Good afternoon everyone. Welcome to the Yale Cancer Center grand rounds. Today we have two fantastic speakers both who are in the developmental therapeutics program of the Yale Cancer Center. And why don’t we get started? I’m delighted to introduce Doctor James Farrell, who is a professor of medicine in the director of the Yale Center for Pancreatic Diseases. He’s an internationally recognized, expert and pancreatic disease.
treatment and research,
and is known for his development of personalized therapy approaches for pancreatic cancer and early detection biomarkers for pancreatic cancer. He received his medical degree from University College Dublin and completed internal medicine training at Johns Hopkins. And a gastroenterology fellowship at MGH and Harvard Medical School. He then completed advanced Therapeutic Endoscopy fellowship training at Massachusetts General and Brigham and Women’s, in addition to his clinical practice and pancreatic disease.
and interventional endoscopy.

His clinical research has focused on early detection of pancreatic cancer, including studying pancreatitis, high risk individuals and pancreatic cysts. His translational research includes the development of personalized therapy.

Approaches for pancreatic cancer and the evaluation of biomarkers and pancreatic disease. Delighted to turn it over to you Doctor Farrell and look forward to hearing what you have to say.

Thank you. Thanks everyone and good afternoon.
Thanks for the invitation.

So we’re going to talk about pancreatic cancer, early detection prevention this morning.

It really is going to be an overview in the time allotted and kind of emphasizing some of the work that we’ve been involved with.

So when you think about pancreatic cancer in terms of overall incidence, it’s actually low down in the list, and maybe sometimes doesn’t get as much prominence as other cancers such as prostate or lung or colon.

But when you look at cancer related deaths,
it jumps up the list, and it’s probably around the third or fourth most common cause of cancer related death. So in 2022, it’s estimated there’ll be about 62,000 cases and just under 50,000 deaths related to it and has long been predicted and certainly on its way by 2030, it’s expected to be the second most common cause for cancer related death. It also needs to be emphasized that yes, there have been improvements in the management and treatment.
00:02:31.154 --> 00:02:32.366 of pancreatic cancer,
NOTE Confidence: 0.638810976
00:02:32.370 --> 00:02:32.842 but really,
NOTE Confidence: 0.638810976
00:02:32.842 --> 00:02:33.786 they have fallen short,
NOTE Confidence: 0.638810976
00:02:33.790 --> 00:02:35.186 although progress still continues
NOTE Confidence: 0.638810976
00:02:35.186 --> 00:02:37.630 to be made and just emphasizing the
NOTE Confidence: 0.638810976
00:02:37.630 --> 00:02:39.660 need for a better and improved early
NOTE Confidence: 0.638810976
00:02:39.660 --> 00:02:41.589 detection for this particular disease.
NOTE Confidence: 0.638810976
00:02:41.590 --> 00:02:44.020 If we're hoping to improve
NOTE Confidence: 0.638810976
00:02:44.020 --> 00:02:45.478 the overall survival.
NOTE Confidence: 0.638810976
00:02:45.480 --> 00:02:45.794 Now,
NOTE Confidence: 0.638810976
00:02:45.794 --> 00:02:47.678 there has been tremendous progress in
NOTE Confidence: 0.638810976
00:02:47.678 --> 00:02:49.880 the world of understanding cancer,
NOTE Confidence: 0.638810976
00:02:49.880 --> 00:02:51.524 biology of pancreatic cancer.
NOTE Confidence: 0.638810976
00:02:51.524 --> 00:02:52.757 Along the bottom,
NOTE Confidence: 0.638810976
00:02:52.760 --> 00:02:55.004 here is a normal progression through
NOTE Confidence: 0.638810976
00:02:55.004 --> 00:02:57.338 low grade and high grade dysplasia
or so called pen and lesions to invasive pancreatic ductal adenocarcinoma. It always typically starts with the activation of an oncogene, and then it’s been several well known characterized tumor suppressor gene mutations, including P53 and SMAD 4. It’s also worth noticing that related to this is another entity of the pancreas called Ipmn or introductive papillary mucinous neoplasm. It also goes through a similar sequence, resulting in an invasive neoplasm with similar mutations, such as in K.
Ras, but also some unique ones.

Which is Gina Genas uncle

Gene observation activation,

but it’s very hard to talk about.

Carcinoma without talking

about the other disease of ipmn.

It’s also worth making the

point that this progression,

we think from the initial K.

Ras mutation to the time of

let’s say metastatic cancer,

is probably of the region

of about 11 years or so.

And so this number is debatable.

But basically it’s a long time for us

to try and intervene and understand
what’s going on during this sequence. However, it’s also worth noting that in its early stages and pre invasive stages with pannin, it typically can’t be seen. Radiologically, when an early stage cancer does arise, this can be seen by radiologic imaging, but in the time required to go from an early stage, resectable, surgically manageable pancreatic cancer to an advanced metastatic stage can be as short as one to 1 1/2 years, and so. At that point, the clock does start ticking.
And it brings up the issue of missed cancers, interval cancers, cancers that may be seen on imaging with more advanced uses of imaging. Now there's no shortage of biomarker signatures for early pancreatic cancer. This is just a selection of some of these, and they all have very promising operating characteristics or AUC. So in the top left is a salivary based 4 gene panel of RNA that we worked with again comparing non worked with again comparing non cancers to patients with cancers with a very respectable AUC of .97. Below is a work of Anoop Sharma. He said who Jim looking at?
DNA methylation markers?

And this is a particular 4 gene cell free DNA methylation panel,

again with very respectable AU C curves.

We’ve kind of come to the age in 2022 where we now have the beginning of commercially available panels,

of cancer in general,

so you have heard of GRAIL and cancer seek,

you’ve heard of cancer seek,

but now Innova has an antibody panel specifically for pancreatic cancer,

in the studies to date at least shows very promising AUC’s
for the differentiation between early stage cancer and control. And in fact, this is currently being tested in a high risk population the Pantheon One study in which we're involved with results of which will be out soon. But the problem is yes, there are all these great biomarker signatures, but they're not being applied or can't be applied to the general population. And this has to do with an issue of mathematics and the 1.6 lifetime risk, and the low,
relatively low prevalence of pancreatic cancer. What that means is that even with a very good sensitivity and specificity, whereas you have a very high negative predictive value, you have a very low positive predictive value. And even as you increase the sensitivity and specificity of these tests in the general population, the positive predictive value only gets as good as about 20%. And what that means is that most of the positive tests that you’re going
to see in the general population
NOTE Confidence: 0.892557816785714
will turn out to be false positive tests,
NOTE Confidence: 0.892557816785714
and this is one of the major
NOTE Confidence: 0.892557816785714
reasons why we haven’t.
NOTE Confidence: 0.892557816785714
Unraveled general population
NOTE Confidence: 0.892557816785714
screening currently.
NOTE Confidence: 0.892557816785714
So as a result of that,
NOTE Confidence: 0.892557816785714
we tend to focus on high risk groups
NOTE Confidence: 0.892557816785714
and the three big high risk groups
NOTE Confidence: 0.892557816785714
which are these enriched groups
NOTE Confidence: 0.892557816785714
that increase the prevalence of the
NOTE Confidence: 0.892557816785714
chances of developing pancreatic
NOTE Confidence: 0.892557816785714
cancer include new onset diabetes.
NOTE Confidence: 0.892557816785714
And I’m not going to go spend
NOTE Confidence: 0.892557816785714
too much time on this today.
NOTE Confidence: 0.892557816785714
Shiraz Shari,
who’s kind of a leader in this area, spoke.

