Rounds we have two speakers today from male to wonderful speakers first or Hegel on my own, introduced and then the cold diesel, who Linda Irwin will introduce. I've known Jorge since before he arrived at Yale. He's now the Lucille P Marquis, professor, microbial pathogenesis and chair of the Department. In his lab studies bacterial infections, he's probably best known for his discovery and characterization of the Type 3 secretion apparatus,
which is this microscopic needle that injects proteins into cells. A fantastic story, and in recognition of this work, he’s received numerous awards and been elected to the National Academy of Sciences, but more recently he’s got interested in the Association between cancer and bacteria, and mechanistically, how does that work, and he’s shown, for example, that some bacterial toxins can induce DNA damage. And therefore are potential carcinogens. And so today we’ll hear about this very exciting work.
So Jorge, the floor is yours.

Thanks Dan,

And yeah as then.

Imly microbes and cancer are a lot

So these are the known causes

That amount to that 20%.
But by all accounts this is probably rose underestimate in terms of the influence in the etiology of cancer of microbes. But Microsoft, either toying with cancer in many other ways. For example, the study of microbial pathogens really have provided fundamental knowledge for the understanding of cancer. You, of course, are aware that Uncle genes really were discovered through the study of a chicken ritualize. And today the study of host pathogen.
interactions have provided insight into cancer that are extremely important for the fundamental knowledge. Of these disease. Of course, infectious diseases as an entity are really a significant challenge in the context of cancer patients. Many of the drugs that we administer to treat cancer or course have immunosuppressive power and increases the susceptibility of patients to infectious diseases and imposes it challenge in many. In many therapeutic set settings. And of course, the elephant in the room.
The resident microbiome, which in the last you know five years or so, is quickly emerging as a major factor, both in terms of cancer etiology and cancer treatment. So what I’m trying to tell you here is something that should be obvious and that this is an extremely important aspect of cancer biology and quite frankly, is one of the most exciting times to be involved in this research space. So the that’s perhaps the reason why maybe some of us were a bit disappointed when the cancer
microbiology piece of the Cancer Center was interrupted. In fact, when I was invited to give this talk, I was invited as a member of the Cancer Microbiology Group, which now doesn’t exist. And although I completely understand why the leadership of the Cancer Center to please this step, they had to tend to an impending Cancer Center grant. That obviously didn’t take many of these things, and it is clear that you know cancer, microbiology or microbes really are...
not the this the so called cancer

establishment from which reviewers will be drawn to review the Cancer Center grant.

I’m not really friendly to the concept of Micros, Ann and cancer.

For for whatever reason,

and even other considerations,

other currencies that are used in the evaluation of these grants,

such As for example in CI grants.

You know,

people work with my girls that that don’t score high on that because it will be a fundraising malpractice.

If you can send your grant when
I need to send it to NCI, which is much less generous and certainly less friendly to these courses. So although I totally understand these, I think is is an opportunity loss for leadership, particularly with the really the the history worse naughty related to cancer immunology.

People like Dundee Moniot or Charles Miller. In the space of Uncle Virus, for example, there is a lot of history here on this space. But life is life and the cancer establishment is the cancer establishment. This is the same establishment worse naughty related to cancer immunology.
It with people like blow it all the late,
allowing all that was advocating for it.
And he was really honestly looked down.
I was a close collaborator,
the law and he always complained.
Of course he was shielded by
the Ludwig Cancer Center.
He didn’t have to worry about,
but anyway,
I think he said more of a loss opportunity.
But I totally understand why
this this decision was made,
so enough venting enough Priscilla Teising.
Let’s get back to business here and in
order to put in context a little bit,
what I will tell you briefly is to consider the general mechanisms by which microbes induce cancer and there are two types of mechanisms. If you will. The direct Uncle Genesis and that is obvious when a virus is introduces an uncle gene itself. This is of course. The mechanisms behind HPB or a BB, for example. Or when it when they integration event itself access and origin, because obviously the viruses integrate upstream of some gene that can drive sort of proliferation and growth. That’s that’s direct on Go Genesis,
but arguably more common is the indirect organ Genesis, and this takes several forms. For example the form in which viruses in a cost, and immunosuppression activates for example. Other two more viruses. In the case of Kaposi sarcoma, is an HIV HIV infection. It comes to mind or when viruses triggers chromosome instability or translocation that eventually die. Of course, leads to cancer and other
aspects of the Director Genesis

more related to what I’m being,

I’m going to be telling you today is,

for example, chronic inflammation,

which is very well established to

be linked to to Uncle Genesis.

The production of proinflammatory

cytokines that have growth promoting

abilities combined with oxygen radicals.

