* For this 50 or 55 years later and based on his name it was called the ruse sarcoma virus that was identified and it took a time for him to be really recognized for this landmark.

7:07

* So, each year, 15% of incident cancers globally. So about 2.3 million cases are attributed to infectious causes.

7:21

* I'm gonna stop sharing for a moment and I'd love to hear from all of you. What are some of the major cancers that you think or that you've heard about are associated with an infectious cause.

7:33

* So if you've heard about are associated with an infectious cause. So if you're online, just raise your hand and infectious cause. So if you're online, just raise your hand.

7:45

* If you're in the room, raise your hand. If you're in the room, raise your hand and Colleen and Michelle, if you could just let me know.

7:50

* Okay.

7:51

* It's a little hard to see people. If they're raising their hands. So if anybody has a specific.

7:53

* Cancer that they think of as having an infectious cause.

7:58

* Sorry, was that?

8:05

* Yes, Cervical cancer.

8:06

* Shh!

8:11

* Okay.

8:19

* Cervical cancer, absolutely. And 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, meaning that HBV infection is present in an estimate 100% of cervical cancers.

8:20

* It's not sufficient to cause cancer. There's other factors that help to progress it, but it certainly is an infectious ideology.

8:33

* Okay.

8:56

* Pencreatic cancer has been an interesting cancer. I think there's hypotheses, for example, there's some interesting work around H pylori infection, for example, there's some interesting work around H pylori infection in pancreatic cancer, but I wouldn't say yet that it's an established cancer with an infectious cause, but there is some interesting hypotheses.

8:57

* Right, so interestingly there's other cancers that HPV causes or a pharyngeal cancer is an example of that.

8:58

* Yeah.

9:06

* Okay.

9:15

* Anal cancer is also caused by HBV infections. 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.

9:16

* Yeah. Okay.

9:20

* I think there had been a misconception that boys would not get HPV related cancers. So I think that's been an important discussion.

9:24

* Okay.

9:29

* And then yes, gastric cancers have an important ideologic cause primarily H pylori.

9:31

* So let me let me share my screen again. And again, can you see my slides here? Okay, perfect.

9:38

* Yeah, yeah, we can.

9:44

* So this is this is a slide from an article from 2,020 and the size of the circle refers to the overall burden of the number of cases of cancer globally.

9:45

* So the larger the size, the more cancers that occur globally. And then the darker green part is the the proportion of the cancer not attributable to an infectious cause and the lighter green is an estimate of the number of cases attributable to the infection.

10:00

* So again, as I mentioned with cervix nearly a hundred percent attributable to HPV.

10:19

* So gastric cancer stomach cancer about 90% of the large burden of stomach cancer that occurs globally, have an infectious ideology.

10:23

* We'll talk about liver cancer in a lot of detail. The 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.

10:28

* Remember the estimate of puberty in a attributable fraction is a function not only the strength of the association of an exposure and cancer, but also the prevalence of that exposure in different populations.

10:49

* We'll also be looking at some of these other cancers that are more rare in the population but actually you know for example nasopharyngeal cancer, Kaposi sarcoma that have a very high infectious ideology.

10:56

* Thank you.

11:17

* And, the, as I sort of talked about with liver cancer, actually the overall proportion of cancer to trivial to infections varies considerably by the type of agent as well as the world.

11:18

* So at the very low end, probably about 4% of all cancers in Australia, New Zealand are thought to have an infectious cause, whereas in sub-Saharan Africa, percentage is as high as 32% and also what the underlying causal agent is.

11:32

* So for example in sub-Saharan Africa you can see about half of all of the infection related cancers are due to human papilloma virus, whereas in let's say eastern Asia, we have a big proportion that's due to a helicobacter pylori and stomach cancer pylori and stomach cancer as well as hepatitis B virus, pylori, and stomach cancer, as well as hepatitis B virus attributed to liver

11:44

* cancer. And you can sort of see across different parts of the world, as hepatitis B virus attributed to liver cancer.

12:12

* And you can sort of see across different parts of the world, Titus B virus attributed to liver cancer.

12:16

* 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, trivial to infection, and as well as the overall levels.

12:18

* Yeah.

12:27

* And so I've also just to say that I've. Shrunk the the people on the zoom so I can't see you so if you have a question or a comment that you wanna wake just raise your hand and Michelle and Colleen I kindly ask you to.

12:28

* Okay.

12:40

* Just let me know if someone's asking a question.

12:41

* Okay. Okay. Okay.

12:43

* I want to talk a little bit about the International Agency for Research on Cancer, which is part of the World Health Organization.

12:45

* They actually have a very formalized process by which they go through and systematically review and classify agents either to be group one which is thought to be known to be Carsonogenic to humans, then they have to be known to be carcinogenic to humans.

12:48

* Then they have 2 kind of subgroups for 2 A and 2 B, which are probably or possibly carcinogenic to humans.

13:13

* And group 3 is there's not, it's not classifiable as to its carcinogenic in a carcinogenicity and that's primarily maybe because there's not enough evidence one way or the other.

13:20

* 2.

13:49

* And then a group 4, which is probably not carcinogenic to humans. And so in this systematic review, there's a hundred 22 different agents based and this is based both on experimental studies, animal studies, and epidemiologic studies where the evidence is felt to be sufficient to classify to carcin to humans.

13:50

* Okay.

13:53

* And if you go to this link at the bottom of the page, it gives you more information about IRCs classification process, and how the, and what specific agents are classified into these different groups.

13:57

* And I'm just saying this because if we look at those 122 agents, a number of the agents are actually infections.

14:10

* And this graph here just looks at the number of infections causes that are associated with at least 5 different cancer sites.

14:20

* So HIV infections associated with as a group one carcinogen for 5 different malignancies.

14:31

* Just as an example, alcohols associated with 7 tobacco 17, but we have HPV infection that's HPV.

14:38

* Yeah.

14:45

* 17, sorry, HPV 16 does it known to be associated with at least 7 different cancer sites.

14:47

* Yes.

14:56

* So as I mentioned, 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.

14:57

* Hi, to, as well as nasopharyngeal cancer. It's interesting if you took blood on a group of adults including in the United States about 90% of individuals have been infected with Epstein-barr virus during their lifetime.

15:11

* Therefore, is this observation surprising to you and is it compatible? Compatible with the Epstein-barr virus being a causal cancer risk factor for these cancers.

15:32

* And why or why not? I'm gonna stop sharing for a moment. We're gonna do our first breakout session.

15:43

* Take a couple of minutes to think about. So we have a causal agent where 90% of the population is exposed to that agent.

15:50

* It's

16:00

* And it seems to be associated with these cancers that are not particularly common. So does how does that make you feel about Epstein bar virus as a causal agent for cancers.

16:01

* Take a about a couple minutes, go to your breakout rooms. And then we'll come back together.

16:12

* Okay.

