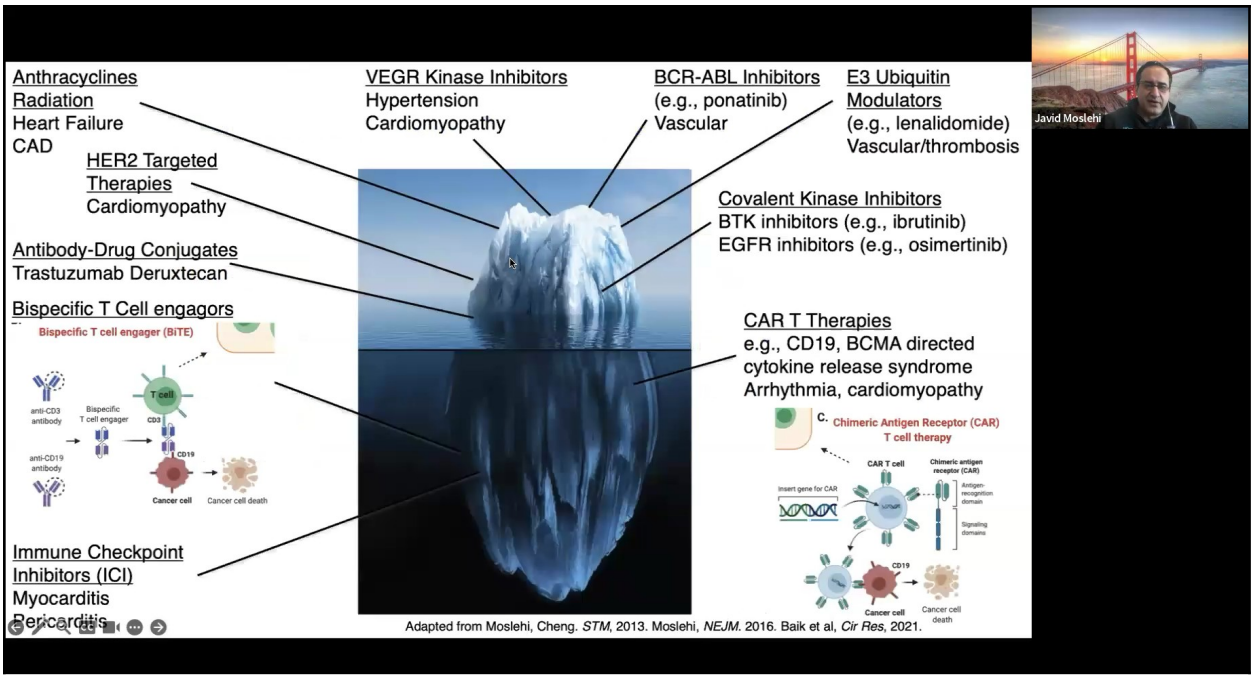
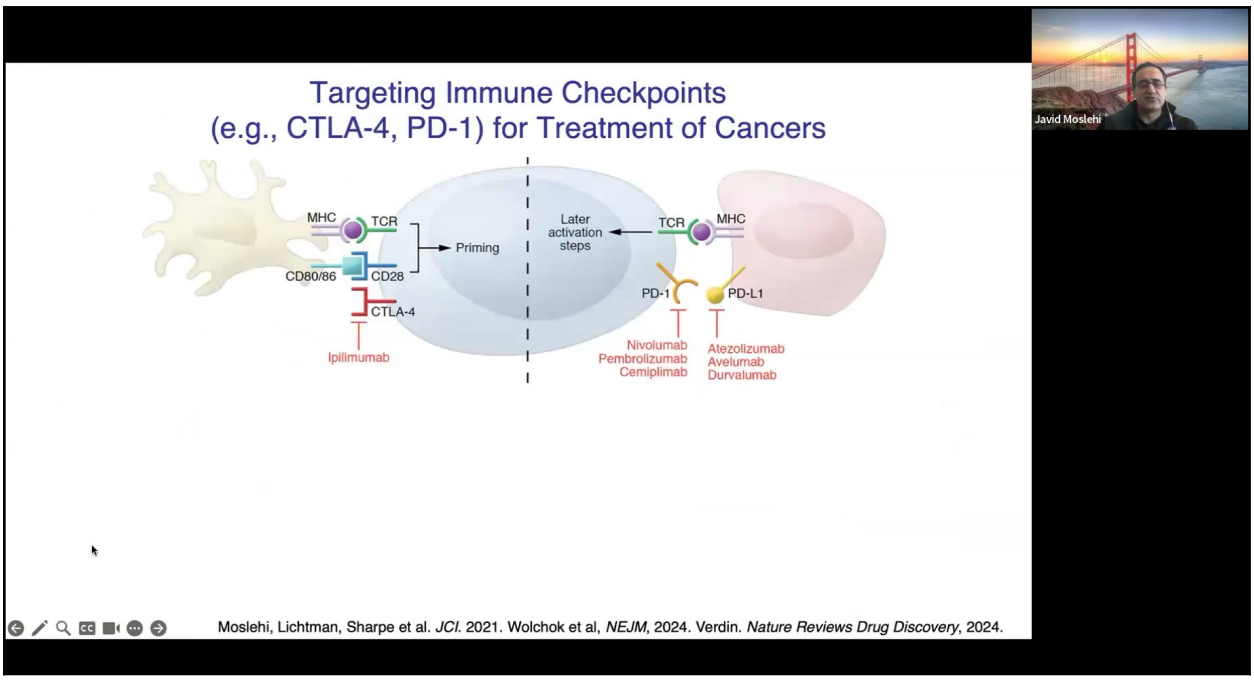