Very passionate about this subject.

Here at Yale several weeks back,

but diabetes interplays with everything

The other two high risk groups.

So what about pancreatic cysts?

So pancreatic cysts, and specifically a type of cyst called an ipmn, 

are incredibly common findings, 

incidentally, found typically on CT scans or Mris of the abdomen.

We use a variety of imaging
features of these incidental cysts, such as high risk stigmata, are they associated with jaundice or amass. Is the pancreatic duct, for example dilated, are worrisome features? Is there a nodule? Is there an intermediate ductal dilation of the main pancreatic duct is assessed greater than 3 centimeters? Is there a change in caliber? Is a cyst getting rapidly bigger over time? So we use these imaging features to try and better understand what’s the risk of? This particular IP man having cancer, and so we think that overall
there's a 1% chance per year of these IP amends developing cancer, and when we look at the imaging, one of the first questions that we end up trying to sort out is should these patients undergo surgery and so we use a combination of the imaging. But even with our best imaging in 2022, it’s likely that anywhere in the region of about 60% of patients are undergoing unnecessary surgery, meaning that we are resecting low grade dysplastic lesions, not the high grade dysplastic, not the invasive cancer patients.
that we’re really trying to find.

And so this kind of begs for an improvement in this particular area and one particular area has been in looking at the role of cyst fluid, understanding the fluid in these cysts. And this can be very helpful for making the diagnosis of the cyst. Like is it an IPMN or some other type of precancerous? But it also has the ability for us to look at, for example, methylation markers,
00:09:21.674 --> 00:09:24.440 and this is very promising 2 panel

00:09:24.440 --> 00:09:26.575 marker that has a very good high

00:09:26.575 --> 00:09:28.250 operating characteristics for separating

00:09:28.250 --> 00:09:30.420 out low grade dysplastic system

00:09:30.420 --> 00:09:32.999 which we don’t want to operate on

00:09:32.999 --> 00:09:35.172 and high grade dysplastic and cancer cells.

00:09:35.172 --> 00:09:37.260 So expect to hear more in time about

00:09:37.315 --> 00:09:39.037 these particular markers and SIS fluid

00:09:39.037 --> 00:09:41.259 as well as other even protein based

00:09:41.259 --> 00:09:42.954 markers in this particular field.

00:09:45.170 --> 00:09:47.210 The other issue with pancreatic

00:09:47.210 --> 00:09:48.842 cysts relates to surveillance,

00:09:48.850 --> 00:09:51.901 and so as we get better at deciding which

00:09:51.901 --> 00:09:54.068 patients shouldn’t undergo surgery,

00:09:54.070 --> 00:09:56.471 it’ll become obvious to people that the

NOTE Confidence: 0.744730942222222
The vast majority of these patients with IPMN
nothing really happens them dramatically.
Over time, they might get a little bit bigger.
Their duct might get a little bit bigger,
but their chances of developing cancer requiring surgery is incredibly low,
but we’re obliged to follow them, especially younger patients,
because we’re telling them your cyst.
As a risk of developing cancer.
And in that, the field of surveillance has really become a very complex issue,
primarily because there’s a lot of cysts involved,
so it’s estimated at about 6 million.
00:10:26.841 --> 00:10:28.369 people in the United States.

00:10:28.370 --> 00:10:30.866 At least have some form of pancreatic cyst,

00:10:30.870 --> 00:10:32.352 and it’s brought up questions of

00:10:32.352 --> 00:10:33.762 when should we stop surveying

00:10:33.762 --> 00:10:35.587 patients that have pancreatic cysts?

00:10:35.590 --> 00:10:36.846 Is there an age?

00:10:36.846 --> 00:10:38.730 Are there Co morbidities that we

00:10:38.803 --> 00:10:41.309 should say outweigh the risk of cancer?

00:10:41.310 --> 00:10:42.913 Is there any way of tailoring or

00:10:42.913 --> 00:10:44.743 having kind of a frank discussion with

00:10:44.743 --> 00:10:46.723 patients to kind of educate them on

00:10:46.723 --> 00:10:48.475 who needs surveillance and who doesn’t?

00:10:48.480 --> 00:10:50.454 And is there any progress we could

00:10:50.454 --> 00:10:52.677 make in the realm of understanding

00:10:52.677 --> 00:10:54.429 the biology of progression?

NOTE Confidence: 0.744730942222222
So we know for a fact that says do change at some says do change over time and some cysts will change even after periods of stability.

On the flip side, we also know that stability, especially for small cyst, is a good hallmark, or it’s not great, but it’s a good hallmark. Nonetheless, in a variety of guidelines that are out there to help us understand who we should be following who we should be, stopping surveillance on the American Gastroenterology Association has made the recommendation that after
five years of CIS stability that you should stop surveillance and this actually has been quite a controversial recommendation. I could choda one of the physicians in our research group had the ability to look at about 18 studies with over 10,000 patients followed for almost 60,000 patient years. And I could look at in these studies that have now long term follow up for patients with otherwise low risk IP men. So patients that we would typically just be following and he was able to notice that yeah,
after five years or so, the risks of them developing progression is probably around 3% per year and the risk of them developing a cancer or an advanced lesion is about 1% per year.

And when he looked at the subgroup of patients, so patients who were stable for five years, there’s still a .2% risk per year of developing cancer long-term out, so we don’t think that there’s enough evidence right now to really be talking about stopping surveillance.