They have a mutation or mutagenesis ability

leads to setting the stage for Franco,

Genesis is the case,

for example with Helicobacter

pylori and gastric cancer,

and in addition something that has been

emerging over the last few years and
that we sort of Pioneer in this area is the fact that certain organisms really produce direct Gina toxins that will drive the oncogenic event. So I say alluded these last two are the ones more relevant to bacteria, which is the type of microbes that we study in the lab. So bacterial is in this context bacterial colonization leads to both inflammation and genotoxin production and exposures of tissues to genotoxin and therefore predisposing those tissues to cancel. What I’m gonna be telling you today
00:08:23.121 --> 00:08:26.088 is the paradigm of two organisms that
NOTE Confidence: 0.79306287
00:08:26.088 --> 00:08:29.354 we study in the lab. Both of them.
NOTE Confidence: 0.79306287
00:08:29.354 --> 00:08:31.066 These organisms are salmonella
NOTE Confidence: 0.79306287
00:08:31.066 --> 00:08:32.350 and campylobacter jejuni.
NOTE Confidence: 0.79306287
00:08:32.350 --> 00:08:34.912 Both of them have been very
NOTE Confidence: 0.79306287
00:08:34.912 --> 00:08:35.766 strongly epidemiological.
NOTE Confidence: 0.79306287
00:08:35.770 --> 00:08:37.940 He associated with the development
NOTE Confidence: 0.79306287
00:08:37.940 --> 00:08:39.676 of cancer Campylobacter jejuni
NOTE Confidence: 0.79306287
00:08:39.676 --> 00:08:41.770 associated with an intestinal lymphoma,
NOTE Confidence: 0.79306287
00:08:41.770 --> 00:08:43.430 and while Salmonella Typhi,
NOTE Confidence: 0.79306287
00:08:43.430 --> 00:08:46.648 one of these family that we study in
NOTE Confidence: 0.79306287
00:08:46.648 --> 00:08:49.240 the lab is really a major cause of
NOTE Confidence: 0.79306287
00:08:49.323 --> 00:08:51.435 Gallbladder cancer and Gallbladder
NOTE Confidence: 0.79306287
00:08:51.435 --> 00:08:55.085 cancer in endemic areas is actually one
NOTE Confidence: 0.79306287
00:08:55.085 --> 00:08:58.410 of the main cancers that affect those.
NOTE Confidence: 0.79306287
00:08:58.410 --> 00:09:01.620 Individuals and it infections with
Salmonella Typhi and associated with a 204 risk of hip, hepatobiliary carcinoma and Gallbladder cancer, so these are important causes of cancer which incidentally are not in that 20% statistic that I told you about. Now, in the case of Campylobacter, what we discovered that was sort of central to understand how these organisms linked to oncogenesis is a characterization of a toxin that we did almost two decades ago.
00:09:36.321 --> 00:09:40.248 actually scary more than two decades ago?
NOTE Confidence: 0.79306287

00:09:40.250 --> 00:09:42.966 That he said toxin that caught our
NOTE Confidence: 0.79306287

00:09:42.966 --> 00:09:45.897 attention because of what you see here in in.
NOTE Confidence: 0.79306287

00:09:45.900 --> 00:09:49.077 In these images,
NOTE Confidence: 0.79306287

00:09:49.080 --> 00:09:51.824 You see them very much expanded with a
NOTE Confidence: 0.79306287

00:09:51.824 --> 00:09:53.955 large nuclei in comparison to control
NOTE Confidence: 0.79306287

00:09:53.955 --> 00:09:56.490 cell at the same excuse me Jorge,
NOTE Confidence: 0.79306287

00:09:56.490 --> 00:09:57.549 your your slide
NOTE Confidence: 0.8167658

00:09:57.550 --> 00:09:59.668 is not. It did not advance.
NOTE Confidence: 0.820451730769231

00:10:00.120 --> 00:10:01.347 Papa you mean?
NOTE Confidence: 0.820451730769231

00:10:01.347 --> 00:10:05.640 I mean what they have you on the 1st slide?
NOTE Confidence: 0.820451730769231

00:10:05.640 --> 00:10:09.060 Oh gosh, that’s that’s not good.
NOTE Confidence: 0.820451730769231

00:10:09.060 --> 00:10:11.780 That can you see them this way now?
NOTE Confidence: 0.820451730769231

00:10:11.780 --> 00:10:14.484 Yeah, that I can see those OK when
NOTE Confidence: 0.820451730769231

00:10:14.484 --> 00:10:17.558 I when I do it that way because OK,
00:10:17.560 --> 00:10:18.580 yeah unfortunately because
00:10:18.580 --> 00:10:20.620 whatever it would have been easier.
00:10:20.620 --> 00:10:23.000 But thank you for letting me know.
00:10:23.000 --> 00:10:25.720 OK so anyway, so here it is.
00:10:28.960 --> 00:10:31.402 OK, so this image is showing
00:10:31.402 --> 00:10:34.754 you the the cells that have been
00:10:34.754 --> 00:10:36.930 intoxicated with this toxin,
00:10:36.930 --> 00:10:39.194 showing this unusual morphology.
00:10:39.194 --> 00:10:42.024 In comparison we control cell
00:10:42.024 --> 00:10:45.352 and the reason these cells have
00:10:45.352 --> 00:10:47.488 that morphology is becaused.
00:10:47.490 --> 00:10:50.698 The cells are stuck on the G2M phase
00:10:50.698 --> 00:10:53.828 of the cell cycle and we found
00:10:53.828 --> 00:10:57.141 that the reason for that is that
00:10:57.141 --> 00:11:00.075 this toxin that we had discovered.
It has a genotoxicity DNA damage in capacity, those this is a toxin typical toxin of we call AB. Toxins have two types of parts. If you will the be part, which is what targets the payload to a particular cell and the payload part. The nucleus is is an endonuclease is actually an unusual in the nucleus in the sense that primary amino acid sequence would not overtly tell you that this is a new case. But when you look at the atomic structure, you can make out the catalytic side. So so this is a typical case of genotoxin that is responsible for for
00:11:48.518 --> 00:11:52.268 driving driving the day on today.

00:11:54.500 --> 00:11:57.930 Cancer development and in fact just recently,

00:11:57.930 --> 00:12:00.460 this has been formally demonstrated

00:12:00.460 --> 00:12:04.243 in an animal model that this

00:12:04.243 --> 00:12:07.158 toxin is responsible for Campylobacter

00:12:07.158 --> 00:12:10.538 jejuni’s ability to promote cancer so.