Immunotherapies haven't quite translated to prostate cancer, but it is very true for other cancers.



One class of immunotherapies, the immune checkpoint inhibitors, we give to a number of patients. This specific class of immune-based therapies takes off the brakes of the immune system.

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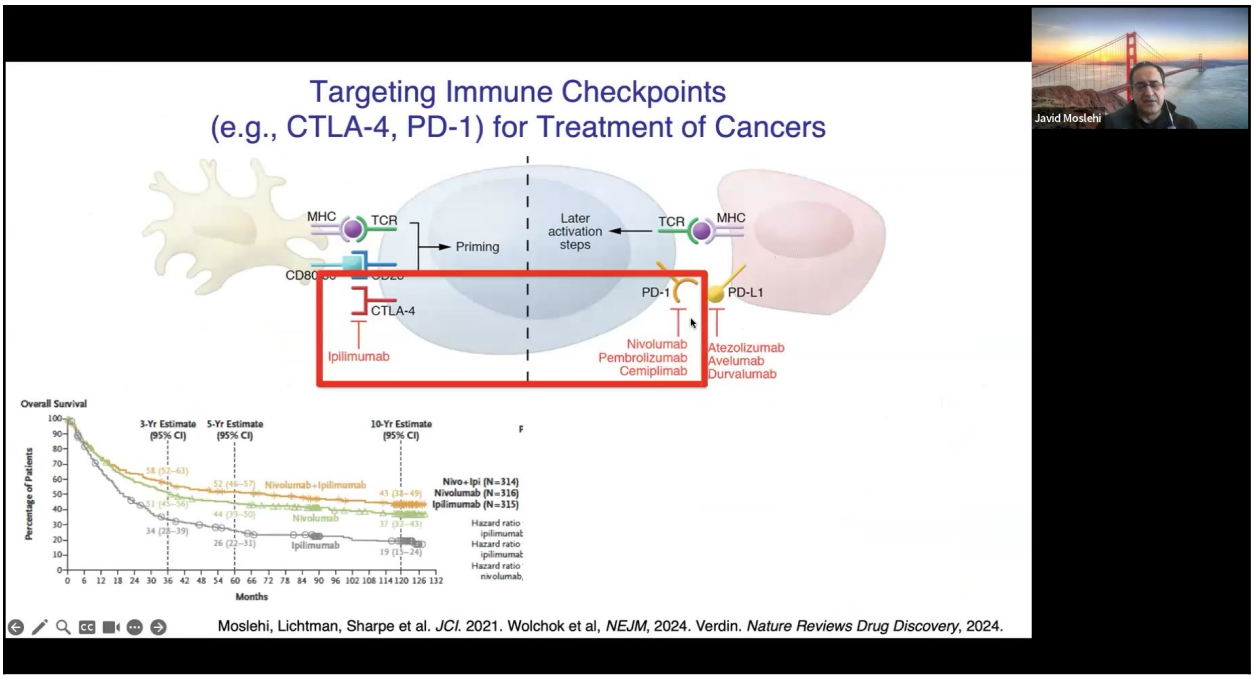
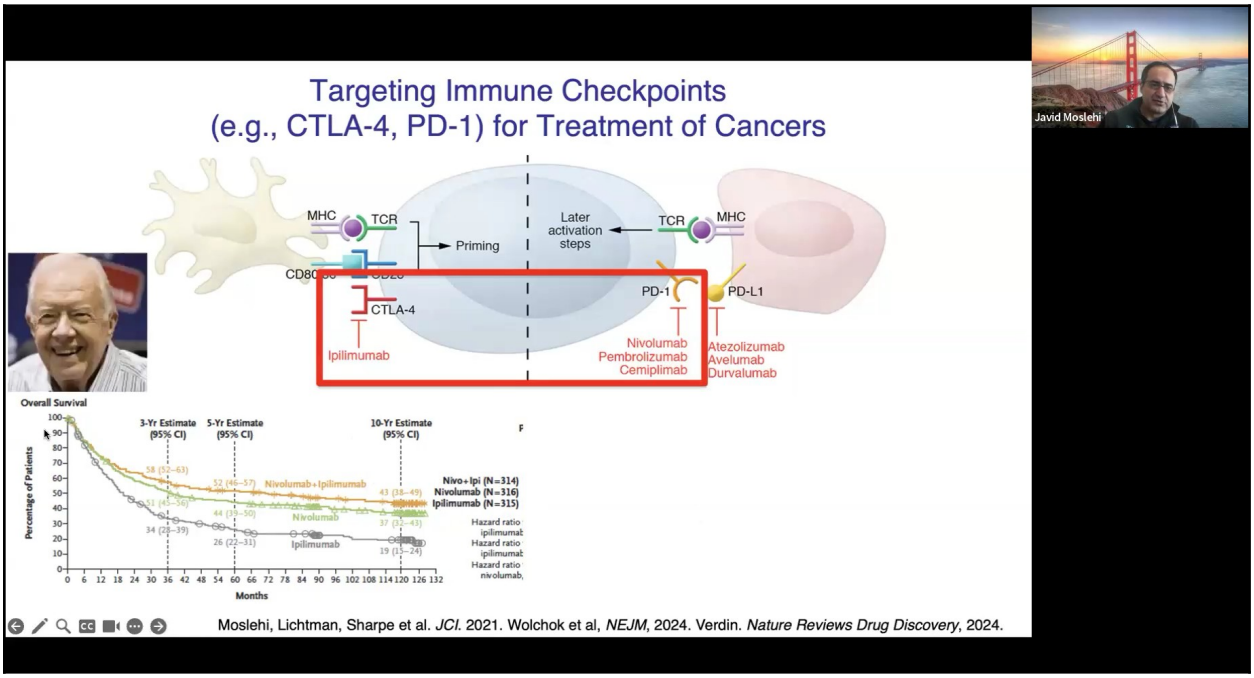