16:18

* I don't know, Colleen and Michelle are the breakout rooms open.

16:19

* I'm gonna open them right now.

16:22

* Thank you.

16:26

* Okay, perfect. Okay, so you'll see on the bar on the bottom it says breakout rooms.

16:27

* You click on that and you just go into one of the breakout rooms.

16:32

* And you guys, yeah, exactly.

16:41

* And you guys will talk here. Well, me at the room so that's not too bad.

16:42

* Okay, perfect. That's sounds great. So we'll take 2 min.

16:46

* So I just send a note to the room, the breakout rooms that will come back together.

18:05

* In about 30 s.

18:06

* Okay, okay, that's no problem. That's great. Excellent.

18:28

* Laura, I just closed the room, so it's going to take 60 s for everyone to reach.

18:29

* Perfect. Great.

19:22

* Yeah.

19:23

* So I'd love to hear some of the discussions. So I'm gonna first, kind of put it to the room.

19:28

* And then we might need, People just to, Michelle and calling to. Just so we can hear it.

19:36

* She's No. Yeah.

19:37

* But any thoughts from the the Kreski FIVO 2 on that question?

19:43

* 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.

19:58

* Cause All the cancer but or not it's not sufficient alone to cause the cancer. That's why you have a bunch of other variables that have been found to be personal kicking, there's just still a lot of.

20:14

* Investigations that can be. Done to better understand the relationship between the and other barriers.

20:28

* Right, no, that's a great point. And I think we see it with other cancers that have infectious causes that the infection alone isn't.

20:35

* Okay.

20:51

* You sufficient but there there might be like as I mentioned in with Berkenson from there seems potentially synergy with malarial infection, maybe there's, you know, other things like diet or smoking that also might interact.

20:52

* Okay.

20:58

* So there may be other host components that are required to be present in order for EBV to work.

20:59

* So that's that's a great answer. What I'm gonna open it up to and ask anybody on zoom some of the discussions you had anything else to add to that conversation

21:04

* Feel free just to say something if you want to. Yeah, go ahead

21:18

* Yeah.

21:24

* I can add from my perspective that's TBV as you said is sufficient, but it's required but not sufficient for the endemic form.

21:25

* Okay.

21:31

* Yeah.

21:33

* Yeah.

21:40

* Okay.

21:43

* Of Berkeley in form as you discuss it. 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.

21:44

* Hmm.

21:47

* Okay.

21:49

* Yeah.

21:52

* Okay.

22:06

* I mean it's mainly in children and and not adults. I mean this type that is EBV and malaria associated so I guess it's a it's it's a composition of a lot of components and EBV plays their 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.

22:07

* Yeah, so 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.

22:12

* Yeah

22:22

* Yeah. What about what about the virus itself or did was any of the conversations that you had about other aspects of the virus, do you think?

22:23

* Okay.

22:32

* Like is it just the virus being there or not?

22:33

* Okay.

22:41

* Well, maybe what I'm gonna share my screen again and I'm gonna show you some data.

22:42

* And maybe this maybe tell me if this gives you any thoughts. So this this was a study that was done in Sweden in Denmark.

22:49

* Looking at Epstein by bar virus and the risk of Hutchins and Foma so Epstein-barr virus also is a cause for mononucleosis.

22:57

* Okay.

23:08

* Okay. Okay.

23:17

* And so this particular 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 Epstein bar virus and the red looks at Epstein bar virus

23:18

* Yeah. Okay.

23:49

* negative and essentially what you can see here is that there's a sort of a distribution of and on the y-axis is the relative risk of lymphoma.

23:50

* Okay.

23:55

* Okay.

24:08

* And you can see in the first 4 years after mononucleosis, the risk of Hutchins and Foma goes up substantially and then starts to decrease although even 10 years out you're seeing about a 4 fold greater risk.

24:09

* Yeah.

24:12

* None of them are associated with the virus of the timing of infection is important and I'll bring up another example with cervical cancer talking about viral load as well.

24:14

* So it may not be just the virus that it's there or not, but it may be the age at which someone's exposed.

24:30

* It might be the amount of viral load that they're exposed to, etc, and all of these things may be really explaining why even though the prevalence of EBB is so high in addition to host factors that it may be other factors associated with the virus itself that may be related to.

24:33

* Okay.

24:57

* Yes.

25:02

* Yeah.

25:14

* Whether or not someone develops cancer and I think what's interesting here again we talked about latency a couple of lectures ago what's interesting here is you can see this is a relatively short latency right between when someone is exposed to Epstein bar virus again through demonstration of mono nucleosis and the tide the peak of time in which someone's developing cancer.

25:15

* Okay.

25:22

* 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.

25:23

* Okay.

25:35

* So the next 2 slides really are not meant for you to memorize, but really to provide an overview of synopsis of all of the viruses and infections.

25:36

* That are felt to be group one agents. So again, according to the international agency for research on cancer, these infections agents are thought to be cancer associated infections.

25:47

* And the the first column are the cancers for which there's sufficient evidence. The next column is where there's more limited evidence.

25:54

* The next column is where there's more limited evidence, but there's more limited evidence, but there's, you know, it's where there's more limited evidence, but there's, you know, it's interesting hypothesis that may be associated.

26:09

* 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.

26:15

* HIV infection. There's very good evidence. Of that HIV associated cancers not only Kaposi sarcoma, but lymphoma's and as well as cancers of the cervix, and is, etc.

26:24

* Bye.

26:41

* We talked a little bit about HPV related malignancies. And then we're gonna talk a little bit about, I'll look back to Pylori and some really interesting evidence around liver floops.

26:42

* 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.

26:51

* That are associated with a schistoma infection. And again, I'm sorry, I can't see people now in the class or on Zoom.

26:56

* Yeah.

27:12

* So if you have a question. Raise your virtual hand or your hand in class and Michelle and Colleen will just let me know if you have a question.

27:13

* Oh

27:18

* So an important question. You might ask is, well, how could infectious agents cause cancer?

27:19

* Thank you.

27:27

* And there's thought to be a number of ways in which this might happen. And, and I, I want to bring in the concept that we talked about a couple of classes ago about some factors.

27:28

* Okay.

27:34

* That are initiators of a cancer. So they're those these are the things that can actually go in and do damage to DNA early on.

27:35

* Okay.

27:46

* And then there's things that promote the cancer. Promoters and these are things that may take a single cell or subset of cells and allow those cells to grow.

27:47

* Okay.

27:56

* In formalize into an actual tumor. So for viruses, some viruses are able to integrate their DNA into, human cell DNA and lead to direct damage and mutations themselves.

27:57

* Okay.

28:17

* Yeah.

28:20

* 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.

28:21

* Sure.

28:32

* So if you think about inflammation as sort of like fueling these subset of damaged cells to grow and and proliferate and and that may also lead to cancer growth.

28:33

* And then in addition, some viruses, for example, can actually lead to immunosuppression.

