Each year, 15% of incident cancers globally. are attributed to infectious causes. What are some of the major cancers that you think or that you've heard about are associated with an infectious cause? So if you're online, just raise your hand. If you're in the room, raiseyour hand. Cervical cancer is an interesting cancer because HPV infection, whether it's, subtype 16 or 18, are thought to be necessary causes of cervical cancer. There's other cancers that HPV causes or a pharyngeal cancer. Anal cancer is also caused by HBV infections. I think there had been a misconception that boys would not get HPV related cancers. And I think this has been really an important thing because I think there's some thoughts in terms of vaccination for HPV, you know, about why boys should get infected. And then yes, gastric cancers have an important ideologic cause primarily H pylori. The proportion that's attributed to infections globally is about 77%, but in different parts of the world different because of the problems of different infections that contribution plays a different role. So gastric cancer stomach cancer about 90% of the large burden of stomach cancer that occurs globally, have an infectious ideology. We'll talk about liver cancer in a lot of detail. About 4% of all cancers in Australia, New Zealand are thought to have an infectious cause. In sub-Saharan Africa, percentage is as high as 32% and also what the underlying causal agent is. And you can sort of see across different parts of the world, as hepatitis B virus attributed to liver cancer. I want to talk a little bit about the International Agency for Research on Cancer, which is part of the World Health Organization. They actually have a very formalized process by which they go through and systematically review and classify agents. And you can sort of see across different parts of the world, different distributions of the types of infectious agents leading to a proportion cancer. IRCs classification process, and how the, and what specific agents are classified into these different groups. And I'm just saying this because if we look at those 122 agents, a number of the agents are actually infections. And this graph here just looks at the number of infections causes that are associated with at least 5 different cancer sites. Epstein bar virus is, was first discovered because of its association with burkets, lymphoma, but it's now been shown to have group one evidence that's associated with Don Hodges's symphoma. HPV 16 does it known to be associated with at least 7 different cancer sites. HIV infections associated with as a group one carcinogen for 5 different malignancies. Epstein bar virus is a causal agent where 90% of the population is exposed to that agent. It seems to be associated with these cancers that are not particularly common. Take a about a couple minutes, go to your breakout rooms. And then we'll come back together. Kreski FIVO 2: One of the things that we talked about was the causal pie and how it could be a component. Of a particular causal pi and there's other factors, variables that when put together. Cause All the cancer but or not it's not sufficient alone to cause the cancer. It's mainly we see it in kids in Africa that present with large stomach so it's also focuses on a specific population of patients. TBV as you said is sufficient, but it's required but not sufficient for the endemic form. So there may be other host components that are required to be present in order for EBV to work. EBV plays a major role in the oncogenesis or the development of cancer, but is Not sufficient and and and Well, at least that's my perspective on the. other kind of host factors in this population. Of children that might make them more vulnerable to an infection like each EBV, together with or without malaria. A study looked at the association between years since infectious mononucleosis as a measure of timing in a person's life of Epstein bar virus. And then the risk of Hodgkins and Foma and sort of the timing of it and so the blue lines represent the cases of where the tumor cells had presence of Epsteinbar virus. There is a relatively short latency right between when someone is exposed to Epstein bar virus again through demonstration of mono nucleosis and the peak of time in which someone's developing cancer. It's a pretty short window as opposed to when Dr. Song talked about colorectal cancer and smoking where you were seeing really about a 20 where 20 year latency between smoking initiation and development of coloreCTal cancer. According to the international agency for research on cancer, these infections agents are thought to be cancer associated infections. So just as for example, we already talked about Epstein-barr virus. We'll talk a lot about hepatitis B and C viruses in their relation to different types of primary liver cancer. We're gonna talk a little bit about, I'll look back to Pylori and some really interesting evidence around liver floops. The one that we won't talk about is something which is felt to be a subset. Of bladder cancers in a specific part of the world. That are associated with a schistoma infection. Some viruses are able to integrate their DNA into, human cell DNA and lead to direct damage and mutations themselves. So these are the types of ways