They've been revolutionary for some cancers, but unfortunately, not for prostate cancer. One example is melanoma, where if you got metastatic melanoma, you were told to go home and die. There was no treatment for you. These studies by Jedd Wolchok were just published in the New England Journal of Medicine a few months ago. A 10-year followup with getting the combination immune checkpoint blockade, 43% of the people were living at 10 years, which is a complete revolution. This is the most dramatic change in treatment in patients we have seen in the last decade or so for anything. It's pretty significant.



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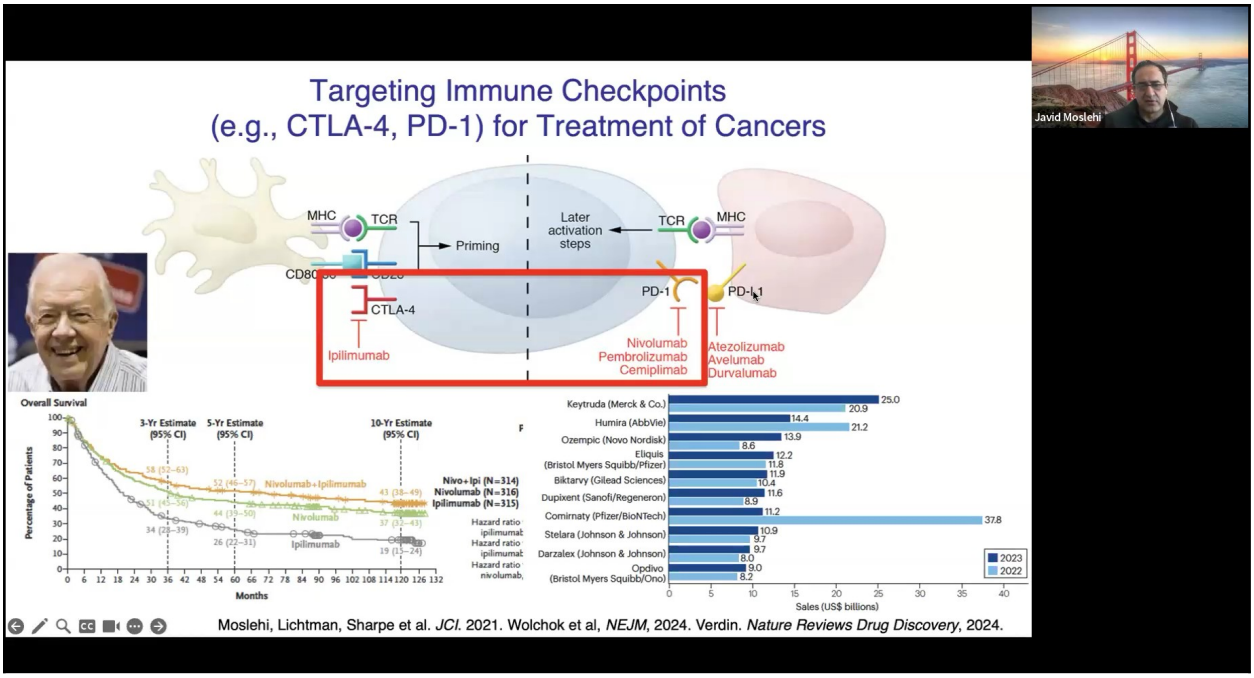
You have examples, like Jimmy Carter, who died a few months ago or so. He had metastatic melanoma that went to his brain at the age of 90, 10 years ago, and after getting one of these drugs, a single agent, PD-1 inhibitor, he was completely cured of his cancer. He died due to other chronic health issues, but cancer was not one of them.



