RODWIGE DESNOYERS: Good morning everybody. I want to thank Clancy for inviting me to give this talk today. I am the first speaker. I hope everybody's awake.

It's a short, short time to discuss this extensive topic involving basically all the HPB malignancies, talking about the environmental factor and genetic risk factors. And not all of the HPB malignancies have some sort of genetic risk factor associated with them, but the majority of them have some sort of environmental risk factor. And those environmental risk factors actually run across the gamut of the HPB malignancies, so, therefore, some of the things that I'm going to mention in one type of cancer is going to carry over to the next type of cancer. There are some of these malignancies that are extremely rare in the United States that I'll briefly touch upon, and the risk factors also are different for different parts of the world. So that's the main take home message. OK.

Now the first slide is to introduce us to pancreatic cancer. Pancreatic cancer is, as you guys know, is the fourth most common cause of death-- cancer death-- in the United States. In 2015, an estimated about 50,000 people will be diagnosed of pancreatic cancer, about 40,000 of those will die. And the incidence is much higher after the age of 45. Pancreatic cancer is one of those cancers that there is definitely a genetic risk factor associated with it, as I'm about to show.

The majority of pancreatic cancers present with an advanced stage, because, you see here, more than 80% of patients are presenting with some sort of advanced stage, and localized cancer, for pancreatic cancer, a diagnosis is only 9% and a five year survival rate is 26%. And, as you can see, the metastatic is 53% at diagnosis and the five year survival rate is about 2%.

Now, the pancreatic cancer risk factors, like I say, out of the HPB malignancies is the one that has the genetic association with it, but, even though, it's less than 20% of cases. The environmental risk factors-- smoking, chronic pancreatitis, alcohol abuse, obesity, and diabetes-- are the main thing that we would deal with in this country. The BRCA 1/2 mutation carriers are well known, as well. The Peutz-Jeghers syndrome is extremely rare, but has a high risk of incidence of pancreatic malignancies.

To go a little bit more detailed in talking about environmental risk factors, smoking contributes about 20% to 30% of pancreatic cancer and is the strongest association-- it has to do with the number of packages of smoking that the patient had-- and it has a relative risk of about 2 to 3. Long-standing diabetes-- although a patient always asks us, has my diabetes preceded my pancreatic cancer or vice versa-- but the relative risk of pancreatic cancer doubles in patients that have long-standing diabetes for more than five years. Doesn't mean that the diabetes caused pancreatic cancer, it's just a meta-analysis of looking at observation study, looking at the incidence of patients presenting with pancreatic cancer and those they have diabetes. In a condition called non-hereditary and chronic pancreatitis, where these patients have a chronic inflammation of the pancreas, and that has been thought to lead to the incidence of pancreatic cancer, with a relative risk of about 2 to 6 [INAUDIBLE]. Obesity, as well, high BMI, and low level activity are all associated with the increased risk of pancreatic cancer.

Now these are-- I'm sorry, this is a busy slide, but-- these are the pancreatic cancer genetic syndromes. They are the first five of the most known and the genes that also associate and are known, which are listed there. Hereditary pancreatitis, which is associated with the PRSSS1 gene, is a germline mutation in that gene. This patient has a 50-fold increase in pancreatic cancer. The person at a younger age had severe pancreatitis and, basically, an increased risk of having pancreatic cancer.

Familial atypical multiple mole and melanoma syndrome-- again, this is another-- the gene has been identified as p16 gene. Those patients have a 10% to 20% fold increase in the incidence of pancreatic cancer, as well as, of course, melanoma.

The hereditary breast cancer and ovarian cancer syndromes are the BRCA1 and BRCA2 gene and the PALB2 gene. Those carry the germline mutation of BRCA2 mutation and have a 3.5 to 10 fold increase in the incidence of pancreatic cancer, as well as the other one-- you know, breast cancer and ovarian cancer. So it's very important not to forget, when you see these patients with breast cancer and ovarian cancer, to screen them as well for the possibility of pancreatic cancer, but I guess we know that already.

But a Peutz-Jeghers syndrome, which is a mutation in the gene STK1, has 100-fold increase of pancreatic cancer. These patients are the patients that present with the mucosa-- [INAUDIBLE] mucosa-- and have extremely high risk of developing breast cancer. Those are extremely rare, but, when you see them, you should pay attention to that.

And the last one is the hereditary nonpolyposis colon cancer, the Lynch syndrome-- the MLH1 and MSH2 have a 4-fold increase in the risk of pancreatic cancer. And these are associated, as you know, with the mismatch repair gene deficiency.