28:37

* And so it's through the immunosuppression that's allowing other agents maybe happening in the host to be more damaging than others.

28:44

* So they really are multiple ways in which infections can actually lead to cancer development.

28:51

* And I think in an example of, immunosuppression and its important role in cancer development.

28:58

* This comes from a. Meta-analysis of studies that looked at what is the association between different infections and the risk of cancer in different in 2 different types of immunosuppress population.

29:06

* So the first immuno press immunosuppress population are each of the positive individuals. The second are patients who are undergoing organ transplant.

29:19

* We're in order to avoid rejection of a donor organ you you suppress the immune system.

29:24

* Hello.

29:41

* So these are 2 groups of individuals that have high immunosuppression. And so these are relative risk measures looking at the association for example between HPV and infection and these different cancers in these 2 groups of immunosuppressing individuals.

29:42

* And I think what may really jump out to you is what you can see for many of these infections, the relative risk of say 10 or even 50 full greater risk of these cancers in the presence of HPV.

29:58

* 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.

30:06

* The hepatitis viruses and liver cancer, you can just see the fact that immunosuppression has, you know, you can see here over a hundred full greater risk of these cancers in the presence of immunosuppression.

30:22

* So, so again, thinking about the role that the host might be playing interacting with infectious agents in increasing the risk of cancer occurring.

30:35

* Thank you.

30:43

* Oh, so, what's been interesting and I along this idea of immunosuppression that with the advent of antiretroviral therapies because these are reducing immunosuppression in HIV positive individuals.

30:46

* There's been a reduction in the incidence of AIDS to find cancers in the HIV positive population.

31:01

* Would spend an important observation.

31:04

* Yeah.

31:11

* So, you know, a lot of time, so one of the things I mentioned, in talking about Epstein bar virus is not only do you get the infection or not but what is the age at which someone's infected.

31:12

* And that's going to be really important for a range of different infections because what it allows depending on the age at which somebody is infected, there might be maternal antibodies, there may be other windows of greater susceptibility, so some infections are more likely to be cleared.

31:25

* Okay.

31:45

* 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.

31:46

* So 2 different proxies for agent exposure to infection, right? Because it's hard to know some some infections are silent, right?

31:49

* You might be exposed to a specific infection and there's no clinical symptoms in that infection. So you actually oftentimes may not know when someone's exposed to an infection.

31:59

* So we use SIP ship size and birth order. As proxies. So I wanna I'm gonna stop sharing for a second.

32:12

* Okay.

32:18

* SIP ship sizes is just the number of siblings in your family. And birth order is where you are.

32:20

* So if let's say there's 3 kids in your family and you're the the middle child you're this your birth order is 2 if you were the first born your birth orders one and if your third your birth order 3 and it and your sib ship size would be 3 So thinking about the probability in the age of earlier infection.

32:24

* What do you think if with a greater number of siblings you have or where you are with a birth order, how might that impact your age at a infection to things that are commonly, that kids are commonly exposed to.

32:47

* Yeah.

33:05

* Maybe let's top up with subship size. 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?

33:06

* When you're a kid. Higher, right, exactly. So 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.

33:15

* Now what about birth order? Do you think? How might that. Play out.

33:28

* Do you think? 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.

33:35

* Later. Right, exactly, because, you know, now kids often will go to daycare so maybe this isn't as translatable but when many times when kids weren't getting exposed until they went to say kindergarten, they weren't getting their first exposure to infections really until then, whereas the younger children, they were getting it smooth from their older siblings coming over.

33:49

* So, so we can use SIP ship size and birth order as proxies for age and infection as well as the overall probability of infection.

34:11

* So there was a study that was done on birth order and citizenship size in relation to the risk of nasopharyngeal cancer.

34:17

* So using the National Health Registers in Sweden, they did a nationwide study, from 1961 to 2,009 and they did sort of a nested case control study or incident density sampling.

34:23

* They had 400 and sorry 251 incident cases of n nasopharyngeal cancer.

34:43

* In this population and then they matched on sex and birth year using density incidents density sampling for 1,255 controls and then they had information on the total number of siblings.

34:49

* Listen, Yeah.

34:50

* As well as the number of older siblings. So what does this data tell you? So this is on the left panel is looking at this.

35:04

* You're between the total number of siblings you had and I'm sorry this is the risk of mono nucleosis.

35:14

* First and then this is looking at the risk of nasopharyngeal cancer. So let's look at the risk of mononucleases first.

35:20

* So this is was part of the say, what did this tell you? About age of exposure to Epstein bar virus.

35:27

* And the risk of mononucleosis. Again, I can't see you. So just speak out or.

35:36

* For Michelle and. Just tell me if somebody is raising their hands.

35:42

* Oh

35:48

* Is it earlier or later exposure to Epstein bar virus that is going to be a more of a risk for mononucleosis?

35:49

* So looking at the PIN on the right, if you have 3 older siblings. Your risk of mononucleosis.

36:05

* Was about 24% lower compared to those without any older siblings.

36:14

* 30.

36:27

* Yeah.

36:30

* Earlier right exactly so the earlier you're exposed to Epstein bar virus the, the, greater the risk of, mononucleosis was.

36:31

* Okay.

36:40

* Now what about Bernasopharyngeal cancer? What do you see? Maybe the associations are quite as strong, but what do you see here?

36:41

* Something different, right?

36:52

* So here it looks like. Whereas earlier exposure to Epstein bar seems to be protective against developing money and nucleosis, it seems actually to be associated with an increased risk of nasopharyngeal cancer.

36:56

* Does that make sense?

37:10

* So the timing of the infection is is quite important.

37:18

* Cool.

37:23

* Alright, so I wanted to this was one of the articles that was the recommended reading for class today and this gets a little bit more about details of the infectious agents itself.

37:24

* Yeah.

37:44

* So this is a study that was done in really leveraging a unique cohort of women who underwent, pap smear screening, in Uppsala, Sweden.

37:45

* They had stored 730,000 pap smear specimens from 146,000 women between 1,969 and 1,995 these were just stored in the pathology lab and they were kind of available, you know, for clinical and epidemiological studies.

37:49

* Yeah.

38:16

* 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.

38:17

* Okay.

38:31

* 608 age match controls from this cohort of women. And then this is looking at, a.

38:32

* Count a viral load. So essentially here, The higher the number. The greater the viral load.

38:38

* And so then this is looking at actually I apologize this is wrong so the lower sorry the lower the viral count.

38:51

* The higher the viral count. The lower that this this CT number is. So going from left to right the higher.

38:59

* 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.

39:09

* The first line with the open circle is one year after the pap's mirror, 4 years after the pap smear and then 7 years after the Pap.

39:22

* So first in terms of viral load based on this figure. Does viral load of HPV 16 make a difference for the risk of cervical cancer?

39:31

* Yes or no?

39:45

* Do you see a different association between higher and lower viral load? And the odds of.