To show the magnitude of how much these drugs are expanding, this is the number one through number 10 revenue generating drugs in the U.S. These data are from 2023. You can see Merck with Keytruda, which is their PD-1 inhibitor, is number one by far with $25 billion. The numbers just came out for 2024. This number is between $27 to $28 billion of revenue for Merck. Number 10 on this list, which is now number eight, is nivolumab, or Opdivo, which is Bristol Myers’ PD-1 inhibitor. What's not captured here is numbers 11 through 20, where a lot of the drugs are immune-based therapies. Every drug company is in on this. It is dramatic. About 50% of patients with cancer are not eligible for treatment with checkpoint inhibitors on top of their existing therapy.

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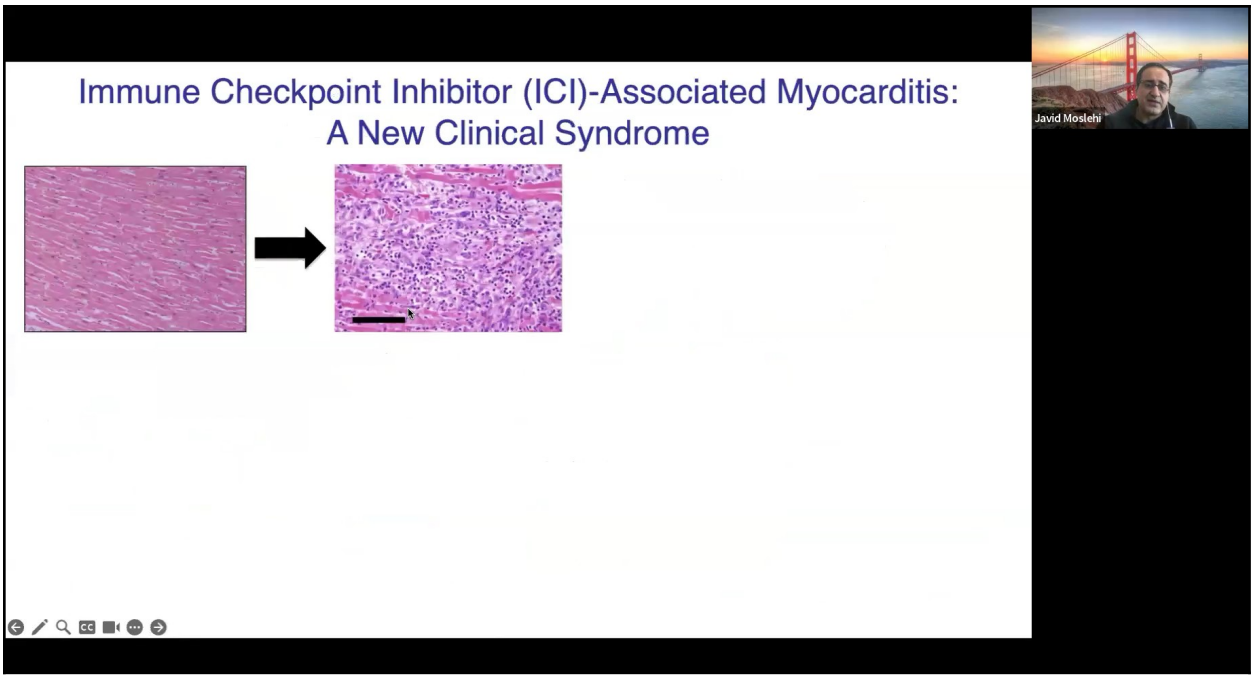