What we do know is that there are
subgroups of patients who we should be probably having a more intelligent conversation with, and particularly patients who have significant comorbidities. We had the ability to look at. 440 patients that we were actively surveying at Yale over a period of about 56 months or so, and in that group of patients, 44 patients died, but the vast majority of deaths on follow-up were not related to pancreatic disease, and in fact, when we took a cut off of a
So an index that takes in cardiac renal pulmonary issues to determine long term comorbidity, a cutoff of four. It’s very good at predicting long term comorbidities, not related to pancreatic cancer, and so now we’re beginning to have these discussions with patients based on their overall prognosis, not just focusing specifically on the issue related to their pancreas. This very useful tool that’s now available. We actually have it on our high risk website.
tool that was initiated and validated in both Dutch, Italian and several US sites for looking at both the five year and the three year and five year risk of developing worrisome features. A high risk of matter if you have a low risk branch. Strict IP men so you as a patient are able to go on to the website. You’re able to put in. The size of your cyst, for example. There’s some other parameters like smoking is your SIS multifocal,
and it’s able to give you a pictorial representation of your risk of the cyst developing into worrisome features and high risk matters, so this is very helpful in discussions with patients overall and ultimately we would like to get greater numbers to be able to calculate individual risk of developing an advanced neoplasia. But I think a key issue is also trying to understand at a molecular level what makes some sense stable for periods of time. What makes certain IP amends decide that they want to take
00:14:40.792 --> 00:14:42.820 off after five years and develop
00:14:42.820 --> 00:14:44.590 into an invasive malignancy?
00:14:44.590 --> 00:14:47.407 And to this end there was a need to
00:14:47.407 --> 00:14:49.637 understand IP mensys progression more.
00:14:49.640 --> 00:14:50.212 To date,
00:14:50.212 --> 00:14:51.928 there have been some limited data
00:14:51.928 --> 00:14:54.141 and the use of organoids derive
00:14:54.141 --> 00:14:55.721 some surgical resection specimens
00:14:55.721 --> 00:14:57.737 so patients who have gone to
00:14:57.737 --> 00:14:59.197 the operating room and people
00:14:59.197 --> 00:15:01.680 have been able to develop ipmn
00:15:01.680 --> 00:15:03.432 organoids for additional study.
00:15:03.440 --> 00:15:05.210 We’ve taken a slightly different approach.
00:15:05.210 --> 00:15:06.536 We were actually interested in the
00:15:06.536 --> 00:15:08.040 groups of patients that were surveying,
so patients who do not go for surgery and using again endoscopic ultrasound.

We've been sampling the fluid from these pancreatic cysts and generating organoid structures.

This is very preliminary data, and these are some of the images that we are identifying similar to what we would see in organoids.

To date we have studied 9 patients with presumed ipms. They're all growing, they're all growing exceptionally slow, but we've been able to passage some of them as well, so this is an interesting
development to allow us to study.

I PM and progression to maybe tailor approaches for individuals,

and maybe offer interventions such as chemoprevention, so stay tuned.

Now the other large area within the risk is your hereditary susceptibility,

or your inherited risk of developing cancer pancreatic cancer raw,

but we think that maybe about 10% of all pancreatic cancers are at risk for developing cancer based on a family history,

and there’s a variety of guidelines that we’ve been involved with specifically.
the CAPS guidelines to help us understand who we should be surveying and who we shouldn’t be surveying. And very simply put, there’s a high risk group that carries a very high lifetime risk of developing pancreatic cancer. It includes individuals with mutations and P16 puts YAGERS, but also individuals who have a family history with three or four first degree relatives. So these people are at a higher risk without a known genetic abnormality. There’s also a low to moderate risk that includes genes that you’re familiar with,
such as Braca one bracket,
two other DNA repair genes
like Paul V2 and ATM,
but also again in there is a family
risk of two first degree relatives
and that carries a significant,
even low risk than those that have
three first three relatives with no
abnormality identifiable in the germline.
To take care of these
individuals several years back,
we set up a pancreatic cancer early
detection clinic at Yale through smile
through the general support of Smile and
Javier Loras group and in this group.
Currently we’re following about 185 patients, most of them in protocol who are at high risk of developing pancreatic cancer, and again, you can see this from this group. The majority of patients are actually individuals who have a strong family history but do not have any genetic abnormality. One of the original studies that was done in this area was that what’s called the Caps three study and these patients are typically imaged with a variety of CT scans. Caps three study and these patients are typically imaged with a variety of CT scans. Mris and endoscopic ultrasounds, and a small percentage of them will have an abnormality that requires surgical resection. So in Caps 3, for example, 225 patients were enrolled.
00:17:52.400 --> 00:17:54.140 Umm?

00:17:54.140 --> 00:17:55.976 A total of 216 were ultimately studied and the majority of these are familial patients.

00:17:59.760 --> 00:18:02.840 This is a multicenter study.

00:18:02.840 --> 00:18:04.020 For the majority of patients, no abnormality was identified,

00:18:04.020 --> 00:18:05.408 but you can see that for some of these patients had a dilated pancreatic duct.

00:18:08.668 --> 00:18:10.894 For example, a cyst, probably an ipmn,

00:18:10.900 --> 00:18:14.176 and a small percentage ended up having a solid lesion.

00:18:14.180 --> 00:18:15.670 and a small percentage ended up having a solid lesion.

00:18:17.160 --> 00:18:18.004 In total, five of these patients underwent surgical resection,

NOTE Confidence: 0.89521025555555

NOTE Confidence: 0.89521025555555

NOTE Confidence: 0.89521025555555
2 of them had high grade dysplasia, and three of them had low grade dysplasia IP and then, although all five of them ended up with having either an intermediate or high grade dysplastic completion. Very interesting data from these CAP studies. In fact has been the ability to collect pancreatic juice and what’s been noticed in individuals who subsequently developed established pancreatic Dr Latner carcinoma is that investigators were able to go back and look at the pancreatic juice of these individuals at a time when
00:18:54.400 --> 00:18:56.410 they had no radiologic abnormality.
00:18:56.410 --> 00:18:58.552 And they were able to identify
00:18:58.552 --> 00:19:00.724 either combinations of P53 mutations
00:19:00.724 --> 00:19:04.006 or P60 mutations long before a
00:19:04.006 --> 00:19:06.409 radiologic abnormality was identified.
00:19:06.410 --> 00:19:09.362 So this is another direction to go in
00:19:09.362 --> 00:19:12.437 in terms of surveying these patients.
00:19:12.440 --> 00:19:15.080 The initial results of the Caps five study,
00:19:15.080 --> 00:19:17.320 which is a much larger multicenter study,
00:19:17.320 --> 00:19:19.938 which Yale was part have just been
00:19:19.938 --> 00:19:22.760 accepted for publication in in JCO in
00:19:22.760 --> 00:19:27.780 Caps 5 almost 1500 patients were studied.
00:19:27.780 --> 00:19:30.588 A total of nine screen detected
00:19:30.588 --> 00:19:32.460 pancreatic cancers were identified,
00:19:32.460 --> 00:19:34.450 of which eight were resectable
00:19:34.450 --> 00:19:36.800
and seven at a stage 1A, and when you put that together with some of the high grade dysplastic lesions, well over 50% of the patients enrolled in these studies had an achievement of what’s called a successful goals surveillance. So we identified either an early stage cancer or a high grade dysplastic lesion. When all the patients from the caps one through five study were amalgamated together, what we were able to demonstrate was that those patients who were diagnosed during a surveillance protocol with pancreatic cancer had a much higher
NOTE Confidence: 0.895210255555555
00:20:08.718 --> 00:20:10.728 median survival than those that were
NOTE Confidence: 0.849172274
00:20:10.730 --> 00:20:13.150 diagnosed outside of surveillance protocol,
NOTE Confidence: 0.849172274
00:20:13.150 --> 00:20:16.420 showing some form of survival benefit
NOTE Confidence: 0.849172274
00:20:16.420 --> 00:20:19.680 within this within this initiative.
NOTE Confidence: 0.849172274
00:20:19.680 --> 00:20:20.920 Anca Chotto you know.
NOTE Confidence: 0.849172274
00:20:20.920 --> 00:20:22.745 Again, being very productive went and
NOTE Confidence: 0.849172274
00:20:22.745 --> 00:20:24.689 looked at some of these surveillance
NOTE Confidence: 0.849172274
00:20:24.689 --> 00:20:26.514 studies that were done more
NOTE Confidence: 0.849172274
00:20:26.514 --> 00:20:28.600 concerned about what was happening.
NOTE Confidence: 0.849172274
00:20:28.600 --> 00:20:30.280 Not so much when patients were
NOTE Confidence: 0.849172274
00:20:30.280 --> 00:20:33.870 initially enrolled, but as they
NOTE Confidence: 0.849172274
00:20:33.870 --> 00:20:35.104 followed over a period of time.
NOTE Confidence: 0.849172274
00:20:35.104 --> 00:20:36.622 He took 13 of the most recent studies
NOTE Confidence: 0.849172274
00:20:36.622 --> 00:20:39.361 and what he noted was that in 53
NOTE Confidence: 0.849172274
00:20:39.361 --> 00:20:41.716 patients that were identified with
NOTE Confidence: 0.849172274
pancreatic ductal adenocarcinoma.