39:49

* Cervical cancer in this dataset.

39:58

* 2. Someone put yes in the chat.

40:01

* Yes, exactly. And so it's pretty striking actually. So for those with the lowest, viral load, you can see the association between HPV 16 and cervical cancer was probably an odds ratio of about 4.

40:07

* Yeah.

40:38

* And then when you look at the higher spiral titers. You can see that the relative risk is dramatically increased so that if with presence of HPV 16 and a high viral load the odds ratio is about 50 And then, so just you can see these 3 different time points between when they, PAP, was taking and the risk of cervical cancer.

40:39

* So now I'm going to ask a question. How do you interpret this in terms of when cancers how cancer screening and early detection you know If you have a detection of HPV, 16 viral load.

40:45

* Present in terms of. Identifying cancers earlier through earlier screening earlier detection. How might you take this information?

41:02

* Like, do you think you need to test somebody every year? Could you wait, for example, 4 years?

41:14

* N be safe, what about 7 years?

41:20

* Yes. 4 years. Yes.

41:28

* 4 years, exactly, right? You can sort of see it looks like. You can probably fairly safely wait.

41:31

* 4 years, although of course, you know, maybe if you're in this highest group, you'd want to do more active surveillance of this population anyways.

41:41

* But right, exactly. So in terms of screening, you can sort of see this difference between what in 4 years versus 7 years in terms of the incidence of cervical cancer.

41:49

* So again, just to read it the message, it's not just whether HPV 16 is present or not, but also the viral load is really an important predictor of future cervical cancer risk.

41:59

* Okay, so I'm gonna stop sharing for a moment and I want to ask the question, are infection related cancers preventable?

42:13

* And if so, how? So just in what we've talked about so far. How could we prevent in of the infectious related cancers we've talked about?

42:21

* How could we? Think about prevention or some of the other cases we haven't talked about. Is first of all is prevention possible.

42:35

* Thank you.

42:47

* Vaccinations perhaps.

42:52

* That's vaccinations, exactly, right, exactly. So for cervical cancer, we have vaccination.

42:55

* Yeah.

43:05

* We haven't talked about it yet, but for hepatitis B virus, which is a major cause of liver cancer, we also now have vaccination which recommended at least in the United States as part of childhood vaccinations.

43:06

* How else? What about, what else for cervical cancer? Can be used for prevention.

43:14

* Hmm.

43:24

* What do we use for early detection to actually prevent the cancer from being? From from happening.

43:30

* It's great.

43:41

* Right, screen. Yeah, Pap users, exactly. So we do screening, right? And the hope with Pap smears is not only will we detect cervical cancer earlier, but will actually detect the pre malignant condition earlier.

43:42

* And remove it before cancer can even occur. So that's another way we can prevent infection related cancers.

43:46

* No.

44:04

* What about, oh, sorry, was there somebody have a comment? In the room. What about something like, what do you know about H pylori or other kind of infections?

44:05

* We, we can treat the infection. Right? We can identify and treat the infection. Yeah, and Dusky be interesting to think about, certain types of Again, what you wanting to identify.

44:15

* Cancers before they become cancer. So identifying those pre malignant lesions. But there's certain types of infections that we can prevent.

44:27

* Okay.

44:39

* I think stomach cancer we've seen dramatic decreases in the United States because of of hygiene has really dropped dramatically in the United States and in Western countries, the incidence of H.

44:40

* Pylori and therefore the incidence of gastric cancer. So there's a number of ways in which we can think about cancer prevention, focused on infections in cancer.

44:52

* And we'll talk a little bit more in some more examples when we get into liver cancer.

45:01

* Hi, I'm going to have a question. Just on the previous slide, the HPB, 16 barrel mode.

45:06

* Yeah.

45:15

* I was wondering, is it showing that this 7 year gap, I guess, in getting a perhaps near is associated with, oh, lower dress but cancer.

45:16

* Yeah, so basically, yeah, exactly. I think what you're the the way this is study with design was they they had you know, all these pap smears from women who were cancer free when the pap smear was taken.

45:28

* Okay.

45:43

* And then the question they asked was, what was the association with cervical cancers that occurred in the first year?

45:44

* In the first 4 years and then not until 7 years later. So it was trying to get at a little bit about.

45:50

* You know, is there sort of an immediate in terms of early detection and immediate increase in the odds of cervical cancer.

45:58

* So you would want to do if you saw somebody had high viral load, you'd want to keep screening them.

46:06

* Very, very regularly. Or, is, is it a slower latency and therefore you, you might be able to, in terms of early detection you might not need to be doing looking every year so I think it was I don't know if it translate directly to early detection because as I said, I think if somebody had a really high HPV 16 viral load, you'd want to have them come in

46:12

* and screen more regularly. But I think what this is getting at a little bit is that how quickly cervical cancer might develop in someone who has a high viral load.

46:38

* Yeah. Yeah. Yeah. One more question in the chat.

46:51

* Did, did that clarify the question or your question? Okay, great. Okay. Hmm.

46:52

* Someone asked, what about EPV? Are there any preventable ways?

46:59

* Oh, that's a great question. So you know, with EBV, as I mentioned, you know, ultimately about 90% of us are going to have serologic evidence that we had prior infection.

47:06

* So, you know, The question really is maybe not if we're going to prevent it altogether, but can we prevent?

47:20

* The the viral load or the age at which someone's infected and it's complicated right because

47:31

* Okay.

47:41

* The association between EBV. And mononucleosis. Or EVV and Burke's lymphoma made different.

47:42

* Okay.

47:51

* So EBV I think is a little more complicated. I don't believe that there's a vaccination.

47:52

* Epstein by virus, right? No, there's not. I don't know if someone has tried to develop one or not, but I guess that could be a strategy.

47:56

* Potentially that there's a vaccination, but currently, and I don't believe there's treatment either.

48:01

* Okay. Any other questions?

48:15

* Okay, great. So, now we're gonna go into, to liver cancer.

48:21

* And so the liver is really an essential organ that plays a number of roles from detoxification, metabolism.

48:26

* It says it stores glucogen. And as a result, You know, it's exposed.

48:34

* Blood blows through the liver and as a result it can be exposed to many different types of toxins, environmental contaminants, dietary factors, etc.

48:45

* As well as viral infections. And then as a result, similarly, it can be actually a common side of metastasis because of the blood flowing through the liver.

48:55

* And so, you know, on our first lecture we talked about different cancers when they do leave the original organ.

49:04

* They metastasize to different organs. When they do leave the original organ, they metastasize to different organs.

49:13

* Well, livers a come in sight, metastasize for breast cancer, and metastasize for breast cancer, metastasized for breast cancer, colon cancer, and lung cancer, colon cancer, and lung cancer, and lung cancer.

49:16

* This is not what we mean when we're talking about primary liver cancer. So I really try to use the word primary liver cancer.