00:12:10.540 --> 00:12:13.308 It’s kind of awkward to have to advise

00:12:13.308 --> 00:12:16.240 it like this, but I will go ahead.

00:12:16.240 --> 00:12:18.388 So the second example is Salmonella

00:12:18.388 --> 00:12:21.296 Typhi and I need to tell you that

00:12:21.296 --> 00:12:23.819 the the basic about something that I

00:12:23.819 --> 00:12:25.883 think people things in context again

00:12:25.883 --> 00:12:28.340 and that is that someone had typhus

00:12:28.340 --> 00:12:30.115 and exclusive pathogen of humans.

00:12:30.120 --> 00:12:31.584 It causes typhoid fever.
One of those historical diseases if you will, but important for Genesis is the fact that those that survived the disease, many of them go on to persistently harbored the Organism. Within the Gallbladder and that is where the rubber meets the road and that is the reason why those individuals that are harboring salmonella typing in the in the areas are prone to develop Gallbladder cancer. And in the case of Salmonella the paradigm is slightly different than the paradigm in Campylobacter jejuni. But it shares it remarkably, is shares more than what would expect.
You need to think in terms of evolution that Campylobacter and Salmonella are they. Couldn’t be more far apart. One is an epsilon bacteria, the other is a gammaproteobacteria. It’s like absolutely no evolutionary connection and yet what is remarkable is that we discover a toxin in Salmonella typhi that we call typhoid toxin. That also has the ability to induce DNA damage, as shown here in this image, and when we characterize this toxin, we were surprised to see that the active subunit of this toxin
was virtually identical, that the active subunit of the completely unrelated toxin Curry by camping of active June. So this is really a remarkable piece of evolution. This is one of those head turning toxins that actually evolution put it together by fusing two toxins, one. That some of you may be familiar, it called pertussis toxin, what makes you a what is central for the pathogenesis of whooping cough. And then these other talks in that I described earlier. They cite a little distending toxin,
so this lower part of the talks in comes from pertussis toxin, and this upper Paradox income from side a little extended talks, so evolution hook them together to make this head turning toxin that Salmonella typhi encodes, and it is responsible for the genotoxicity of these organisms. And easy sent unusual toxin in many different ways that I don’t have time to go into, but one of the remarkable ways in which this toxin is unique is that it is other patient to the human host.
And what do I mean by that? Well, the receptor for these talks, you know the receptors. I should say we discovered two proteins, part of policing, one in epithelial cells and CD 45 in. In immune cells, but what is important here is what does the toxin see on this block of proteins and is the glycan power and we through like Andres and other types of studies for to address these kinds of questions we discovered that what Typhoid toxin likes if you will is glycans terminated in the sitting room.
We know that many Kacian hooked to galactose and to glucose or setting glucosamine in this particular fashion. And why is this relevant? Well, this is important because you may not know these or many of you may is that we humans are actually rather unusual mammals in many ways, and one of the ways in which terribly unusual is in our glycosylation pattern. All our sciullo glycans are terminated in a city neuraminic acid, but all other mammals in fact, like answer, terminated in Blakely, neuraminic acid,
and the reason is that the enzyme that is responsible for.

Can you see this slide and?

Well, whatever I continuously the inside that is responsible for putting these acts.

Oxygen here is mutated in humans.

We have a pseudogene there and therefore we are unique in that fashion and typhoid toxin combined likens exclusively terminated in a city in America.

And in fact, if you just change one oxidant in any of these glycans that Typhoid toxin likes and you already meaning in an array make like an array,
typhoid toxin does not bind. It also has the ability to distinguish. Just one Atom of oxygen. Remarkable piece of evolution that makes it able to target human cells and have that oncogenic effect. But in addition to having a genotoxin somewhere, typhi is actually has the 241. In other words, is also the chronic inflammation part that plays a role in the Uncle Genesis of Salmonella Typhi. And so it’s something that I think causes chronic inflammation of the
Gallbladder and that chronic inflammation, as is well known, leads to the development of cancer or contributes to development of cancer and the paradigm here is well known where as I said, the production of growth. Promoting cytokines combined with or radical oxygens that Armenta Genic eventually leads to the development of cancer angiogenesis. Growth stimulation and so on and so forth. So the issue is how does salmonella trigger inflammation now on this on? On the surface, this could be a rather simple story
and you may know that we are in now with innate immune receptors famously put into the scientific space by the late Charlie Janeway here at Yale and this innate immune receptors have the capacity to recognize bacterial products. You name it, many bacterial products can be detected by this innate immune receptors. Them essentially coordinate an inflammatory response and that inflammatory response eventually leads to pathogen rejection and.
they acquired immune response.

So this is central to the way we hosts,

But all mammals defend against microbial.

Pathogens now it turns out that then

from these framework it will be very

simple to think that someone other

because he has plenty of LPS.

He has plenty of these product

and is the detection of the

host that drives inflammation.

In other words,

this will be like a host centric view,

but work that we have done in our

lab for the last 15 years or so has
completely turn around this paradigm and discovered that that’s actually incorrect in the case of Salmonella, that salmonella really has a specific adaptations. Evolve by similar to trigger inflammation. So this is a pathogen driven process, not a host driven process, and the reason is very simple or not so simple. Salmonella, like many other microbes, when they encounter a mucosal site, being an intestinal being the Gallbladder mucosa, they need to compete with resident
microbiota who has a foothold on that issue and really put up a good fight. This is actually over. One of our main barriers against bacterial pathogens, particularly in this time, is the resident microbiota. The inflammatory response crosses it causes profound dysbiosis, which is essential for someone else to be able to colonize and replicate. Not only that, inflammation makes nutrients available, electron acceptors camper sourcers that otherwise would not be available in the an inflamed tissue,
and that drives the replication of the aluminum.