As we and others have found, you can have effects on the heart that can be deadly.

This is a discovery we made when I was at Vanderbilt.

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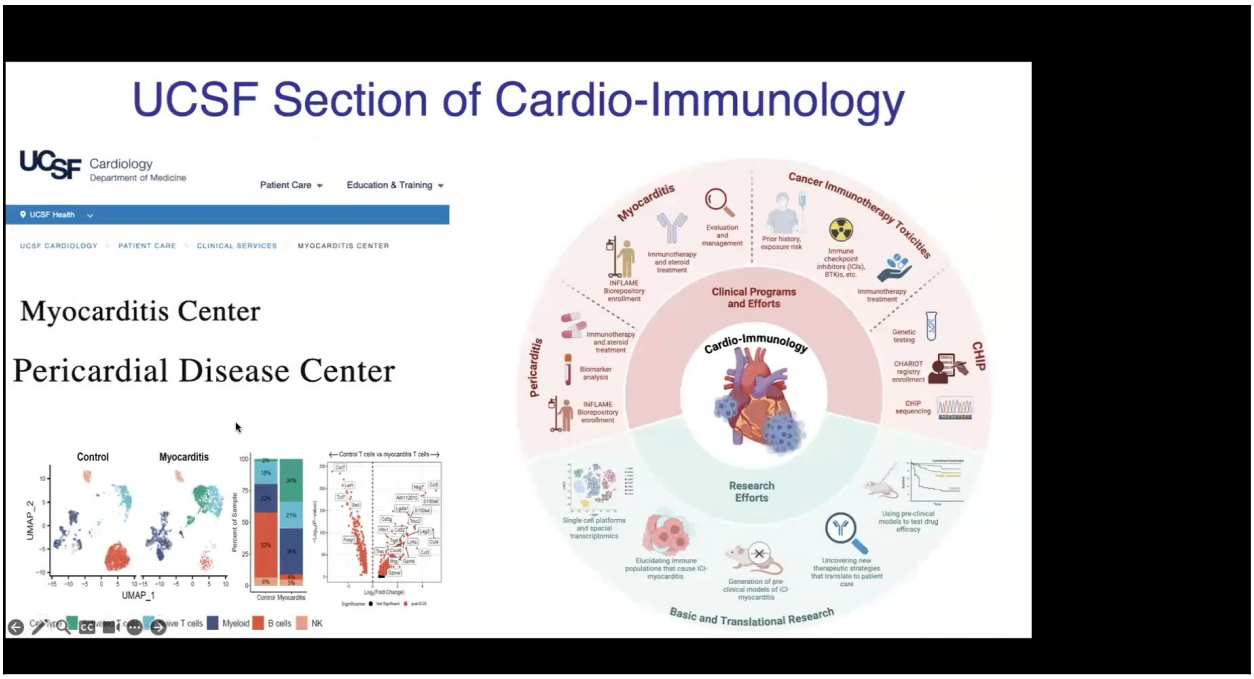
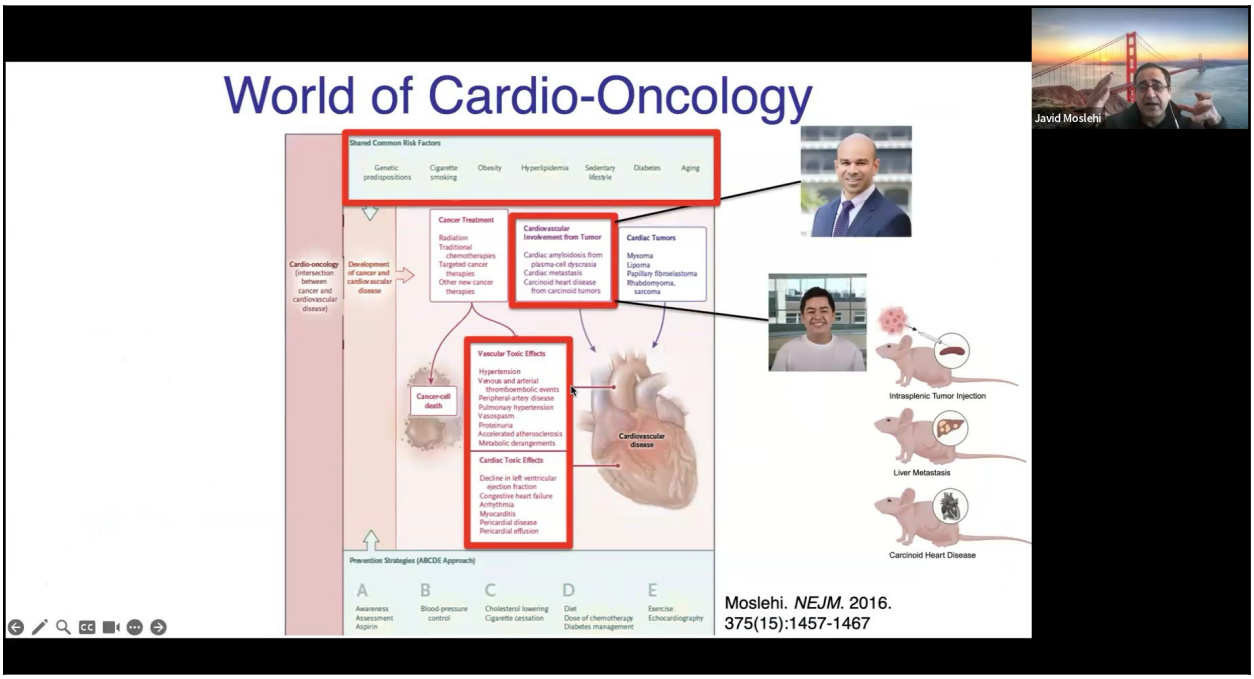