49:21

* So I really try to use the word primary liver cancer. So I really try to use the word primary liver cancer.

49:26

* So I really try to use the word primary liver cancer instead of just liver cancer because it because liver is a common side of metastasis.

49:27

* There's a number of histologic type the most common of the histologic types is hepatitis cellular carcinoma.

49:28

* I'm also going to be talking about collagenio carcinoma which occurs in the bile ducts of the liver, whereas, hepat a cellular carcinoma is cancers that are arising in the hepatocytes.

49:40

* So I'm going to, Click on this link here and can can you see now the IRC website?

49:53

* Yes.

50:03

* Okay, perfect. Yeah, so I just wanted to kind of, I thought it'd be nice to kind of go through a little bit using this because I think you'll be using it for your descriptive epidemiology.

50:04

* But this is looking at the overall incidence of primary liver cancer across the world, incidence of, primary liver cancer across the world for both.

50:13

* Oh sorry, this is for all cancers. Let me sorry. Let me let me put it for liver cancer specifically.

50:24

* So this is for liver and intra hepatic bild ducks. This is not metastatic liver cancer.

50:28

* Okay.

50:41

* This is cancers that are primary to the liver. And so what you can see is when we look at both sexes together and this is data for 2022 we have different parts of the world with a higher burden, particularly you can see in Mongolia the, different parts of the world with a higher burden, particularly, you can see, in Mongolia, the, incidence is

50:42

* 96.1, per 100,000 in the United States. Instead, it's, it's 6.8 per 100,000.

50:58

* Okay. Okay.

50:59

* So you can see there's countries with really high incidents and then other areas for example Brazil with much lower incidents.

51:03

* So I wanted to show that we can also compare. Different populations so here we can compare different countries together across a range of different cancers.

51:11

* Etc. so i just wanted to kind of I like here if we go back here if we look at what the incidence of.

51:27

* Cool.

51:36

* Liver cancer is. Among. So this is both. Genders if we look at men.

51:37

* No.

51:45

* Okay.

51:52

* Kind of very similar patterns and if we look at women, I think the only difference is that across the board the incidence is much lower in women than it is in that.

51:53

* Oh.

51:58

* And then if we look at moreality, the countries are fairly similar as well. Someone to switch back to this slide here.

51:59

* Good.

52:04

* Yes.

52:09

* Can you see the slide again? Okay, perfect. So each year globally it's a major cause of cancer.

52:10

* There's about 865,000 in cases of primary liver cancer and 758,000 cancer deaths that occur.

52:11

* And sorry, I'm just the. Air conditioner just popped down a little bit. Open the store so it turns off.

52:24

* In 2022. All right, so this is a figure looking at on the left in blue are the incidents rate per 100,000 individuals and on the right are the mortality rates and this is looking at different continents.

52:31

* What does this figure tell you in terms of the ratio of incidence to mortality?

52:47

* They're proportional. Yeah. Their first question.

53:01

* Sorry, couldn't hear with the, They're proportional. So what does that mean in terms of is this a highly fatal cancer?

53:03

* Would you say is that do you think the fatality is high?

53:14

* Good morning.

53:19

* There's a lot of nodding around.

53:22

* Was that sorry? Yeah, a lot of nodding exactly. Yes. I think somebody in the chat said.

53:23

* Yes, yep, exactly, right. So that fatality is quite high. And as a result, and the incidence is moderate so the prevalence of people living with liver cancer is fairly low actually.

53:29

* And so this is data from the United States that we looked at earlier. Each year it's about 41,000 new cases a primary liver cancer 29,000 deaths estimated in 2,023.

53:44

* When you look at five-year survival and when Colleen and Michelle give a lecture later. They're gonna talk about different concepts in survival.

53:56

* They'll talk about what relative survival is. Essentially it's fairly low. So 5 years out, about 20% of patient diagnosed with liver cancer, only 20% will be alive.

54:05

* So this, can you, can you see my arrow by any chance? No. Yes, you can.

54:16

* Yeah.

54:19

* Alright, perfect. So there was an interesting over time sort of somewhat decline. And this is looking at death rates among men and then since 1,990 there's been an alarming increase in mortality rates from liver, primary liver cancer over time.

54:20

* Again, not metastatic diseases, primary liver cancer. And we're seeing it also in women as well.

54:39

* Okay.

54:49

* So it's an alarming trend given how fatal this cancer is. Oh, it affects in the United States people differently.

54:50

* You can really see the dramatic difference in the incidence rate per 100,000 between men and women and then there's groups of individuals with very high risk.

54:52

* So for example in American Indian and Alaska Native populations, you have very high rates also in Hispanic populations.

55:05

* There's also certain Asian and Pacific Islander populations, which we'll talk about in a moment, that are very high risk as well as black non-Hispanic individuals.

55:13

* Yeah.

55:25

* So, 2 of the major infection related causes of primary liver cancer are hepatitis B and hepatitis C infection.

55:26

* Okay.

55:31

* 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 and as I talked about earlier in this lecture, it can actually lead to directly to damage.

55:32

* Okay.

56:06

* It also can lead to inflammation along the way if chronic infection results. And this is important to think about hepatitis B we call almost like a perfect carcinogen because it's both in initiator and a promoter.

56:07

* Smoking is thought to be that way too, that it both can initiate lung cancers to happen as well as promote it through inflammation.

56:15

* Hepatitis C and said is considered to be, it's a virus DNA, it doesn't integrate into the DNA, so it's not thought to be a promoter DNA, so it's not thought to be a promoter, but it's certainly concrete with a chronic infection a lot of inflammation, but it certainly can create with a chronic infection a lot of inflammation that

56:22

* ultimately can lead the cancer to reform. And I'm talking about chronic infection, which is really an important concept with hepatitis B and C.

56:39

* Because most people with hepatitis B will actually clear the infection if they're exposed.

56:43

* And as only if they become chronic carriers of hepatitis B or C that they will be at risk for developing primary liver cancer.

56:55

* 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.

57:04

* Whereas for newborns if they're born to moms that are carriers of hepatitis B, 90% of them will become chronic carriers.

57:17

* So again, thinking about prevention. This is really an important thing in terms of prevention of transmission of hepatitis B infection to babies.

57:23

* In contrast, what you can see for hepatitis C, that a large proportion of individuals who are exposed to hepatitis C infection will become chronically infected.

57:40

* So that's a really important factor in terms of the future risk of liver cancer. Primary liver cancer as well as other types of infections.

57:48

* I'm sorry, other types of liver diseases. So hepatitis B was the first of the virus that was found to be associated with primary liver cancer.

58:03

* It preferentially infects hepatitis. Which are the cells that lead to hepatitis cellular carcinoma, which is the primary subtype of primary liver cancer.

58:14

* As I mentioned, it integrates into the host DNA. And there's this is what the virus looks like.

58:24

* And the reason I'm showing this is if you look here on the lower right, the hepatitis B surface antigen.