Population of salmon are so, so is the inflammatory response that causes even though someone else and intracellular pathogen the bulk of the bacterial replication comes from this lumenal population that is fed from the inflammatory response triggered by this in this bacteria.

Here. So a nice division of Labor. Now how does someone even managed to trigger an inflammatory response?

Mucosal sites which are actually is pretty difficult because mucosal
sites are subject to various stringent negative regulation of his native. Respected receptors precisely to prevent this microbiota that in theory can also stimulate in Amy receptors to trigger an inflammatory response and for all of us to be working with IBD or Crohn’s disease. To avoid that they’re very precise mechanisms to keep those innate immune receptors in check, and somebody had to trigger inflammation in that environment has does he do it? Well, it does sit through this amazing machine that Dan alluded earlier that
we discovered more than two decades ago. It’s an amazing sort of bacterial injection device if you will. That injects bacterially encoded proteins that. Have the capacity to modulate many signal transduction pathways. And it’s the ability to stimulate those signal transduction pathways and modulate cellular process for the benefit of the pathogen specifically relevant to inflammation are three of these effective proteins that activate Rho Family GTPases by either being exchange factors of
the Pro Family GPs is or forcefully

In the case of this particular effector that wouldn’t activate endogenous change factors and activate that,

and that leads to the activation of CDC.

and then the activation of CDC 42 leads to transcriptional responses that really are proinflammatory

This was a bit puzzling for a number of years because CDC 42 had never been linked to innate immune responses until very recently,

where we sort of cracked this little
puzzle and we discovered that the activation of CDC 42 by Salmonella leads to the formation of a noncanonical signaling complex made by pack one. A target of CDC 42 and these other components. Trap 6 Tab Tak, One Tab 1 Tab 2 that leads to the inflammatory response and what is what explains the whole thing is that these signaling complexes identical to the signaling complex that is tripped by narimi receptors. So what someone in essence is doing is going down the signaling pathway.
so that so as to avoid the negative regulatory system and trigger essentially an innate immune response. But by non-Canonical methods, so he uses other type of mechanism similar to this going downstream of Canonical signaling pathways. But since my time is up I just gonna put up a sort of a summary of these and sort of to give you a flavor or how these effector proteins can go down. Different signaling pathways intersect with signaling pathway. For example this effector can activate the rig I and MD I5. A nucleotide sensing pathway,
but without the need of nuclear dice. It just simply activates regay by interfacing with dream 56 and trim 65. Two regulators of this pathway you. We could make them activates them and trips this signaling pathway without the need of The Agonist of those receptors, and the same applies to another effector here that it actually inhibits an anti-inflammatory pathway. So, but since I don’t have time. I had to skip it, so I hope that you got a sense of the sophistication by which bacterial pathogens manipulate cells in in ways.
that benefit them but doesn’t benefit us.

And through the production of Gina toxins or inflammation, it leads to the predisposition to cancer and then finally last but not least, people that were involved in this work obviously and talked to work that was done a number of years ago as well, and thank you very much.

but for the inflammation pathway, who we? Indiana were involved and one whose did all this work and Mary, of course, had made the pioneering discoveries of the Genotoxin in Campillo Bacter and set in motion all this work. And thank you very much.
And with that I’m gonna stop sharing if I can.

And.

OK, well thank you very much.

Jorge is very interesting.

Very exciting work.

I don’t know how to swim.

I should know how to stop sharing.

but you help me on that one.

Yeah, OK.

If people have questions,

you can type them into the chat,

or Renee’s, or way

to unmute them.

We can, if you’d like, sure.
I’m asking a quick question. I was very struck by that by what appears to be the convergent evolution of these two nuclease.

Yeah, it’s really very striking.

Is there? What is the advantage of the bacteria to induce cell cycle arrest? What cell cycle arrest actually is also growing inflammatory? So probably one of the main drivers is the Pro inflammatory response and also in the case of some type is using this activity to target immune cells. So obviously if you’re a virus and you know a thing or two about them and you integrate your
genome in the host, you’re free.

You know.

That’s the way you can persist as long as you want.

If you’re somebody that I feel you have.

4761 those are the number of open reading frames,

potential antigens you need to hide.

You can’t do that right?

So the way somebody that he does it is by creating a sort of immunological suppression around the site,

wherein colonizes and these toxin is central for that.

For the persistent infection,
by targeting immune cells.

So, and in the case of Campylobacter, inflammation is central for the bug and and this proinflammatory aspect of DNA damage. Is probably what evolutionary selected for these, you know, toxins and the in the process.