This is the subset of patients who can get myocarditis, so inflammation of the heart.



I talked a lot about treatment effects on the heart, but the thing we're recognizing now is a growing appreciation that there are common risk factors that predispose to both cancer and heart disease. For example, everybody knows if you smoke, you have a high risk of having lung cancer and other cancers and a high risk of having heart disease. But now we appreciate things like obesity, hyperlipidemia (elevated levels of fats in the blood, including cholesterol), and

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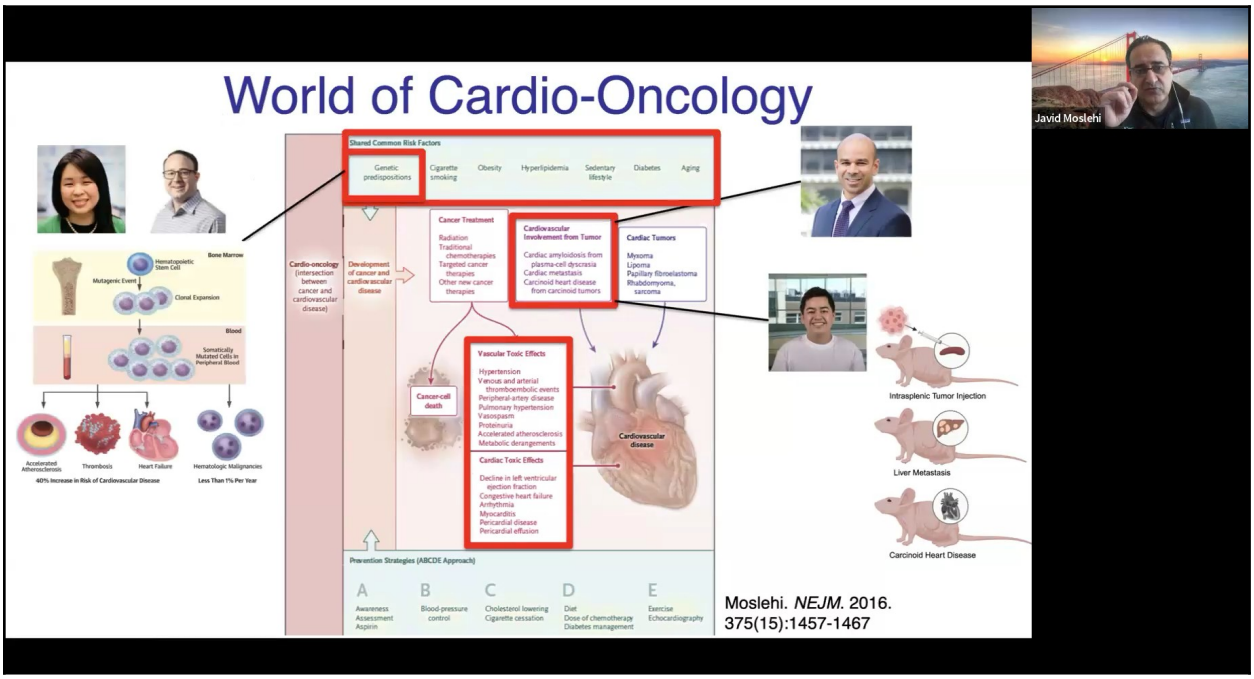
diabetes are also important risers of not only cardiac disease, but also cancers. With some of the obesity drugs, we see a better effect on total mortality, and not just the net effect on cardiac disease. This is a really important concept. It introduces this question that was asked about, “What are the risk factors and can we affect the cardiac risk?” If you are on Metformin for your diabetes or for your highest sugar, there's also a potential effect on your prostate cancer. These are studies that are being done right now on that effect. If you're on a statin, that may not only have a beneficial effect on your heart, but there may be this effect on prostate cancer and the prostate cancer recurrence as well. These studies are being done prospectively. That's what the observational data suggests.