58:27

* It's an important biomarker because it's a measure of acute or chronic infection and 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.

58:38

* So it unfortunately over 300,000 individuals around the world have chronic hepatitis B infection.

58:51

* There's a lot of variability in around the world as I mentioned, a high prevalence of chronicity in infants who are born to hepatitis B.

59:05

* Infected mothers. So given and compared to 10% who are teenagers when they're first exposed, how do you think then let's talk about birth order remember so the Later you are.

59:11

* Born, the greater the likelihood you're exposed earlier. To an infection. What do you think the association is between birth, order, and primary liver cancer?

59:30

* Do you think it's a positive association or an inverse association or no association?

59:43

* So.

59:55

* So the higher the birth order, the earlier you're exposed.

59:56

* Okay.

1:00:00

* And it looks like the earlier you're exposed, the more like you are to become a chronic carrier.

1:00:02

* Okay.

1:00:13

* Well, it's sort of so the earlier you're exposed to happen times be the more likely you are to become a chronic B, the more likely you are to become a chronic carrier of hepatitis B infection.

1:00:17

* Therefore, the greater your risk of hepatitis B infection, therefore the greater your risk is going to be a primary, therefore the greater your risk is going to be a primary liver cancer in the future.

1:00:20

* Okay. Hello. There's a

1:00:30

* One of, oh, sure. There's a comment. Yep. Oh, yep.

1:00:31

* Yeah.

1:00:40

* Hey, Lori, I just have a question about, when you say chronic areas, does that mean that they're is that having to do with like the DNA?

1:00:41

* Getting us affected by the virus or Like, I think I'm just like overthinking. Yeah.

1:00:48

* Yeah, no, no, no, I think it's a really good question. I think what it, it kind of means is that your body is able to just get rid of the virus.

1:00:55

* Right.

1:01:04

* Whereas with a chronic carrier, you're not getting rid of the virus. So the virus is going to continue to be able to do damage to DNA and it's going to be able to continue to lead to inflammation.

1:01:05

* Hmm.

1:01:16

* Whereas like, you know, like just if you think of like a common cold Most of the time you get exposed to a virus, a cold virus, and then you're able to just get clear it from your body and that virus is no longer.

1:01:17

* Part of your body. So right, the chronic. Carriers are more likely where it's in integrating into your DNA and remaining part of your body and leading to that chronic.

1:01:32

* Inflammation and doing more damage.

1:01:44

* I see. So is it like if you have chronic inflammation then that is an indicator that It is like chronic case of hepatitis.

1:01:46

* Yeah, that's a great question. So there's a lot of different causes of.

1:01:55

* Hmm, I see.

1:02:16

* 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.

1:02:17

* Oh.

1:02:22

* That's going to be the best marker to show that you're chronic carrier of infection.

1:02:23

* Thank you.

1:02:25

* Gotcha. Thank you.

1:02:26

* And I'll talk, I'll show you kind of this model that synthesizes how all the risk factors might be playing a role in, in the development of primary liver cancer.

1:02:28

* So one of the really early studies that really helped us establish, hepatitis B virus being associated with, hepaticellular carcinoma was a study done by Demetrius Jacobis who was a former chair of epidemiology at the Harvard School of Public Health.

1:02:33

* He did this hospital base case control study in Greece. He recruited at 80 patients that had been diagnosed with the padocalio carcinoma.

1:02:50

* 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.

1:03:05

* So I guess why do you think he included? Both primary and metastatic. Liver cancer. What as well as controls.

1:03:21

* If you wanted to show that hepatitis B virus infection was a causal agent. For bimary, hepatocalial cursor.

1:03:31

* Why did he include metastatic?

1:03:40

* Yeah.

1:03:42

* Liver cancer do you think in this hospital based case control design?

1:03:43

* What did we do a quick breakout? Is it is it hard to set up?

1:03:56

* No, I can do it.

1:04:00

* Alright, while we take a quick break out and just talk for a minute, let's soon like, 90 s, for this and talk about what is the importance, in this hospital-based Case control study.

1:04:01

* That he thought to include metastatic liver cancer in addition to hospital-based controls in the study.

1:04:16

* Alright, so go ahead and join a breakout room or in class turn to your neighbor and let's have a 90 s discussion.

1:04:27

* Should we, if we close out the rooms now, Michelle, do we, that gives them a minute.

1:05:27

* Yeah, I can do that.

1:05:34

* Okay. I, I can do it too.

1:05:36

* Perfect.

1:05:41

* Good morning.

1:06:36

* Okay, is everybody back? That's it. Okay, perfect.

1:06:37

* Okay, now everyone should be back.

1:06:40

* Oh, perfect. Fantastic. That's great. Excellent.

1:06:41

* Yeah.

1:06:48

* So let's, I'm gonna turn to our, colleagues on Zoom to ask first, what were some of your discussions about why do you think Dr.

1:06:49

* Chakopoulos included. Metastatic liver cancer as well as hospital base controls. In this study.

1:06:54

* Any thoughts any, what were some of your discussions?

1:07:11

* We weren't really sure that. In common fashion, I'll shout out one of my.

1:07:18

* Yeah.

1:07:25

* Thank you. Perfect, perfect.

1:07:26

* My breakout roommates. Meeting said that, it could just be that they're associated.

1:07:27

* Okay.

1:07:29

* With both.

1:07:31

* Oh, that's interesting, right. So, you know, it maybe there's some way in which hepatitis.

1:07:33

* B infection could damage the liver, so making it more vulnerable. That's an interesting hypothesis.

1:07:41

* So actually, so in maybe I'll turn to the room then any thoughts from the room about why They were included.

1:07:48

* Okay.

1:07:56

* Okay.

1:08:00

* Any thoughts?

1:08:05

* Well, remember, this was a hospital based case control study and the controls. You know, you kind of always worry a little bit about selection bias.

1:08:09

* Because the controls were taken from the same hospitals, so might have had other conditions. And so actually, The hypothesis was that hepatitis B, virus should not be associated with metastatic.

1:08:23

* Yeah.

1:08:42

* But it should be with. The other cancer if there is an association. So it's almost like an additional.

1:08:43

* Second type of 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.

1:08:48

* So that was sort of his his rationale.

1:09:02

* Okay.

1:09:05

* Alright, so let me share. Does that make sense?

1:09:06

* Thank you.

1:09:14

* And so then another question, when was blood in this study taken in relation to cancer diagnosis? Was it taken before the cancer diagnosis?

1:09:15

* Or after the cancer diagnosis.

1:09:23

* Okay.

1:09:31

* Anybody, anybody at all?

1:09:35

* What's that actually?

1:09:38

* It was after exactly right. So they identified the cases, they identified the controls, and then they took blood.

1:09:40

* Now this is important because for many reasons, when you're asking about with a questionnaire you might have recall bias. You might have recall bias.