that were things that we call initiators. And then there's additionally some of these same infections or viruses that, lead to sort of this chronic level of inflammation. There are multiple ways in which infections can actually lead to cancer development. In order to avoid rejection of a donor organ you you suppress the immune system. And so it's through the immunosuppression that's allowing other agents maybe happening in the host to be more damaging than others. The relative risk of say 10 or even 50 full greater risk of these cancers in the presence of HPV. Compared to the absence. And then when we look at other types of infection related cancer, so for example, Epstein bar virus, human, herpes virus 8. The hepatitis viruses and liver cancer, you can just see the fact that immunosuppression has. The age at which someone's infected is going to be really important for a range of different infections. Some infections are more likely to be cleared. Depending or or on the flip side, more likely. to become a chronic affection depending on the age. at which somebody is exposed to the infection. SIP ship sizes is just the number of siblings in your family. And birth order is where you are. So thinking about the probability in the age of earlier infection. Do you think that if you have. 3 siblings living in your house is your probability of getting exposed to an infectious agent greater or less? SIP ship size has been one proxy for just the probability of infection to childhood infections as well as the age of which are infection. Now what about birth order? Do you think? How might that. Play out? If you're the first born in your house, do you think you're gonna get be exposed later or earlier to infections compared to say your younger siblings. Sweden did a nationwide study, from 1961 to 2,009 and they did sort of a nested case control study or incident density sampling. They had 400 and sorry 251 incident cases of n nasopharyngeal cancer. And then they matched on sex and birth year using density incidents density sampling for 1,255 controls. The earlier you're exposed to Epstein bar virus the, the, greater the risk of, mononucleosis was. Now what about Bernasopharyngeal cancer? What do you see here? Something different, right? So here it looks like. Whereas earlier exposure to Epsteinbar seems to be protective against developing money and nucleosis, it seems actually to be associated with an increased risk of nasopharynGEal cancer. Does that make sense? This is a study that was done in really leveraging a unique cohort of women who underwent, pap smear screening, in Uppsala, Sweden. And so, this study was done by Hanzo Lafadami and his team, where they linked the pap smears with information are in the Swedish cancer registry to look at 478 cervical cancer cases. The higher the viral count. The lower that this this CT number is. So going from left to right the higher. Viral load is associated with a lower CT count here. And then this is looking at the association between viral load and the relative risk or odds ratio for cervical cancer. If with presence of HPV 16 and a high viral load the odds ratio is about 50. Could you wait, for example, 4 years? N be safe, what about 7 years? Yes. 4 years, exactly, right? You can sort of see it looks like. You can probably fairly safely wait. The viral load is really an important predictor of future cervical cancer risk. So in terms of screening, you can sort of see this difference between what in 4 years versus 7 years. So again, just to read it the message, it's not just whether HPV 16 is present or not. Pap smears can be used for prevention. We also now have vaccination for hepatitis B virus, which is a major cause of liver cancer. What about something like, what do you know about H pylori or other kind of infections? We can identify and treat the infection. There's a number of ways in which we can think about cancer prevention, focused on infections in cancer. And we'll talk a little bit more in some more examples when we get into liver cancer. Yeah, and Dusky be interesting to think about, certain types of Again, what you wanting to identify. Cancers before they become cancer. The study was trying to get at a little bit about. is there sort of an immediate in terms of early detection and immediate increase in the odds of cervical cancer. So you would want to do if you saw somebody had high viral load, you'd want to keep screening them. Very, very regularly. Someone asked, what about EPV? Are there any preventable ways? Oh, that's a great question. The question really is maybe not if we're going to prevent it altogether, but can we prevent? The the viral load or the age at which someone's infected and it's complicated right because Okay. The liver is really an essential organ that plays a number of roles from detoxification, metabolism. It says it stores glucogen. And as a result, You know, it's exposed. Blood blows through the liver. As a result it can be exposed to many different types of toxins, environmental contaminants, dietary factors, etc. Liver is a common side of metastasis. This is not what we mean when we're talking about primary liver cancer. There's a number of histologic type the most common of the histologic types is hepatitis cellular carcinoma. I'm also going to be talking about