This is a really important concept. This is a New England Journal of Medicine paper I wrote about the state of cardio-oncology. I specifically wanted to make this not just about toxicity, which is right here in the middle, but about this growing appreciation of common risk factors.



Another concept is genetic predispositions that we don't necessarily inherit from Mom and Pop, but which come around.

This is another concept called clonal hematopoiesis, or CHIP, and we recognize that's both a risk factor for cancer, but also heart disease. (The incidence of clonal hematopoiesis has been found to rise dramatically with age. Recent studies have demonstrated that less than 1% of the population under age 40 but approximately 10-20% of the population over age 70 has observable clonal hematopoiesis.[4][5][6] Having clonal hematopoiesis has been linked to a more than 10-fold increased risk of developing a blood cancer, though the overall likelihood is still low.[4][5] Clonal hematopoiesis does not typically give rise to noticeable symptoms, but does lead to increased risk of cardiovascular disease.[1][5][11] Patients with solid tumors or lymphoma and clonal hematopoiesis have been shown to have an inferior outcome.)

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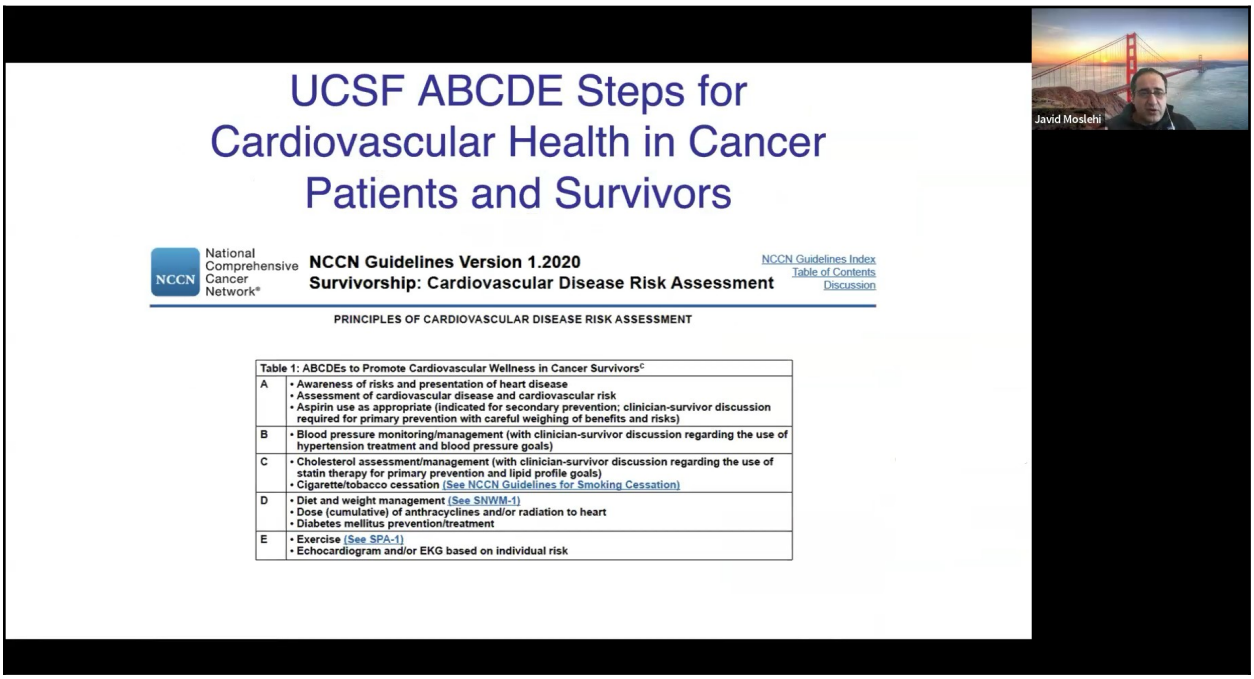