1:09:46

* In this case, with the biomarker, the cancer itself can often influence bias. In this case, with the biomarker, the cancer itself can often influence levels of different biomarkers actually.

1:09:55

* Okay.

1:10:08

* So it's something to take into account with this type of case control study that you can think that the cancer, for example, might lead to immuno suppression and therefore might lead to reactivation or increased viral load etc.

1:10:09

* So you want to kind of think about with these types of study where the when the blood was taken in relation to the cancer being developed.

1:10:14

* And as you interpret things. So these are the results of the study. The first column or data looking at the association for primary hepatacella persona on the right is metastatic liver cancer.

1:10:21

* So they actually, this was kind of early on in this type of literature. They weren't exactly sure which was the right biomarker to look at.

1:10:37

* So they looked at hepatitis B surface antigen as a measure of active and chronic infection, other 2 other types of biomarkers and then 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 B surface antigen and the risk of primary liver cancer.

1:10:48

* There was a suggestion of an elevated risk, but not really as substantial for the hepatitis B surface antigen.

1:11:06

* And the reason is that these other 2 biomarkers are not really specific for chronic infection.

1:11:18

* Yeah.

1:11:29

* They might be kept capturing passive infection, but not chronic infection. And then it was interesting, really 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 and that's why you're seeing this kind of interesting positive association.

1:11:30

* So that was kind of one of the early studies. And now since many studies including cohort studies have confirmed this strong positive association.

1:11:48

* This was a really important cohort analysis of pregnant women in Taiwan. You can see the cohort was over 2 million pregnant women where all of them had a papatized v. Surface antigen status at the time of pregnancy enrollment.

1:11:56

* And what you can see here is looking at the hazard ratio for all causes of death except for liver cancer and those comparing those who are positive versus negative for hepatitis B.

1:12:16

* Really no association. Excess risk of developing death from liver cirrhosis. As well as a really strong positive association for death from palace cellular carcinoma.

1:12:31

* 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.

1:12:45

* And this was a, this is different from the hospital based. Case control study because here what they did was they took a cohort study.

1:13:06

* Okay.

1:13:32

* From the Shanghai's men in women's studies. They had 56,000 women who gave a blood sample in 1,997 to 2,000 46,000 men who gave a blood sample between 2,002 and 2,006 none of them had primary liver cancer they then followed them respectively until 2,012 identified primary liver cancer cases.

1:13:33

* Okay.

1:13:38

* It's a sampling and identified controls and then went back in the freezer and pulled out the bloods.

1:13:39

* Okay.

1:13:45

* Okay.

1:13:59

* From the freezer to test the biomarker so here you don't have that reverse causation that the cancer itself is isn't likely to be causing the reactivation of the virus and what you can see here is that those who had hepatitis B surface anogen but low viral load the odds ratio for primary liver cancer was 2.2, but in the presence of both high viral load

1:14:00

* and high surface antigen, you see this strong positive association on problem, primary liver cancer.

1:14:11

* No, hepatitis C, virus is looking globally just at the prevalence.

1:14:18

* Hepatitis Ca virus around the world. A lot of geographic variability. And 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.

1:14:19

* This, again, was just looking at a cohort of 20,000 residents in Taiwan.

1:14:46

* They were enrolled in 1,991 none of them had cancer at that time they were followed respectively through 2,008 during which time 477 of them developed incident, hepatitis, or carcinoma.

1:14:52

* That what the question they wanted to look at not only was is hepatitis C alone in important But what about hepatitis C and hepatitis B together?

1:15:07

* So in the reference group for both of those was being negative for both infections and the blue bar represents the incidence rate per 100,000 women and the green bar represents the incident rate per 100,000 men.

1:15:15

* The first is for those who are only positive for hepatitis B surface antigen. The second after that is those who are positive for hepatitis C viral infection and though those for both positive.

1:15:38

* So compared to those who were negative for both infection, the hazard ratio, 95% confidence in drills for having both infections was about 18 to nineteen-fold greater risk of primary.

1:15:53

* Does this suggest there's having both viruses is worse and having any one virus alone.

1:16:08

* And I guess vice versa is there an independent effect of hepatitis C infection on hepataselia carcinoma.

1:16:22

* Based on this data.

1:16:30

* Okay.

1:16:33

* Okay.

1:16:44

* Just for a show of hands, I'm gonna stop sharing. Here, just a raise of hands.

1:16:45

* Who thinks this demonstrates? A stronger increase in incidents. Of having both. Viruses compared to any one virus alone.

1:16:47

* Raise your hand if you're on the zoom just

1:17:00

* And who's perfect? Anybody else and who thinks it doesn't suggest a stronger effect of having both viruses and any one virus alone.

1:17:04

* Okay.

1:17:22

* Okay.

1:17:29

* Okay, some people are not voting. No problem. So yeah, I think these, data to me, if I look at this data given that you see, the increase instance rate per 100,000 people for those who have both infections compared to any one infection alone to me suggests that there's synergy in in terms of increased incidence of hepasolar cursing of having both

1:17:30

* infections.

1:17:45

* Now I'm gonna turn, change gears and talk about aflatoxin. So alpha toxin is also considered a class one carcinogen.

1:17:48

* It's a food contaminant. Remember Ed was talking about different ways in which diet can play a role in cancer.

1:17:53

* Risk? Well, aflatoxin and it's association with a padicola carcinoma, I think is a classic example of a food contaminant.

1:17:59

* So There are certain types of molds. That grow on corn, nuts, and beans, and particularly warm and humid climates you can see in this picture here on the upper right that's what the mold looks like that can produce a toxin called aflatoxin.

1:18:12

* And this is kind of a around the world. You can see in green are countries with very, very lower prevalence of this and the red or areas of the world with the higher prevalence of epitoxin as a food contaminant.

1:18:30

* So there was a really interesting study that was done in the Shanghai Men study that we just talked about among 18,000 men.

1:18:43

* They had actually both Food frequency questionnaires where they ask people, hey, did you eat corn?

1:18:52

* Did you eat beans? Did you eat nuts, etc. And then they also had urine.

1:18:57

* So when they assessed afflatoxin or measured afflictoxin based solely on the food frequency questionnaire, And then they compared high versus low dietary intake.

1:19:04

* Okay.

1:19:19

* There didn't look like much of an association between aflatoxin in the diet and risk of a patasilo cursor. Right? Can you see that?

1:19:20

* Okay.

1:19:24

* Like for those who were categorized as high aflatoxin based on the food frequency questionnaire, essentially no association with Hao Parsonoma.

1:19:25

* Versus when they use biomarkers and they use 2 different types of biomarkers in urine.

1:19:33

* One suggested, you know, if you have the presence of the DNA addict for aflatoxin, the risk of hepatito carcinoma was nine-fold greater compared to those negative for the addict.

1:19:34

* Why do you think, why do you think this is? Why do you think you think there was a difference between the food frequency questionnaire and using the biomarker.