Ataxia-telangiextasia is a rare syndrome associated with-- this patient has all types of cancer, including leukemia. The mutation is that the anchors render the ability to repair the DNA very unable to repair the DNA, basically. And that's what predisposes them to several malignancies, such as leukemia and pancreatic cancer, and Li-Fraumeni syndrome associated with the P53 gene mutation.

Is it so far so good? You got a good understanding of what I'm saying? Good.

Now I'm going to move on to hepatocellular carcinoma. Hepatocellular carcinoma worldwide, about a million cases-- 500,000 to a million cases worldwide in the United States, about 20,000 new cases, actually. The ratio from male to female is about 2.4 to 1. The incidence of hepatocellular carcinoma over the past five years has increased in the United States. HCV related hepatocellular carcinoma is the fastest rising cause of cancer death in the United States. And cirrhosis is present in about 80% to 90% of these patients. Cirrhosis basically is the-- it's actually the step that most hepatocellular carcinoma is going to originate from, but not all of them are-- you don't have to have cirrhoses to have to have HCC.

This is the path to-- physiology about the genetics of hepatocellular carcinoma. As you can see, your liver gets exposed to all kinds of toxins in hepatitis C, diabetes, alcohol, all the risk factors. And what you get at the end of that is chronic hepatitis, which lasts for about 15 to 40 years. Then you have development of cirrhosis. And by 3% to 5% per year it leads you toward having to develop a hepatocellular carcinoma. So really, truly, a cirrhosis is basically what you first have, and then develop a hepatocellular carcinoma. The longer you have it, the higher the risk of having hepatocellular carcinoma.

So this is the estimated standard incidence of rate of liver cancer around the world, and this is closely associated with incidence where the HCC and hepatitis B virus is endemic. You have sub-Saharan Africa, and Republic of China, and, basically, a hotbed of HCC where there is a greater than 9.4 cases per 100,000. The United States is basically the place in the world where the incidence is the least-- excuse me, about 6.0. Canada is less than us. Basically, as you know, as the incidence of hepatitis B and hepatitis C rises, the risk of hepatocellular carcinoma also is higher.

This is another slide showing-- from the New England Journal of Medicine showing, from Doctor El-Serag-- showing, again, the increase in incidence of age-adjusted hepatocellular carcinoma. And the survival is about 12%, or five years.

Now this study was presented at [INAUDIBLE] GI by Dr. Kim. What he did-- it's a community study looking in Olmsted County, Minnesota. It looked at the incidence of hepatocellular carcinoma and what's driving it. As you can see, it has a definite jump by decade, between 2000 and 2008 incidence has increased significantly. And, basically, the main driver of this incidence, as he shows here, is hepatitis C, to confirm what I just talked to you about earlier, that it seems that the hepatitis are driving the increased incidence of hepatocellular carcinoma.

He also looked at the incidence of hepatitis [INAUDIBLE] and patients on the transplant list. He looked at 34,000 people registered for transplantation, and 1,900 of them had hepatitis C, which was about 6% of them. And he looked at what it is that-- of the 19,000 patients that have hepatitis C-- what are the main risk factors? Basically, again, the hepatitis C and B are the main drivers, as well as hereditary hemochromatosis, Wilson disease, and alcohol.

So, to go a little bit detailed in the respect to hepatitis B virus responsible for about 80% of the worldwide cause of HCC, there is a developing HCC increase by 100 fold. The majority of these patients will have cirrhosis in their background. Hepatitis C accounts for about 30% to 50% of the HCC in the United States. Just as hepatitis B, cirrhosis is also present, but the prevalence of cirrhosis in hepatitis C virus infected patients is much higher than that of HBV. Alcoholic liver disease accounts for about 15% of the hepatocellular carcinoma. Nonalcoholic fatty liver disease-- which is a liver manifestation of obesity. Metabolic syndrome, which predisposed the patient to HCC, this is not in high risk of incidence in the United States, but this is changing because of a demographic of more of us becoming obese and the metabolic syndrome increasing in the United States. And the other rare form, hemochromatosis, Alpha 1-atitrypsin, and autoimmune hepatitis.

Gallbladder cancer-- Gallbladder cancer is the most common cancer of the biliary tract. Worldwide incidence is about 2.2 per 100,000. United States-- about 5,000 new cases in the United States. The mortality varies strikingly around the world. Whereas, in Chile, the second most frequent cause of cancer death among women is gallbladder cancer, and the ratio of gallbladder cancer around the world from female to male is about 2 to 6, basically. It's one of those cancers more common in females.