In these 13 odd studies or so.

Whereas 22 patients or 41% had goals of surveillance achieved so in early cancer,
a high grade dysplastic,

almost 60% of patients had an advanced lesion including metastatic lesions.

He tried to look at some of the factors that might be associated with these late stage presentations.

It had nothing to do with surveillance modality,
a baseline imaging abnormality,
a germline mutation.

A lot of the patients who presented were actually asymptomatic.

We were able to look at the timing of preceding imaging and most patients had a normal preceding image.

There was some questions about diagnostic errors in the limited data that was available and there was some issue of surveillance adherence.

In some of this data.

And what this leads into is kind of a growing conversation about how we can do better.

You’re going to see more and more
of these types of studies in the next couple of years or so. This is the initial study that proved this point. These are patients who had a diagnosis of pancreatic ductal adenocarcinoma made, and when we went back over a year or so, it was said that the pancreatic cancer could be identified. So a variety of methods were looked at in these individuals. But issue is with issues relating to abnormalities that were identified on imaging that could be seen and maybe radiomics or some
other feature could help figure that out.

I think it's important to say, just to summarize, I'm sorry.

That the the stage of pancreatic cancer at an early stage is improving, especially in younger populations, and the overall survival related to early stage pancreatic cancer is increased from about 44% in 2004. And now getting closer.

This is unclear why this is happening, but may be related to increased use of abdominal imaging.
and perhaps some of the surveillance programs.

So we're beginning to gather some information about the benefit of both surveillance programs as well as.

Are the outcomes related to those surveillance programs?

Notice something to kind of look forward within the CAPS cohort of patients at Hopkins. Currently there is now open a mutant Karas targeted vaccine for patients at risk of developing pancreatic cancer. This is a phase one study that
00:23:26.099 --> 00:23:27.260 requires multiple intramuscular
00:23:27.327 --> 00:23:29.385 injections over a period of time.
00:23:29.390 --> 00:23:31.440 The initial outcome is for
00:23:31.440 --> 00:23:32.670 safety and tolerability,
00:23:32.670 --> 00:23:35.622 but they are going to look at changes in
00:23:35.622 --> 00:23:39.578 K Ras specific CD8 and CD4T cells at 2.
00:23:39.578 --> 00:23:41.566 And that four years.
00:23:41.570 --> 00:23:43.551 I'm also interested to know that modern
00:23:43.551 --> 00:23:45.929 it does have an M RNA based KRAS target.
00:23:45.930 --> 00:23:47.850 These are typically being
00:23:47.850 --> 00:23:50.250 used in in oncology trials,
00:23:50.250 --> 00:23:52.092 but may actually have a role
00:23:52.092 --> 00:23:54.342 in the high risk population to
00:23:54.342 --> 00:23:56.727 ultimately prevent and the the
00:23:56.727 --> 00:23:58.710 development of pancreatic cancer.
So in summary, therefore just looking at the time. We currently are not performing screening in the general population. We are focusing on high risk groups, such as pancreatic cysts. Although we’re trying to get better at surgical selection, but also get better at tailoring individuals who should be surveyed and those that should not be with respect to the familial pancreatic cancer cohort patients. we’re getting better at documenting some of the outcomes associated with these studies. Really,
with the view to improving those outcomes long term. And I think you’ll hear more about nuance. Set diabetes. It certainly plays a role. And it it. It helps us stratify our patients with pancreatic cysts and familial pancreatic cancer. And I would use this talk just to say that there are plenty of opportunities within our group for collaboration, for additional biomarker developed development and validation, but also in the realm of imaging.
And just to say that really it takes a group of people to try and keep these studies going.

This is a picture of Ankit who’s been incredibly productive and helpful. Getting our group up and running by there. Several other individuals such as Scott and disease and Ling helping on the steady side as well as our really close and productive collaboration with Doctor, Hutch, and Doctor Sharma’s lab.

Thank you.

Wonderful doctor Farrell.

Thank you so much for that really nice overview.
I don’t see any questions in the chat, but if there are those watching who have a question, please type it in and I’ll make sure to ask it.

I have a question for you, so it’s thinking about the sort of root cause of the increased incidence in pancreatic cancer. Because we’re seeing an increase incidence nationally, but also in the state of Connecticut, correct?
that have pancreatic cysts.

It was.

It seemed like a quite large number, typically 6,000,000,

is a number that’s quoted.

Yeah, if you would do extrapolation from imaging studies and extrapolate.

Up to to the general population,

so are we seeing an increase in the instance of cysts or is it diabetes and therefore with diabetes? Is it obesity?

So what do you think is the root cause driving this increased incidence?

There’s different explanations given for the different increases specifically for pancreatic ductil adenocarcinoma.
It’s felt that it’s also related to an aging population, so as the population ages, that’s driving up the overall incidence of it, so that’s one explanation.

Likely metabolic explanations and obesity would be one explanation. Trying to link that then to pancreatic cysts. The reason for the large volume of cysts are perception that there are more.

This is really to just do with the use of imaging. So the prevalent use of MRI scans
CT scans has really been driving why we see more assists. Also, imaging scans are getting better so we can see 3 millimeter, says 2 millimeter cysts on MRI scans done routinely. Now the question is. Can finding those cysts be converted to a better early detection strategy for ipms the OR for pancreatic cancer? The issue is that maybe those cysts account for 10-15% of the total volume of pancreatic ductal adenocarcinoma. OK, thank you David.