Thank you are there are there other questions for Jorge? Alright, well thank you very much. I think I think Dan froze. You were frozen Dan. Oh, I’m sorry, frozen.
I guess introduce you, Melinda Kay. Great don’t we love the advances in technology. Thank you Doctor Glenn that was fabulous Ann. I am now delighted to introduce Doctor Nicole Diesel to present her research on environmental carcinogens and thyroid cancer. Doctor Diesel is an associate professor of environmental health in the Yale School Public Health and she received her PhD in her Masters in industrial hygiene from the Johns Hopkins School of Public Health. Her environmental exposure assessment...
strategies aimed to reduce exposure
NOTE Confidence: 0.8219546
misclassification for epidemiological.
NOTE Confidence: 0.8219546
Studies and in advance understanding
NOTE Confidence: 0.8219546
of the relationship between exposure
NOTE Confidence: 0.8219546
to environmental environmental
NOTE Confidence: 0.8219546
chemicals in the risk of cancer
NOTE Confidence: 0.8219546
in other adverse health outcomes,
NOTE Confidence: 0.8219546
she serves as the Pi of a study funded
NOTE Confidence: 0.8219546
by the American Cancer Society and
NOTE Confidence: 0.8219546
investigating exposure to flame retardants,
NOTE Confidence: 0.8219546
pesticides,
NOTE Confidence: 0.8219546
and other persistent pollutants in
NOTE Confidence: 0.8219546
thyroid cancer risk and of note,
NOTE Confidence: 0.8219546
she is the winner of the Yale Cancer
NOTE Confidence: 0.8219546
Center 2020 Research Prize in population.
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Science for her research on this topic,
so we’re delighted for your presentation.

Doctor diesel.

Take it away.

OK, thank you so much Melinda for the generous introduction.

Very pleased to be here to share some of my recent work with you.

I really enjoyed Doctor Galanes presentation looking at exposure to microbial pathogens and the associated toxins,

and I’ll be switching gears a little bit to look at work looking at the Epidemiology of exposures to chemical toxins and thyroid cancer risk.
can let me know if there’s any issue there.

I first wanted to take a moment just to tell you about the motivation of my research and the research I’ll be presenting today and talk about environmental risk factors for cancer. We know that third of cancers are attributable to modifiable factors. We often think of things related to diet, alcohol, tobacco, these so-called lifestyle factors. But this also includes infections which we just heard about as well as pollution. So how much of cancer cases can we attribute to this pollution? While a doll and Peto in their landmark...
A study estimated about 7% of cancer deaths could be attributable to occupation, pollution and industrial products, in many experts agree that this percentage is likely grossly. Under arrest made due to the extremely limited data on the commercial chemicals that we encounter in our day-to-day lives. So in the United States there are 80,000 chemicals that are licensed for commercial use, and of those only 200. So not even a percentage of them have been screened adequately for carcinogenicity. And every time I share this statistic,
I find it really striking.

Another reason why this is so important is that you know many of these exposures are outside individual control. These are things in air pollution or water supply, the food supply, our workplaces, so we really rely on the government to protect us from exposure to these potentially harmful chemicals and our regulatory system really is quite inadequate to serve this purpose. The way it’s structured. Chemicals have to be proven harmful rather than proven safe at the outset,
so it normally requires researchers like myself and others in my fields who study chemicals you know for decades before we acquire enough evidence to demonstrate harm for particular chemical. And also importantly, we know these exposures are not distributed equitably across populations and that populations experiencing other social disadvantages are often disproportionately exposed to certain pollutants, and some of these points are highlighted in a forthcoming book chapter that I worked on with Doctor.
NOTE Confidence: 0.8562479
00:31:51.250 --> 00:31:53.686 So turning to the specific research
NOTE Confidence: 0.8562479
00:31:53.686 --> 00:31:56.369 I want to talk about today,
NOTE Confidence: 0.8562479
00:31:56.370 --> 00:31:58.938 which is related to thyroid cancer,
NOTE Confidence: 0.8562479
00:31:58.940 --> 00:32:01.929 thyroid cancer is one of the
NOTE Confidence: 0.8562479
00:32:01.929 --> 00:32:03.210 fastest growing malignancies.
NOTE Confidence: 0.8562479
00:32:03.210 --> 00:32:05.766 It has nearly tripled over the
NOTE Confidence: 0.8562479
00:32:05.766 --> 00:32:07.044 past few decades.
NOTE Confidence: 0.8562479
00:32:07.050 --> 00:32:10.046 As you can see in these graphs
NOTE Confidence: 0.8562479
00:32:10.046 --> 00:32:12.859 of SEER cancer incidence data.
NOTE Confidence: 0.8562479
00:32:12.860 --> 00:32:16.644 You can also know by looking at the
NOTE Confidence: 0.8562479
00:32:16.644 --> 00:32:21.204 Y axis that females have three times
NOTE Confidence: 0.8562479
00:32:21.204 --> 00:32:24.699 the incidence compared to males.
NOTE Confidence: 0.8562479
00:32:24.700 --> 00:32:27.640 Can thyroid cancer, you know,
NOTE Confidence: 0.8562479
00:32:27.640 --> 00:32:30.570 has a very good prognosis.
NOTE Confidence: 0.84964806
00:32:30.570 --> 00:32:35.266 It’s more than 90% survival after 20 years.
However, survivors face many physical, psychological and financial challenges. With the prolonged treatments, increased surveillance risk of second primary cancer and other quality of life issues. So this increase is likely certainly due at least in part to improvements and changes to diagnostic techniques, imaging techniques and an fine needle biopsy’s. So there’s some debate about what proportion can be attributed to this increased diagnostic scrutiny, but many analysis suggests that about half of this.
Trend can be linked to these diagnostic changes, leaving half for environmental or lifestyle factors. I’ve hypothesized that increasing exposure to thyroid hormone disrupting environmental chemicals such as these flame retardants or PVD ES may be partially driving this increasing trend. So I’ll just talk a little bit more about these people. These are actually a lot of thyroid hormone disrupting environmental chemicals in use in the environment. These flame retardants were widely added.
Too many different products.
The polyurethane foam in mattress is an couch, cushions and vehicle seats, including baby car seats. They were also added to electronics like phones, cell phones, televisions, computers and the reason they were added was to meet a flammability standards such that if these products you know caught fire they would burn. More slowly, which is a good thing from a public health perspective. However, these chemicals once added to these products,
did not stay bound in the matrices as indicated by their manufacturers and instead have migrated out into our homes. At home environments, cars, workplaces, etc. So due to this widespread use as well as disposal and improper disposal of these chemicals, they aren’t ubiquitous and more than 90% of the population here in the US and globally are exposed to these chemicals. And this also they are extremely persistent once they get into their homes or our bodies, they do not degrade very easily, so they stick around for years and decades. So due to concerns about this
persistence and potential toxicities, these particular group of chemicals, the PDE’s were phase outs were initiated over the last. Past decade, however, exposures do continue for the reasons I described. Their persistence, you know, their presence in products made before then. As well as their presence in the food supply and elsewhere. One other group of chemicals that will be talking about today are the polychlorinated biphenyls or PCB’s.
These were also used widely in electrical equipment, hydraulic machinery construction materials. These were banned in 1979, so again, you might say why? Why are we even studying these now? Well, there’s still around and they’re still around in our our bodies. Our bloodstreams in the environment, and in fact here in Connecticut there’s been some renewed concern about these legacy chemicals. They were commonly used in buildings, including schools constructed in the 1950s to 1970s.
and many of these schools now are in need of repairs and renovations, and there have been some notable schools in Connecticut that I’ve had PCB levels exceeding safe levels. Closures of schools you know, insufficient funds to do a proper and safe remodeling or renovations, and again, often these are in. Kind of environmental justice communities. So another reason to study these legacy chemicals is as they get phased out, new chemicals come to take their place, and many of those are also also have similar properties and so understanding.
These may help us inform greener chemistry or future regulations of other chemicals.