1:19:53

* What does this suggest to you?

1:20:03

* Do you think, do you think the by which data do you believe, I guess?

1:20:10

* Raise your hand if you believe the food frequency data more so about a measure of aflatoxin.

1:20:16

* Alright, raise your hand if you believe the data that alpha toxin measured as a buyer marker.

1:20:23

* Yes.

1:20:30

* Yeah. Exactly, right. So this is a case where it's it can be hard. To measure the level of a contaminant because, you know, especially our food now is really global, right?

1:20:31

* And so it can be, you know, maybe there are certain farms where or certain batches of food where the aflatoxin was present because the mold was growing because of this season the food was growing.

1:20:42

* 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.

1:20:56

* So affluent toxin now is considered a group one carcinogen because of its association with a patasalic persona.

1:21:04

* In the United States and Europe. Particularly because hepatitis B. And see infections are lower.

1:21:13

* Particularly since now in many countries there's vaccination against appetite B, other causes of primary liver cancer have really started to emerge as likely risk factors primary liver cancer.

1:21:20

* They're kind of many of these are related to metabolic health. Alcohol seems to be its own risk factor independent of viruses.

1:21:36

* His concept of non-alcoholic fatty liver disease because of increased consequences on metabolic health.

1:21:47

* And then there's 2 factors where there's evidence suggesting an inverse association. Coffee consumption.

1:21:54

* Thank you.

1:21:59

* Oh.

1:22:06

* And aspirin seemed to be protective. For lowering the risk of primary liver cancer. So this figure here kind of summarizes.

1:22:07

* The population attributable fraction. For hepatitis, carcinoma.

1:22:10

* 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.

1:22:18

* You can really see pretty big variability. So in sub-Saharan Africa, a big proportion of hepatitis cellar carcinoma risk can be attributed to hepatitis B.

1:22:27

* And C virus because the prevalence of the virus is much greater. Whereas if you look in other parts of the world, let's say in Western Europe.

1:22:36

* It's much lower. In contrast, you can start to see things like alcohol, obesity being much bigger risk factors in Western Europe as well as in other parts of the world.

1:22:49

* So you can really see how the although the relative risk of associations of hepatitis B virus and the risk of a palace cellar carcinoma seemed to be pretty similar across different populations.

1:22:56

* So the size of the effect of the risk factor and the cancer is similar, the prevalence of the exposure varies.

1:23:16

* And that's why the proportion that's attributable to each of these factors differs in different parts of the world.

1:23:22

* And as I mentioned a little bit earlier, all of these things together have a lined in this model of how primary liver cancer, particularly a pascellular carcinoma, develops.

1:23:32

* All of these major risk factors do damage and lead to chronic inflammation of the liver, which leaves to liver disease.

1:23:44

* Cirrhosis of the liver that ultimately can lead to tumors occurring. So this model of this chronic inflammation, but things like aflatoxin and hepatitis B virus actually can do direct.

1:23:54

* Damage to the DNA. Itself, but all of these are through this model of Passover carcinoma.

1:24:11

* So in the last bit, I just want to end with a really interesting cancer. Clandio carcinoma which is much more rare.

1:24:18

* Yeah.

1:24:53

* Primary liver cancer so in most population 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 so parts of Thailand's in in Hong Kong in parts of China and in particular there's a part of Thailand that where the majority of primary liver cancer is due

1:24:54

* to clandio carcinoma. Really interesting descriptive epidemiology that led researchers to wonder why was Clantio carcinoma occurring as such a predominant component of primary liver cancer.

1:24:57

* See.

1:25:16

* Well, in particular in this this part of Thailand so, this is looking at Thailand in the countries.

1:25:17

* That are the highest, incidents, of clandio carcinoma also seem to have a very high prevalence.

1:25:19

* Of a an infection known as liver flukes. And this is a type of parasite, a form of a worm.

1:25:29

* That preferentially infects the bile ducts. And if you remember The bile ducts are where colonial carcinoma comes from.

1:25:39

* So hepatitis, L to have had a cellular carcinoma, glandio carcinoma comes from the bile ducts and it was discovered that by consuming raw foods whether it was fish and snails and this this picture here D is what these liver flukes look like.

1:25:47

* These can actually then infect the bile ducts and lead to the development of clandio carcinoma.

1:25:59

* It's largely preventable. By cooking fish, it kills the liver flukes and therefore will not lead to cancer forming.

1:26:13

* So, Claire, liver flicks are considered now a group one carcinogen. Again, really interesting.

1:26:23

* Example of how descriptive epidemiology of this cancer led to the discovery of liver flukes.

1:26:31

* And these are 2 different types of liver flukes that are considered to be group one carcinogens.

1:26:38

* So presence of these liver flukes is associated with about a 5 to tenfold greater risk of clandio carcinoma compared to those who do not have the liver flukes.

1:26:41

* Just in terms of other risk factors for clandio carcino, it does seem that hepatitis B and C.

1:26:50

* 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.

1:26:59

* So just to end this conversation and summary, infections are a major cause of cancer, but they're also largely preventable.

1:27:11

* So we can think about with hepatitis C virus, for example, now there's actually treatment.

1:27:19

* Yeah.

1:27:30

* For hepatitis C. And the question is, by the time someone's discovered to have hepatitis C it often can be after a lot of damage has been done.

1:27:31

* Okay.

1:27:36

* So big question is can treatment of hepatitis C. At that advanced stage lead to prevention and that's an interesting question right now.

1:27:37

* We've talked about vaccinations for against hepatitis B viral infection. We've talked about screening.

1:27:45

* For preventing from the cancer occurring in the first place and also things like treatment of a H by lorry as well as general cleanliness and hygiene principles.

1:27:48

* And as I as we talked about, infections can be promoters. Leading to inflammation.

1:28:05

* They can be initiators of cancer. Hepatitis B virus is really interesting as a model of both an initiator and a promoter.

1:28:12

* Liver cirrhosis really seems to be this unifying model understanding the ways in which ideologic factors are leading to cancer.

1:28:20

* Warming. And it includes both viral and non-viral causes and as the prevalence of some of the viral causes is going down.

1:28:28

* Okay.

1:28:45

* The non-viral causes may seem more strongly associated also as things like poor metabolic health are coming into different populations, obesity is growing, those non-viral causes may emerge as more a greater proportion of the population.

1:28:46

* Okay.

1:29:03

* 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.

1:29:04

* So I'm going to stop sharing in the last minute any any questions.

1:29:06

* Any observations, any thoughts?

1:29:14

* Okay.

1:29:17

* Okay, great. Well, wonderful to see you all. Colleen and Michelle, any final thoughts or words or comments about the class?

1:29:22

* Just make sure we're working on your projects and if you're hoping to meet with us the designated person, and if you're hoping to meet with us the designated person for your specific cancer.

1:29:30

* Yeah, and 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 so 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.

1:29:44

* YeahAll rightThank you