You may ask, “What should we do about this?” I sit on the Guidelines Committee for NCCN. This is what we came up with. It's the ABCDE approach to cardiovascular wellness in cancer survivors. I would argue this is true for cancer patients as well. The reason we go through this, A, B, C, D, E is that every patient is empowered. Everybody knows to check these things. Everybody knows to treat them. The only thing we can say at this point is that if your cholesterol is high and you just went through a bout of radiation for either breast or prostate cancer, if your cholesterol is high and you go on a statin that will help you from a cardiac perspective, but also, given that there is potentially this common risk factor. This would potentially translate because of the underlying thing. There are studies being done with benefits for your cancer as well. That's why we, for the first time ever, introduced this language. This is the algorithm we came up with for our program for the NCCN.

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CHAT DISCUSSION

00:17:45 Hilary: Hilary Elkin. Care is now at UCSF. Advanced endometrial CA, IIIC1, Mesonephric-like adenocarcinoma (MLA), dx 1/24, sx 2/24, cx 4/24, rx 8/24, completed trt 9/12/24.
00:19:37 Helene: No audio
00:29:48 Rick Davis, AnCan Foundation: Very deceptive for prostate.... needs explanation. Prostate deaths are trending in reverse to these graphs.
00:36:04 Roger Royse: pancreatic cancer rates have increased (doubled) in the last 20 years
00:37:47 Rick Davis, AnCan Foundation: In general, breast and prostatenew cases have increased over 50% since 2010.
00:42:51 Brad Power: I had doxorubicin as part of my chemotherapy cocktail (R-CHOP) for lymphoma. I don’t recall hearing that I was at risk of heart disease.
00:43:13 Helene: I’m on Avastin, and have developed high bp, on second bp med to upgrade the first. Dx ovarian cancer, rarest type, mesonephric-like adenocarcinoma. Chemo with avastin. After chemo - avastin continuing. Total 22 sessions
00:43:14 Brad Power: What is the % of patients that have heart disease side effects?
00:43:26 Rick Davis, AnCan Foundation: Q for later... is there a cardiac risk to getting a couple of RT treatments to the chest to prevent gynecomastia?
00:44:55 Roger Royse: my calcium score went up (a lot) while I was on chemo - was that from the chemo or just coincidence?
00:47:08 ari akerstein: Followup to Brad’s question: for RCHOP at , say, 300mg/m^2, is there a delta w/r/t heart damage if received earlier in life vs. later?
00:56:40 Jack Baruch: Do you agree with prophylactic use of metformin, statins, beta blockers while remaining of androgen deprivation therapy
00:59:35 john antonucci: A prostate cancer man asked me about changing his losartan for telmisartan. Cell culture work. Any comments?
01:00:51 David Plunkett: I am on Lupron and abiraterone treatment for prostate cancer. If I have a heart attack and die, will it be considered death due to prostate cancer or due to heart disease for the purpose of the annual statistics?
01:01:11 Jeffrey Dwyer: What is your opinion concerning proton beam radiation and reduced cardiac risk from the radiation exposure?
01:01:38 Jack Baruch: Do you agree that LHRH antagonists are safer than the agonists
01:01:55 Helene: 1) I understand that Avastin has a half life at 20 days (AVASTIN PHARMACOKINETICS
Elimination
Half-life: ~20 days) , however it is administered to me every 21 days. What are the long term effects on BP and heart with this type of assault on these systems, and by a drug whose lasting efficacy is in preventing recurrence is question. Trying to understand how to combat the side effects on my heart. I see a cardiologist regularly on my own.
01:02:50 Alane Watkins: Question: Do you see any impact on Lipo (B) and Lipo (a) with any cancer treatments?