So we hypothesize that these PV East could be contributing to that increasing trend in thyroid cancer.

Here is a graph showing increasing exposure over a similar time period where we saw thyroid cancer cases start to go up.

So these are measurements taken from blood samples from a blood bank. In the US.

You can see about a doubling every five years of these particular chemicals.

So looking at more recent data, I, as I mentioned, these have been somewhat phased out.
You can see that well levels have come down since those some of those earlier years, but then they really have somewhat plateaued. Or are, you know some some particular congeners of these? In this family of chemicals are still increasing slightly an we see similar. Trends with the PCB’s that levels have come down since they were banned, but then they reached this plateau in the population because of their persistence and then as new chemicals come on we may be introduced to those on top of these exposures.
Hey and so why? Why do we think these may be linked to thyroid cancer? These chemicals are established thyroid hormone disruptors. Their endocrine disruptors and over here I have an image of our thyroid hormone thyroxine and then thyroid hormone thyroxine and then the PCB's and the PVD ES and their general chemical structure so you can see immediately how structurally similar these chemicals are. Shut thyrax, and we've got the two. Aromatic rings and then while thyroxine has iodine, these chemicals have other halogens.
They have either chlorine or bromine’s. Just to further illustrate when for example this particular PDE gets metabolised, it gets this hydroxyl group added. And now even more closely resembles Thyrax in so the in vitro studies have shown that these chemicals can competitively binds with thyroid transport proteins and results in reduced circulation of thyroid hormones, which could then result in dysregulation of the transport and signaling pathways, potentially leading to. Overproduction, of hormones to compensate.
proliferation in the thyroid and potentially neoplasia. So as you know the hypothalamus, pituitary, thyroid axis is this very well choreographed system. These perturbations or dysregulation of these systems can perhaps trigger some of these. Some proliferation of the thyroid and potentially lead to thyroid cancer. I’m just showing this slide to also illustrate that some hypothesized mechanisms, such as, have been shown to be capable to directly bind to DNA,
leading to mutations and could potentially lead to carcinogenesis that way. So before we launched our study, there had only been two other studies examining this hypothesis. This idea that these PPDS could be linked to thyroid cancer. So the first two rows of this table or the two prior epidemiologic studies in the third row was the study that I lead. A couple things to point out here is that the case is the studies that came before us had moderate study populations, and ours was larger. We also looked at more...
chemicals and importantly, we looked at single and multi pollutant models so.

So what I mean by that is that in the real world you know we’re not exposed to one chemical at a time, where typically exposed to groups of chemicals or mixtures of chemicals and traditional environmental. Epidemiologic studies have looked at chemicals just one at a time, and in my work we’re looking at these so-called mixtures using different modeling techniques to look at the joint effect of exposures to multiple chemicals.
Similarly for the PCB’s, the other chemicals there were also only two previous studies before we did ours. Also the other studies were a bit smaller and we also looked at mixture modeling. One other one shortcoming, I wanted to point out actually in reference to at least one of the other studies is that our study was a case control study. So we did collect serum samples to do our. Environmental chemical measurements after diagnosis. Whereas one other study collected pre diagnosis samples, we think you know.
So we’re using this post diagnosis sample to try to capture exposures in the past. While it’s not optimal, we think this is actually a pretty strong and reasonable assumption, because we know that these chemicals have half lives of years and decades. Ends may well reflect past past you some past exposure.

OK, so just a few more details about the study we conducted. I LED a study within a study and that larger study was the Connecticut thyroid cancer case control study, which was led by Yahweh Chung, who was our former colleague.
here at the Yale Cancer Center.