collagenio carcinoma which occurs in the bile ducts. This is looking at the overall incidence of primary liver cancer across the world. Different parts of the world with a higher burden, particularly you can see, in Mongolia, the, incidence is 96.1, per 100,000 in the United States. In Mongolia, it's 6.8 per100,000. Each year globally it's a major cause of cancer. There's about 865,000 in cases of primary liver cancer and 758,000 cancer deaths that occur. So you can see there's countries with really high incidents and then other areas for example Brazil with much lower incidents. Liver cancer incidence is moderate so the prevalence of people living with liver cancer is fairly low actually. So that fatality is quite high. And so this is data from the United States that we looked at earlier. They're proportional. So what does that mean in terms of is this a highly fatal cancer? Would you say is that do you think the fatality was high? Each year it's about 41,000 new cases a primary liver cancer 29,000 deaths estimated in 2,023. When you look at five-year survival and when Colleen and Michelle give a lecture later. They'll talk about what relative survival is. About 20% of patient diagnosed with liver cancer, only 20% will be alive. Hepatitis B infection, really is a different type of virus than hepatitis C, hepatitis B is considered to be what's called a DNA virus, which means the viral DNA can actually directly integrate into human DNA. It can actually lead to directly to damage. It also can lead to inflammation along the way if chronic infection results. Hepatitis B is almost like a perfect carcinogen because it's both in initiator and a promoter. Smoking is thought to be that way too, that it both can initiate lung cancers to happen as well as promote it through inflammation. Most people with hepatitis B will actually clear the infection if they're exposed. Only if they become chronic carriers of hepatitis B or C that they will be at risk for developing primary liver cancer. Hepatitis B was the first of the virus that was found to be associated with primary liver cancer. It preferentially infects hepatitis. And so what you can see from hepatitis B infection that of adults who are exposed to hepatitis B, 95% of those individuals will clear the infection and not become chronic carriers. The hepatitis B surface antigen is an important biomarker because it's a measure of acute or chronic infection. It's the biomarker that's most often used in epidemiologic studies to look at the association between hepatitis B and risk a primary liver cancer. Over 300,000 individuals around the world have chronic hepatitis B infection. The higher the birth order, the earlier you're exposed. To an infection. The earlier you are exposed, the more like you are to become a chronic carrier. Therefore, the greater your risk of hepatitis B infection, therefore the great your risk is going to be a primary liver cancer. Chronic carriers are more likely where it's in integrating into your DNA and remaining part of your body. Inflammation and doing more damage. So is it like if you have chronic inflammation then that is an indicator that It is like chronic case of hepatitis? That's a great question. There's a lot of different causes of. leading, you mean in doing liver damage, etc, and seeing the inflammation in the liver, but there's many things that can cause it so it doesn't necessarily mean you have hepatitis B, you would really have to do a blood test to show that you positive for hepatitis B and you do it for that hepatitis B surface antigen. He recruited at 80 patients that had been diagnosed with the padocalio carcinoma. He also recruited 40 patients who had metastatic liver cancer. And then EDH sex match controls and then he took blood specimens from all of these individuals to measure different hepatitis B biomarkers. Dr. Chakopoulos included. Metastatic liver cancer as well as hospital base controls. In this study. Any thoughts any, what were some of your discussions? We weren't really sure that. In common fashion, I'll shout out one of my breakout roommates. Hepatitis B infection could damage the liver, so making it more vulnerable. That's an interesting hypothesis. The hypothesis was that hepatitis B, virus should not be associated with metastatic. But it should be with. The other cancer if there is an association. So it's almost like an additional. negative control with this idea that the the selection forces for going to the hospital for primary liver cancer might be similar for metastatic liver cancer. The cancer itself can often influence levels of different biomarkers. So it's something to take into account with this type of case control study. And so then another question, when was blood in this study taken in relation to cancer diagnosis. Was it taken before the cancer diagnosis? Or after the cancer diagnosed. Study looked at hepatitis B surface antigen as a measure of active and chronic infection, other 2 other types of biomarkers. Compared to people who are negative for both of the hepatitis B biomarkers and what they showed was the really strong positive association between hepatitis Bsurface antigen and the risk of primary liver cancer. No association for hepatitis B surface antigen with metastatic liver cancer, what was interesting