Stage ones went from 40, 52
00:27:33.430 --> 00:27:35.150 some to 80 some percent.
NOTE Confidence: 0.87344297

00:27:35.150 --> 00:27:37.586 Survival is that due to greater
NOTE Confidence: 0.87344297

00:27:37.586 --> 00:27:40.291 diagnosis in stage one and have
NOTE Confidence: 0.87344297

00:27:40.291 --> 00:27:42.295 high stage diagnosis decreased.
NOTE Confidence: 0.843321582173913

00:27:43.850 --> 00:27:46.714 So this this phenomenon is from is from
NOTE Confidence: 0.843321582173913

00:27:46.714 --> 00:27:49.618 SEER data and all the positive glowing
NOTE Confidence: 0.843321582173913

00:27:49.618 --> 00:27:52.689 phenomena has been related to stage one a.
NOTE Confidence: 0.843321582173913

00:27:52.690 --> 00:27:55.426 So it has been the increase in incidence,
NOTE Confidence: 0.843321582173913

00:27:55.430 --> 00:27:57.415 the increase in survival associated
NOTE Confidence: 0.843321582173913

00:27:57.415 --> 00:28:00.834 with stage one as the decrease in age of
NOTE Confidence: 0.843321582173913

00:28:00.834 --> 00:28:03.649 diagnosis and it’s not seen in the other.
NOTE Confidence: 0.843321582173913

00:28:03.650 --> 00:28:05.974 The other stages it’s not even seen
NOTE Confidence: 0.843321582173913

00:28:05.974 --> 00:28:08.570 in stage twos and for sure it’s not
NOTE Confidence: 0.843321582173913

00:28:08.570 --> 00:28:10.150 being seen and advanced stages.
NOTE Confidence: 0.843321582173913

00:28:10.150 --> 00:28:11.800 So there’s something going on
NOTE Confidence: 0.843321582173913

53
and so it’s pure speculation.

Whether it’s related to the fact that people are more worried about pancreatic cysts,

you know our surveillance programs in high risk individuals that count for certain population,

but I’m not sure they account for all that population to switch it,

so there’s something going on that’s changing,

as rather than the global numbers in in pancreatic cancer,

and then with that year period of stage one progressing to metastatic,

that’s probably explaining in 2030 being the.
Second, cancer mortality related to pancreatic cancer, correct?
I think that’s true, and I think also because there have been some significant improvements in other cancers, right? So you’re seeing you know they’re being slow improvements and having some improvements in the therapeutic side for pancreatic cancer. But you know, we really need to make a real dent for the early detection to really kind of begin to move that needle a bit better.
Rosa is there also an increase of incidence in patients with young onset? And I believe you just. They said that in answering David’s question, the age of the diagnosis for stage 1A’s is going down, not for the other councils but for the other stages, but the stage one age of diagnosis has gone down. There are data about the overall decrease in the age of diagnosis of pancreatic cancer, and it may in fact be associated with slightly different types of genotypes and molecular profiling and some of that data has been kind of presented here at Yale in the past.
so certainly focusing in on the younger population, hearing about a younger population. With pancreatic cancer, which is certainly very concerning. Well, thank you so much. It’d be great to continue our work here with the focus on Connecticut and how we can really improve upon the lower incidence and or mortality. So thank you so much. Thanks very much. OK, if you can stop sharing and I’m now delighted to introduce
Doctor Bacillus Vessella who is chair of our Department of Environmental Health Sciences in the Yale School of Public Health. He’s also the Susan Dwight Bliss professor of epidemiology and of ophthalmology and visual science and of the environment. He received his bachelors in Chemistry and PhD in biochemical pharmacology from the University of Ioannina in Greece and then he trained in gene environment interactions, molecular toxicology and pharmacogenetics at the Department of Environmental Health in the College of Medicine.
He's established an internationally recognized research program that's been continuously funded by NIH since 1997 and his research interests include the etiology, The molecular mechanisms of environmentally induced human disease such as liver disease, obesity and diabetes, cancer and neurogenic neurodegenerative diseases. His laboratory uses state of the art integrated approaches that include metabolomics, lipidomics,
expoza, omics tissue imaging,

mass spec,

deep learning as well as human
cohorts and genetically engineered
mouse models and we are delighted
to have him here today to talk
specifically about alcohol and cancer.

Thank you Vasilis.

Thank you many days my microphone.

Yes, my microphone is on.

Thank you very much for your nice work
and thanks also James for pointing
out our T32 who has helped on the
studies before before I start mine I
also want to address a little bit of
the question of Melinda your question
regarding the increasing density of cancer lately one of the things that I would like to point out is we have. Some increases in environmental exposures, especially for the perfluorinated compounds, namely PFAS, which may have contributed in all kind of tumors. I wish we should have a round table another time to discuss about all these factors. So today what I’m going to talk to you about it is molecular mechanisms of alcohol and cancer, and so we have. We have edited 3 books on alcohol. You cancer and one special issue on chemical biological interactions which
00:32:32.750 --> 00:32:37.180 was based on my third international
NOTE Confidence: 0.594001571666667
00:32:37.180 --> 00:32:38.940 conference on alcohol and cancer,
NOTE Confidence: 0.594001571666667
00:32:38.940 --> 00:32:42.377 which we held it here in Newport.
NOTE Confidence: 0.594001571666667
00:32:42.380 --> 00:32:45.915 A couple of just before the COVID
NOTE Confidence: 0.594001571666667
00:32:45.920 --> 00:32:47.120 As a matter of fact,
NOTE Confidence: 0.594001571666667
00:32:47.120 --> 00:32:50.228 we just received a note from
NOTE Confidence: 0.830666932
00:32:51.020 --> 00:32:53.827 from Springer that our books doing so
NOTE Confidence: 0.830666932
00:32:53.827 --> 00:32:56.887 good and alcohol and cancer and they want
NOTE Confidence: 0.924430438
00:32:56.900 --> 00:33:02.216 we to write another one very much.
NOTE Confidence: 0.924430438
00:33:02.224 --> 00:33:07.224 is this association between alcohol
NOTE Confidence: 0.924430438
00:33:07.224 --> 00:33:09.355 and cancer and it’s actually, you know,
NOTE Confidence: 0.924430438
00:33:09.362 --> 00:33:12.760 there is epidemiological evidence that
NOTE Confidence: 0.924430438
00:33:12.760 --> 00:33:15.990 is kind or is convincing that alcohol.
NOTE Confidence: 0.924430438
00:33:15.990 --> 00:33:17.878 Is associated with several
NOTE Confidence: 0.924430438
00:33:17.878 --> 00:33:19.355 cancers listed in here.
Mouth fighting, slurring, esophagus, colon and breast for women and you know there is some more breast and liver based on IRC and there is a probable liver and colorectal for women. One of the things that I have not included in this presentation though and I have to say that as well they have been epidemiological studies which indicates that alcohol in sometimes. Is a positive factor in preventing alcohol, so I don’t have time to go with that. I’m gonna stick with the mechanisms today. Molecular mechanisms of the alcohol induced cancer.
So let me before we go to that.