We focused on women because they have that three times higher risk.

I showed earlier about 90% of our cases were white, so we.

Focused on the white population because our numbers were really small for looking at other demographics.

I do think now this is something I would like to follow up on.

more in another population, we focused on papillary thyroid cancers.

That’s about 85% of the new cases or papillary.

We also collected very detailed
00:44:48.590 --> 00:44:50.180 information about demographics, lifestyle, diet.
NOTE Confidence: 0.8271222
00:44:51.158 --> 00:44:54.092 Many other risk factors that we can control for other factors.
NOTE Confidence: 0.8271222
00:44:54.092 --> 00:44:56.620 We collected the blood sample at the time of the interview and then measured the participants blood samples for 11 different peyizan 32 PCBS, some pesticides like DDT, which are also structurally similar to these.
NOTE Confidence: 0.8271222
00:45:08.090 --> 00:45:10.958 which this analysis also gave us.
NOTE Confidence: 0.8271222
00:45:10.960 --> 00:45:16.220 These classes of chemicals.
NOTE Confidence: 0.8271222
00:45:16.220 --> 00:45:22.127 And again we looked at both pollutants, one at a time, like like most studies do and then multi pollutant models.
NOTE Confidence: 0.8271222
00:45:29.310 --> 00:45:31.872 OK, so here’s some results from
00:45:31.872 --> 00:45:33.153 our study population.

00:45:33.160 --> 00:45:35.295 These are factors that differed between cases and controls,

00:45:35.295 --> 00:45:37.003 so our cases had a lower educational attainment compared to controls.

00:45:39.824 --> 00:45:41.720 They did have a history of benign thyroid disease.

00:45:41.720 --> 00:45:43.855 That’s a strong risk factor for thyroid cancer.

00:45:45.570 --> 00:45:48.002 Alcohol consumption was actually.

00:45:48.002 --> 00:45:50.434 Higher, lower, lower in cases.

00:45:50.440 --> 00:45:54.628 This is one of the few cancers where alcohol actually has been consistently shown to have a protective effect.

00:45:54.630 --> 00:46:00.482 Higher, lower,

00:46:00.482 --> 00:46:02.968 lower in cases.

00:46:02.968 --> 00:46:06.028 shown to have a protective effect.
An cases also had a history of thyroid cancer and higher BMI, which has been shown now in several studies indicating another possible risk factor that can also be interrelated to like endocrine disrupting chemicals and also.

OK, so here are some results from our single pollutant models where we looked at one chemical at a time. These are increasing categories of exposure within each of these different pollutants. You know, odds Ratio 1 means no effects, and anything above one would indicate an Association with thyroid cancer.
So you can see here that there’s really not much going on with these individual models. If anything, the odds of thyroid cancer seem to be lower than those who are exposed compared to the reference group of low exposure. The medium and high groups are not at an elevated odds of thyroid cancer except for this one chemical. This PB 153.

So when we move to our multi pollutant models, the results are also somewhat null. We have two multi pollutant models.
Here using Bayesian modeling, which I won’t get into here. But here you can see that it’s the picture is still pretty null except for. In this case we have this other, a different chemical PDE 100. Was associated with elevated odds of thyroid cancer using both those models. And then finally we did this one more mixture type approach of principle, components analysis and in this work we found that people who had had this. Combination of exposures which was higher. An lower PDE 209 had an elevated odds of thyroid cancer. So then moving on to the PCB use in this...
for this one because we had so many, we had 32 different chemicals. I’m just going to present some some groups of structurally similar PCB’s, which was another approach we used to look at groups of chemicals. So in this model this kind of we’re just looking at one group at a time. Odds ratios are hovering around 1:00, so again pretty null findings. Not. We’re not seeing a link between exposure and thyroid cancer. However, it said the most intriguing part of this study was when we took a closer look at the groups of people,
people who are exposed. During who were younger during peak production, who were born during peak production of PCB’s. So presumably would have their highest exposure in very early life. They consistently had higher odds of thyroid cancer, including this group of PCB’s that were particularly structurally similar to thyroid hormones, so this was quite intriguing to me, suggesting maybe the timing. Of exposure could be important. OK. So just to summarize,
some of the key takeaways from both.

Of these studies.
Strengths were that we looked at this larger population and incorporated these different models to account for Co exposure to multiple pollutants. The results were generally null.

You know, we did see a few chemicals here and their associated with elevated odds of thyroid cancer. Particularly, this was more consistent when we looked at the group of women who were born during peak production of PCBS. However, this we only have 3 studies now.
For these, each of these groups of chemicals so. There’s really insufficient evidence to rule them out, and I think there can be some improvements to the study design to try to look at this more carefully. I think looking at early life would be important, and using a prospective design where we could have samples collected pre diagnosis could help you know. Really, try to nail nail down if anything is going on here. And then finally I just want to talk
about how where I’m taking this work.

I have now expanded this work in adults to looking at children.

So with my collaborator Xiaomei MA, also very active in the Cancer Center.

We are looking at environmental exposures and pediatric thyroid cancer,

We are looking at environmental exposures and pediatric thyroid cancer,

so here’s some incidents.

Data on pediatric thyroid cancer.

It has also been increasing over time.

An children are less likely.

Targeted for increased screening and diagnosis and imaging,

so these trends are concerning,
so we have some projects underway to try to look at environmental exposures in this more vulnerable population. And with that I would like to acknowledge all my wonderful collaborators and my funding from American Cancer Society as well as the Yale Cancer Center for getting me started in this line of research. Thank you.