was it did seem like the fact that these people have metastasis in their liver may have reactivated past infection. So that was kind of one of the early studies. And now since many studies including cohort studies have confirmed this strong positive association. There is no association between hepatitis B and death from liver cirrhosis. There is a really strong positive association for death from palace cellular carcinoma. This was, a really interesting study as well that just looked at instead of the blood levels of the imagin for hepatitis B also looking at how viral load from the DNA might play a role. Hepatitis C, virus is looking globally just at the prevalence. Hepatitis Ca virus around the world. A lot of geographic variability. Similar to hepatitis B, there's now been a number of studies that have really established a strong and causal association between hepatitis C infection and the risk of hepatcellular carcinoma. Hepatitis C and hepatitis B together are more likely to cause cancer. Study looked at 1,991 women and 2,008 men. 477 of them developed incident, hepatitis, or carcinoma. 95% confidence in drills for having both infections was about 18 to nineteen-fold greater risk of primary. Data suggests that there's synergy in in terms of increased incidence of hepasolar cursing of having both infections. Now I'm gonna turn, change gears and talk about aflatoxin. So alpha toxin is also considered a class one carcinogen. And I guess vice versa is there an independent effect of hepatitis C infection on hepataselia carcinoma based on this data. Aflatoxin and it's association with a padicola carcinoma, I think is a classic example of a food contaminant. There are certain types of molds. That grow on corn, nuts, and beans, and particularly warm and humid climates can produce a toxin called aflatoxin. When they assessed afflatoxin or measured afflictoxin based solely on the food frequency questionnaire, And then they compared high versus low dietary intake. There didn't look like much of an association between aflatoxin in the diet and risk of a patasilo cursor. Versus when they use biomarkers and they use 2 different types of biomarkers in urine. One suggested, you know, if you have the presence of the DNA addict for a flatoxin, the risk of hepatito carcinoma was nine-fold greater. Aflatoxin is considered a group one carcinogen because of its association with a patasalic persona. In the United States and Europe. Particularly because hepatitis B. infections are lower. So it can be, here we can see questionnaires can be great for measuring diet in some capacities for alpha toxin it was not so great. Alcohol seems to be its own risk factor independent of viruses. Coffee consumption. And aspirin seemed to be protective. For lowering the risk of primary liver cancer. Oh. So this figure here kind of summarizes. The population attributable fraction. For hepatitis, carcinoma. For different risk factors. And I kind of just want to highlight. This if we look at the first column is hepatitis B virus hepatitis C virus. In sub-Saharan Africa, a big proportion of hepatitis cellar carcinoma risk can be attributed to hepatitis B. And C virus. Whereas if you look in other parts of the world, let's say in Western Europe. It's much lower. In contrast, you can start to see things like alcohol, obesity being much bigger risk factors. The majority of primary liver cancer is due to hapadascellular carcinoma, but in certain selected Asian populations it seems like colonial carcinoma is a larger proportion. Clandio carcinoma which is much more rare. All of these major risk factors do damage and lead to chronic inflammation of the liver, which leaves to liver disease. Liver flukes are a type of parasite, a form of a worm. That preferentially infects the bile ducts. These can then lead to the development of clandio carcinoma. It's largely preventable. The disease is called primary liver cancer. It is the most common form of liver cancer in adults. Liver flicks are considered now a group one carcinogen. By cooking fish, it kills the liver flukes and therefore will not lead to cancer forming. Viral infections are associated alcohol seems to be a risk factor as does obesity diabetes, maybe not smoking, but these are thought to be probable risk factors for clen do carcinoma. Hepatitis B virus is really interesting as a model of both an initiator and a promoter. Liver cirrhosis really seems to be this unifying model understanding the ways in which ideologic factors are leading to cancer. And as I as we talked about, infections can be promoters. Leading to inflammation. They can be initiators of cancer. Warming. Non-viral causes may seem more strongly associated also as things like poor metabolic health are coming into different populations, obesity is growing. And I think hopefully also this talk gave some examples of how we use biomarker-based studies in cancer epidemiology and some of the principles of those biomimicry based studies as well. I might even add to that just, to do a direct email rather than going through Canvas for some reason Canvas sends my emails into a weird Mailbox that I don't check off in. Just email us directly to set up a time to meet that we really just want to talk about the presentation in your risk factor and give any advice we can.