And since we're talking about epidemiology, I want to tell you the categories of association between alcohol consumption and cancer and there is first case is sufficient.

There is limited and suggestive evidence of unappreciation. Inadequate or insufficient to determine whether an association exists.

This has been described very well in a
paper by our junior faculty just wach. It was in 2020 in the International Journal of Epidemiology, and this is worth reading it. One of the problems with alcohol. Epidemiological studies is most of the studies are based on a questionnaire and rather than having clinical data in terms of the alcohol consumption and we know there are certain biases that could really interfere with the outcome of the studies, and this is most of the time people really are.
You know, don’t tell the truth.

So answering the question, well maybe 1, maybe you know and could be just a bottle. Of Hard Liquor per week. Of Hard Liquor could create some problems, and this is what I’m trying to introduce. A new term which called the ALCOM, which is a panel of markets that could indicate what is your alcohol consumption throughout the years of your life.

So in December 2020 I was involved in an NCI workshop that we presented. You know the existing.
Evidence and gaps across the cancer continuum regarding the alcohol and cancer. So we have looked at from epidemiology to and biology of the alcohol and cancer risk. What needs to be addressed and how can really work in preventing you know this alcohol consumption that could lead to cancer. Again, this is a readily available to everybody. And I’m going to go directly to the mechanism, so I’ve been working with alcohol metabolism since day one of my graduate studies, and that was the metabolism of alcohol.
which actually is involved is been.

Consider it as the mechanism of inducing cancer so your alcohol, your ethanol, is metabolized by alcohol dehydrogenases to an aldehyde which is a powerful electrophile, which is capable of interacting with DNA and protein and forming adducts and, this is a very important molecule in here, so ethanol can also be metabolized by catalase and also by cytochrome P. The 50s, mostly cytochrome P452 want and to a lesser extent by 182.

What happens during the ethanol metabolism. P4, fifties.
You have generation of reactive oxygen species.

You have glutathione depletion which leads to oxidative stress and as you will see later on we have the formation of further aldehydes namely 4-hydroxy nonenal and malondialdehyde which are further capable of causing DNA and protein adducts so.

Ald H2 is the major enzyme which metabolizes acetaldehyde.

The major product of ethanol, and it is converted to acetate and then from the acetate can go to kcal coenzyme, which can be used as a building.
biomolecule for a lot of.

Cells, including the cancer cell, that's another story.

We don't have the time to go over that today, so as you can see, the other heads and the reactive oxygen species are very important.

My lab is focusing in all aldehyde metabolism and I'll show you a little bit more.

This is aldehyde dehydrogenase enzymes which they take us at aldehyde and convert it to acetate.

So again you can see for the risk.

Factors in terms of alcohol drinking as mentioned earlier there is aids,
00:38:49.590 --> 00:38:51.198 the personal history, family history, race and also diet,
00:38:54.422 --> 00:38:55.930 physical activity, obesity,
00:38:57.650 --> 00:39:00.989 As Melinda and James were mentioning above.
00:39:00.990 --> 00:39:03.546 So what Mike what we’re doing in my lab and I have a center funded by the NAA
00:39:03.546 --> 00:39:06.330 is and I have a center funded by the NAA
00:39:06.330 --> 00:39:09.178 as we have all you can see here is this.
00:39:09.180 --> 00:39:11.024 The ethanol metabolism and also glutathione metabolism.
00:39:11.024 --> 00:39:12.407 The synthesis of your major.
00:39:12.410 --> 00:39:15.248 They the synthesis of your major.
00:39:15.250 --> 00:39:17.740 Antioxidant of your system here and what you can see on those red letters.
00:39:17.740 --> 00:39:21.599 Are the enzymes involved in these pathways and we have single and
00:39:23.710 --> 00:39:25.915
double knockouts of all these enzymes which are involved in the eye in the ethanol metabolism and the interplay and essentially trying to clear up the reactive oxygen species generated and protecting yourselves. So we just published a review in cancers on molecular mechanisms of alcohol. And yours. Colorectal cancer so this is one of the area that my lab has been focusing for a number of years. We had EU one which I'm planning to go for the renewal as well and essentially again you can see that ethanol metabolism is involved in
here and we have what I described you before the pathways here. But one of the things I want to tell you is the ethanol per se is not only metabolized by cytochrome P452 one, constantly induces increases the levels of cytochrome P452E1 why? This is important? Because 2 E one it can metabolize the processing loggens into the carcinogens and that is very important and other area of the cytochrome P. For the two one it can increase the cell proliferation and also
as we discussed it can create reactive boxes and species. The other is the important roles of both sides. From P452 you are and also you know the aldehyde dehydrogenases in retinoic acid homeostasis, which they been also involved in the whole process. Another important issue here is the ratio between NADH and NAD which is completely changed based on the ethanol metabolism. Another area which ethanol could affect is the one carbon metabolism and that has effects on the DNA.
methylation which can really give a lot of changes in DNA methylation associated with cancer, as I told you before, I get there may can be used as macromolecule biosynthesis including in the cancer cells we have a lot. I don’t have the time to go, I just want to give you a brief overview of what’s going on. So one of the major thing. So here if we can focus is you have the the adduct formation, the DNA and the proteins.
I’m just going to show you some examples of the DNA. And we’re gonna talk about some the inflammation as well, and we’re gonna go from there.

So what happened with the acetaldehyde and also the other aldehyde generating the DNA attacks? These aldehydes are both in electrophiles, they can interact with bases of the DNA, and these adducts then they are responsible for causing mutations into your transcripts. And I said aldehyde by.
Also interact with various amounts. Can give a crotonaldehyde and this also conform further.

Adducts in here at the same time as I mentioned before, you also have an increased lipid peroxidation from acetaldehyde, which is due to the glutathione depletion which generates further aldehydes for hydroxyzine on and all, and so on. So you have another type of the ethanol the shock should go on Guana sitting here. Another type of attack. So it is very well documented that
both acetaldehyde per se or the byproduct atheists that can interact with DNA that can cause addicts, and these others can lead to mutations and they can cause the cancer. This is a causative effect, and this is what helped to establish and put.

That the goodbyes, as ethanol as a cancer agent. Another area I am not going to go on this aspects in here what I want to tell you is that ethanol also can induce inflammation and changes in the cytokines and chemokines and then they can have a various effects into all the signaling which
00:43:34.970 --> 00:43:37.316 essentially they can affect the DNA repair mechanisms into the system.
00:43:39.480 --> 00:43:41.820 So the importance this is less
00:43:44.480 --> 00:43:47.900 We should emphasize and as a matter of fact,
00:43:47.900 --> 00:44:00.540 you know, this is what I'm going to tell you.
00:43:49.760 --> 00:44:51.356 What we're planning to do in here,
00:44:51.360 --> 00:44:53.260 but you know, again,
00:44:53.260 --> 00:44:56.797 it is a pathway that ethanol could affect all these pathways in here,
00:44:56.797 --> 00:44:58.900 including the DNA damage,
00:44:00.540 --> 00:44:01.770 and you know,
00:44:04.022 --> 00:44:05.180 further mutations.
00:44:06.190 --> 00:44:07.178 So one of the
areas that I am planning to expand

is the immuno metabolism and

this is the interplay between the

monological and metabolic processes.