Thank you Doctor Diesel, that was fantastic. A little alarming. I would say when we start to think about how many you know, carcinogens exist in our environment.
in the fact that I’m intrigued by
the policy statement that we have to show harm before anything can be done
and have these substances banned.
Do you think there’s any potential to being able to reverse that or change that policy?
Or will it take years and more data to do so?
Yeah, so a lot of the chemicals were kind of grandfathered in when we established the Environmental Protection Agency in 1970.
There is a new act that is supposed to reverse this burden of proof, but I don’t think it’s going to be retroactive, so I am encouraged to with
the current administration that we may start to move towards a different model. Also, in Europe they have stronger precautionary policies where if there’s a safer alternative you have to use it. And you know not to wait until we prove something with certainty to take some sort of action. Great, right? So there’s a couple of chat questions I’ll just quickly read them. Heard a Chow asked about any data on Agent Orange and thyroid cancer. Yeah, so Dioxin’s is one of the constituents of Agent Orange. Well, Agent Orange. Had you know these defoliant chemicals?
So various herbicides?

And then? Dioxin’s

That’s a great question,

’cause they’re also very structurally similar to the other chemicals

I presented, but I’d have to,

and some of the chemicals we looked at.

Some of the groups were dioxin, like.

I’m not, I’m not sure of any

specific studies coming to mind,

but it it seems likely that

eative a similar.

Well, they’re structurally similar

to the other chemicals. OK,

great and then Jeffrey Townsend
has a question where you do see elevated odds of thyroid cancer?

Do you have any evidence discriminating between the two hypotheses of effects that occur due to hormone disruption compared to effects that might be arising due to induction of carcinogenic mutation?

Do you see ways to do this? Yeah, that’s a great question.

I don’t really do this type of mechanistic work.

I know the thyroid hormone disruption hypothesis.

There’s been a lot more
mechanistic work in that area,
but I’d be open to suggestions for
how this could hopefully maybe
inform some mechanistic studies.
I think it would be,
and vice versa.
The study could inform mechanistic
work and vice versa.
Yeah,
that’s a great point.
And then Ashida had mentioned in regards
to the policy of showing harm that
Europe does the reverse of the US.
Do they see as a different trend?
Actually, thyroid cancer cases
00:55:19.044 --> 00:55:21.270 are going up globally and the
NOTE Confidence: 0.8658378
NOTE Confidence: 0.8658378
00:55:23.440 --> 00:55:25.565 Actually, they were first observed
NOTE Confidence: 0.8658378
00:55:25.565 --> 00:55:28.171 in Sweden where they have breast
NOTE Confidence: 0.8658378
00:55:28.171 --> 00:55:31.041 milk banks an they saw these flame
NOTE Confidence: 0.8658378
00:55:31.041 --> 00:55:33.241 retardants going up in human milk
NOTE Confidence: 0.8658378
00:55:33.241 --> 00:55:35.552 samples which caused a lot of alarm.
NOTE Confidence: 0.8658378
00:55:35.552 --> 00:55:38.016 At that time we didn’t know if
NOTE Confidence: 0.8658378
00:55:38.016 --> 00:55:40.300 they were carcinogenic or not,
NOTE Confidence: 0.8658378
00:55:40.300 --> 00:55:42.701 but given that you know babies were
NOTE Confidence: 0.8658378
00:55:42.701 --> 00:55:45.779 going to be exposed to these chemicals,
NOTE Confidence: 0.8658378
00:55:45.780 --> 00:55:46.890 that sort of.
NOTE Confidence: 0.8658378
00:55:46.890 --> 00:55:48.740 Triggered this whole area of
NOTE Confidence: 0.8658378
00:55:48.740 --> 00:55:51.024 research on these flame retardants
NOTE Confidence: 0.8658378
00:55:51.024 --> 00:55:52.497 and other chemicals.
NOTE Confidence: 0.8658378
00:55:52.500 --> 00:55:52.860 Great
and then I just have one final question.

The email that we all received last week about benzene being in some of the hand sanitizers for COVID-19 protection? Do you have any thoughts or comments on that? Yeah, I read that I read some of the materials. I think benzene you know is a known human carcinogen. However, it is present in many sources, so I would really want to understand how risky this is. I think we need to know how much. Benzene and how does that compare to? Like putting gasoline in your car,
you know or being walking near the roadway
NOTE Confidence: 0.8349844
so I didn’t raise too many alarms yet,
NOTE Confidence: 0.8349844
but I would need.
NOTE Confidence: 0.8349844
I feel like I need more data to
NOTE Confidence: 0.8349844
be able to reach that conclusion.
NOTE Confidence: 0.8349844
And I mean, the so yell health,
NOTE Confidence: 0.8349844
environmental, safety and health
NOTE Confidence: 0.8349844
said like let’s be precautionary.
NOTE Confidence: 0.8349844
Let’s just get rid of these sanitizers,
NOTE Confidence: 0.8349844
you know, let’s take an action
NOTE Confidence: 0.8349844
before we have all the answers,
NOTE Confidence: 0.8349844
so I think that’s, uh,
NOTE Confidence: 0.8349844
you know, very sensible.
NOTE Confidence: 0.8349844
Approach OK great.
NOTE Confidence: 0.8349844
Well
NOTE Confidence: 0.803357
thank you so much Dan.
Do you have any other closing comments? I'll just thank both our speakers today. Two terrific talks. I learned a lot. Thank you. Yes, thank you. Have a great day. Thanks.