The risk factors associated with gallbladder cancer are cholelithiasis-- 65% to 90% of the patients with gallbladder cancer have gallstones, but not all gallstones lead to gallbladder cancer. Chronic inflammation due to salmonella, S. typhi, and helicobacter infection has been associated. That, again, has to do with chronic inflammation of the gallbladder or the bile ducts, leading to gallbladder cancer.

Gallbladder polyps also have been associated with the development of gallbladder cancer, and polyps particularly greater than 1 centimeter, have the highest malignant risk. Now, with the polyps, inflammations are not necessary to be present to have cancer, you could just have the polyp without the inflammation going on.

Now this condition called anomalous pancreatico biliary duct junction, which is common in Asian population, also is associated with increased risk of gallbladder cancer. And other-- such as female, obesity, smoking, and medications such as [INAUDIBLE], and so on, all have been associated with increased risk of gallbladder cancer.

Cholangiocarcinoma, which is the second most common primary hepatic malignancy, is clinically divided into intrahepatic/extrahepatic cholangiocarcinoma. The extrahepatic include the perihilar cholangiocarcinoma. Extrahepatic are the most common. There's about 3,000 new cases of intrahepatic cholangiocarcinoma in the United States, but 10,000 new cases of extrahepatic cholangiocarcinoma. Now, these cases are quite difficult to get at because of the way we code the ICD code for cholangiocarcinoma. There was not a definitive ICD code for-- in the past, that is, before we had ICD-10, and that's more descriptive-- but it's very difficult to know exactly what the exact etiology or incidence of cholangiocarcinoma is, because, in the past, these were associated with, basically, if [INAUDIBLE] any cancer arises from the liver. And they differ in their biology. There's a lot of work going on in the biology of cholangiocarcinoma that we'll talk about later this afternoon.

This is basically a graph showing you what the divisions are of intrahepatic, the perihilar and distal extrahepatic cholangiocarcinoma.

And this is the worldwide distribution of cholangiocarcinoma. Where it's mostly prevalent is in Southeast Asia, in Thailand. Where it is least common is in Canada and the United States, basically.

Those are the risk factors associated with cholangiocarcinoma. They are both risk factors for intrahepatic/extrahepatic. Some of them share the risk factor, but there are some risk factors that are predominately associated with one or the other, such as hepatolithiases are mostly associated with intrahepatic cholangiocarcinoma, whereas the abnormal pancreatico-biliary junction with bile ducts dilation are associated with extrahepatic cholangiocarcinoma. Hepatitis C and hepatitis B, although very weak data for those, are associated with mostly intrahepatic cholangiocarcinoma. Whereas the rest, such as the liver fluke, viverrini, are associated with both intrahepatic and extrahepatic cholangiocarcinoma. Choledochal cysts and caroli syndrome is associated with both. And this agent, that is no longer in use, called Thorotrast, is also associated with cholangiocarcinoma, both intrahepatic and extrahepatic.

And to go a little bit in more detail, in terms of the risk factors for cholangiocarcinoma, primary sclerosing cholangitis have a 13% lifetime risk of cholangiocarcinoma, mainly the perihilar form, and 30% of cholangiocarcinoma are diagnosed, actually, in patients with PSC. The liver fluke, O. viverrini-- incidence of cholangiocarcinoma is high in endemic area, but I'll show you later a slide that would show you an example of what's going on in Southeast Asia. Choledochal cyst, Type I and IV, has a lifetime risk of 6% to 30% development of cholangiocarcinoma. Caroli's disease, as well as hepatolithiasis, has 5% incidence of cholangiocarcinoma.

Any questions? Too early to ask questions. All right.

So this is what's the evidence for O. viverrini for cholangiocarcinoma. Anybody know which country is this? No, too early, OK. So Southeast Asia. This is Malaysia here, and this is Korea, and so on. So the northeast of Thailand-- it's mostly associated with an increased incidence of the liver fluke, and that's where you see the cholangiocarcinoma. That's all it is, is less incidence of the viverrini, and so that's where you have a less incidence of the viverrini.

HCV, as a risk of cholangiocarcinoma, is associated, as I've mentioned before, to intrahepatic. Cohorts to the United States confirm the related risk of 2.55. And genetic disorders that are associated with cholangiocarcinoma, the Lynch syndrome and biliary papillomatosis-- this condition is a condition where the patient has several polyps within the bile duct, which predisposed them to have cholangiocarcinoma. Diabetes mellitus has increased both intra- and extrahepatic cholangiocarcinoma and has a relative risk of about 1.6. And obesity, as well as H. pylori and HIV infection, increases the risk of hepatocellular carcinoma. And that's, basically, the liver fluke.

And that's what I'm going to leave you with. Thank you.