And as a matter of fact we have

published several papers on the role

of glutathione in the control of

the T cell and macrophage fashions.

But essentially again you can see the

mitochondrial metabolism here and how

the ethanol metabolism can interfere

with that in terms of the cancer.

Incidents. As I told you before,

the ethanol can also.

I mean, alcohol can also affect the

one carbon metabolism and ethanol
can block the absorption of the folic acid and can interfere with all the folate and cycle, and the methionine cycle which eventually and as you can see here in very stages through the either interacting with proteins and you know forming adducts or interacting with pathways or absorption or stuff. Essentially, we have a DNA hypermethylation which can be associated with cancer. And of course, you know that’s the other pathway that you know by interfering
with the one carbon metabolism,

you can have decreased through the thione,

which really you know gives rise to oxidative stress,

which is a result of reactive oxygen species generated by the cytochrome P-450 metabolism of the P42 and taking a break here.

What I wanted to tell you is,

in the slide before here is the broker synonyms.

We have a lot of Procter

synonyms exposed in our lives,

so if alcohol induces the site from P452 you want,

then we have increased levels
of the two you want.

So I’ve been exposed to dimethyl nitrosamine, for example the nitrosamines or the P.

Then you can have a further activation of this carcinogens and you can have this generation of reactive.

Which is in species and further mutation.

I’m gonna end up very quick.

I’m not gonna spend my time you all know the incidence of my time you all know the incidence of the colon cancer and what is going on.

But my lab has been focusing on the colon and alcohol metabolism we have.

We were the first to clone the
secondary enzyme. If you remember, said aldehyde is metabolized to acetate by the aldehyde. Progenesis Ald. Stew is the major enzyme, but we did found we cloned this enzyme and mitochondrial enzyme which is very similar to a LH2 and we cloned it. We expressed it throughout the years we made beautiful antibodies. We made the cover pages of several journals and we found that first of all that metabolizes acetaldehyde with very high affinity, which is makes it as equal as a LD. It’s too in terms of clearing.
The acetaldehyde but also what we found out is this enzyme is also involved into the retinoic acid metabolism, which is very important. So one of the things in early we found out that aldh 1B1 is a potential biomarker for colon cancer, so we have screened several panels of humors, and we found that especially for colon cancer, every single column cancer sample. But we have tested. It really expresses AL H1B1 at the very high level, very.
00:47:48.030 --> 00:47:50.350 high level and which we didn’t see it
NOTE Confidence: 0.849234321333333
00:47:50.350 --> 00:47:52.806 in long breast on ovary or anything.
NOTE Confidence: 0.849234321333333
00:47:52.810 --> 00:47:55.048 And it was especially this it
NOTE Confidence: 0.849234321333333
00:47:55.048 --> 00:47:57.660 was not a LH1A1, it was a L
NOTE Confidence: 0.849234321333333
00:47:57.660 --> 00:47:59.860 H1B1 and this has to do also.
NOTE Confidence: 0.849234321333333
00:47:59.860 --> 00:48:01.540 You know with the colony
NOTE Confidence: 0.849234321333333
00:48:01.540 --> 00:48:02.884 formation and everything else.
NOTE Confidence: 0.849234321333333
00:48:02.890 --> 00:48:06.410 So we also in addition to colon cancer.
NOTE Confidence: 0.849234321333333
00:48:06.410 --> 00:48:09.626 We have also found out that
NOTE Confidence: 0.849234321333333
00:48:09.630 --> 00:48:11.328 ADH 1B1 plays a really big.
NOTE Confidence: 0.849234321333333
00:48:11.330 --> 00:48:12.694 Call in pancreatic cancer.
NOTE Confidence: 0.849234321333333
00:48:12.694 --> 00:48:14.399 Trying to make a connection
NOTE Confidence: 0.849234321333333
00:48:14.400 --> 00:48:17.160 with James talk earlier on,
NOTE Confidence: 0.849234321333333
00:48:17.160 --> 00:48:22.084 so this is the AL H1B1 and then you can
NOTE Confidence: 0.849234321333333
00:48:22.084 --> 00:48:24.329 series really high expression of this
NOTE Confidence: 0.849234321333333
So one of the things that actually you can use that as a prognostic market is you can take the tumor and then you can really isolate aldh positive and aldh negative sales, and then you can put them in culture. As you can see, if aldehyde hydrogenase is not present, you have very small formation of the colonies, but if they LDH positive you have really have seen the tumor formation. So for somehow this a LDH is involved in the tumor proliferation initiation. I don’t know we’re still looking at the
role of this throughout either through the DNA repair mechanisms,
or through retinoic acid. It’s an active area, so we have several papers on the Catherine Pathway and the also P1K they get signaling pathway, but the most important thing, this is a work that we have identified that it is immunohistochemical market for. Further, for colorectal cancers and we look
at that and several several samples and including some comparisons that we have done here at Yale. So it’s a very strong market for that. And whereas as I said, we’re still looking on what is going on. So one of the ways that we have trying to address the role of this is we have generated specific knockouts, so it’s a tissue specific inducible knockout. We know that the they are forming, forming many cancers.
So anyway to make time is running. We have generated a triple knockout with a PC and everything. This mice we have found out that this is the ASPCA knockout and this is the well typed knockout mice and this is the experiment. This is how we generate it. It was a painful process. Triple knockout is not an easy way to do it, but the way that you’re doing that is you have an industrial model, you treat them with tamoxifen, you delete the gene and then you can further figure out of what’s going on. So we did not find anything.
NOTE Confidence: 0.849208734
00:50:51.770 --> 00:50:53.770 any difference in the.
NOTE Confidence: 0.849208734
00:50:53.770 --> 00:50:56.650 Vehicle treated mice and also in
NOTE Confidence: 0.849208734
00:50:56.650 --> 00:50:58.710 the tamoxifen treated groups at
NOTE Confidence: 0.849208734
00:50:58.789 --> 00:51:01.039 the numbers were not evident in
NOTE Confidence: 0.849208734
00:51:01.039 --> 00:51:03.430 jejunum or ileum in these mice.
NOTE Confidence: 0.849208734
00:51:03.430 --> 00:51:06.490 However, we did find the
NOTE Confidence: 0.849208734
00:51:06.490 --> 00:51:08.330 carcinoma colorectal adenomas,
NOTE Confidence: 0.849208734
00:51:08.330 --> 00:51:11.432 which in the knockout developed significant
NOTE Confidence: 0.849208734
00:51:11.432 --> 00:51:14.149 loan numbers of the macro and enormous.
NOTE Confidence: 0.849208734
00:51:14.150 --> 00:51:17.691 And there was a significant reduction in
NOTE Confidence: 0.849208734
00:51:17.691 --> 00:51:19.750 the total macroadenomas in the knockout.
NOTE Confidence: 0.849208734
00:51:19.750 --> 00:51:22.246 So, when we knockout the gene
NOTE Confidence: 0.849208734
00:51:22.246 --> 00:51:23.910 in a model that.
NOTE Confidence: 0.849208734
00:51:23.910 --> 00:51:25.150 Induces
NOTE Confidence: 0.67769972444444
00:51:27.310 --> 00:51:32.134 colorectal and the normas, uh it is the gene.
NOTE Confidence: 0.67769972444444
If you knock out the aldehyde progenesis, you reduce you can see that you reduce. This confirms our initial studies. The ALDH 1B1 is involved in the development of under cellular carcinomas. We have been trying to dissect more involvement of this gene and we didn’t see any difference at the P53 level. But we did see a decreased expression of the beta catenin in the knockout, a LH now. Expression which you know that Becca took Catenin is plays an important role in the development of colon carcinoma. So the expression of of 191 could be used as
a novel biomarker in identified colorectal cancers and also in pancreatic cancers.

The Althe knocked down because the dramatic reduction of humor, growth, and loss of function of APC, and options of.

Maybe it’s trying to be 1 reduces the column adenoma and in turn delays that emerged in the progression of cancer in that to that effect.

I have collaborated with. And cuts and we have developed special specific inhibitors of the aldehyde dehydrogenases that could be used for delaying the expression,
00:53:03.538 --> 00:53:06.158 delaying the progression of the tumor once it’s been detected so.
NOTE Confidence: 0.783430214736842
00:53:06.158 --> 00:53:11.080 It looks like the Ald H1B1 is a key player in this carcinogenesis,
NOTE Confidence: 0.783430214736842
00:53:11.080 --> 00:53:13.458 so if I can go back a little bit on the molecular mechanisms to conclude my studies in here and the the directions is the alcohol metabolism is a key player through the cytochrome P-450, or through the aldehydes generated in here and then.
NOTE Confidence: 0.783430214736842
00:53:19.158 --> 00:53:21.518 You have also the changes in the NADH NADH ratio, which we can have also have epigenetic modifications.
NOTE Confidence: 0.783430214736842
NOTE Confidence: 0.783430214736842
00:53:24.210 --> 00:53:26.894 They can cause the inflammation
that can lead to cancer.

In addition to that, you also, as mentioned, this is very important here. This is especially with increased exposure to environmental casino egens. The high levels of the two one they can lead to DNA damage segmentation. Then they can cause cancer. And of course you know the DNA repair can be also be affected by both the two U one and also the alcohol. Double so a very important process in here. And this is where we’re focusing as well. Is how ethanol metabolism could the could.
Have a defect in the day DNA repair as well and as I mentioned, also you know we have the one carbon metabolism and DNA methylation. I didn’t have time to go on your micro RNA in here but also I did mention the crosstalk between these pathways. The alcohol and the immune system which eventually they can end up in causing epigenetic modifications that they can cause the cancer. This is a slide that the best, slide that I’ve seen in terms of. Mark concluding all the effects of the alcohol in terms of the cancer, and this was from the former director.
00:54:59.609 --> 00:55:02.178 of the metabolism of the NAIA SAMSARIC,
NOTE Confidence: 0.783430214736842

00:55:02.180 --> 00:55:04.434 who is a very good friend and
NOTE Confidence: 0.783430214736842

00:55:04.434 --> 00:55:05.400 colleague of mine,
NOTE Confidence: 0.783430214736842

00:55:05.400 --> 00:55:08.740 and I want to tell you this slide is I’m,
NOTE Confidence: 0.783430214736842

00:55:08.740 --> 00:55:10.558 you know, a little bit sad,
NOTE Confidence: 0.783430214736842

00:55:10.560 --> 00:55:12.985 but my next fifth international
NOTE Confidence: 0.783430214736842

00:55:12.985 --> 00:55:15.410 conference on alcohol and cancer
NOTE Confidence: 0.783430214736842

00:55:15.494 --> 00:55:18.159 was going to be in in Greece 2021.
NOTE Confidence: 0.783430214736842

00:55:18.159 --> 00:55:20.324 Unfortunately with the COVID we
NOTE Confidence: 0.783430214736842

00:55:20.324 --> 00:55:23.398 have to move it ahead and probably.
NOTE Confidence: 0.783430214736842

00:55:23.400 --> 00:55:24.870 It’s not gonna be 2022.
NOTE Confidence: 0.783430214736842

00:55:24.870 --> 00:55:25.818 It’s gonna be probably
NOTE Confidence: 0.8762074775

00:55:26.530 --> 00:55:31.118 2023 and I expect to see quite a few of our
NOTE Confidence: 0.755934514

00:55:31.270 --> 00:55:33.500 Yale colleagues here. Thank you,
NOTE Confidence: 0.755934514

00:55:33.500 --> 00:55:35.000 Melinda. I’m going to stop and
NOTE Confidence: 0.755934514

97
get some time for questions. Thank you vicellous. Count me in on a trip to Greece. I know you just returned and I wasn’t invited. Anyway to the topic at hand. I was intrigued at the beginning of your talk when you were talking about measurement error and the fact that often we measure alcohol intake through questionnaire and we know there’s a lot of misclassification with that underreporting, perhaps, and then that misclassification really attenuates the, say, the hazard ratio to the null.
So in reality the impact of alcohol on cancer is probably even higher than noted in studies, but you then mentioned what do you call an alcohol zone or something of a channel of. Can you discuss that briefly? A little bit more So what we see. Also show me this term similar to the Exposome and I'm trying to pattern actually this word, so I'm trying to figure out through animal studies and human studies how I can define a.
by looking at the blood and finally modeling it to how much alcohol the one person has consumed during lifetime. This is not an easy task. OK, so because one of The thing is remember you can drink alcohol and then even if you measure a few of the enzymes, if you have apathic enzymes if you have. If you have abstinence of alcohol. Delivery cover so you don’t know to how much alcohol you have drunk, So what we’re trying to do is we’re trying to have a a more educated.
thing as the explosion concept.

As I said, it’s not easy, but we’re trying to do that and we’re trying to do with animal studies and also with human studies.

This is one of the ways that it can help.

Really, the epidemiology to assess you know the causal effects of alcohol because this is another area of big debate.

Melinda, as you know, you know, there was a couple of years ago there was one paper from New Zealand and it’s saying all the women, even if they have one drink.
Per year they can develop colon cancer, I mean breast cancer and if you look at really of these studies they were, you know, based everything on just the questioners. And as I said, this is not the accurate measure to do this. Yeah, yes, I agree. So much work to be done. Well. Thank you so much to both of our speakers today and if others who tuned in have questions, I’m sure you can reach out to both our speakers via email and hopefully there will be some collaborations.
Initiated from today’s talk. Thank you.

Both have a great rest of the day.

Thank you.