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## **Head and neck cancer forum**

**Saturday, July 21, 2018**

### **A/Prof Martin Batstone – Role of human papilloma virus (HPV) in head and neck cancer**

MARTIN BATSTONE: Good morning, everyone. Good to see lots of familiar faces in the audience. Marty asked me to give this talk. So thank you for inviting me, Marty. I hesitate to say, I'm not a virologist or virus specialist, but I do know quite a bit about human papilloma virus. My aim this morning is not to frighten myself or anyone, but to put all of this into a perspective for everyone.

For those of you who don't know me, I am an Oral and Maxillofacial Surgeon, I work 500 metres that way most of the week. Pretty much in head and neck cancer and not much else.

So there is a little bit of science in this talk. There won't be a test, so just relax, enjoy it, forget the bits that you are not interested in and try and pin the ones that you are interested in.

So what is the hype all about? It is a virus, human papilloma virus, the name gives it away. For those of you who don't know what a virus is, it's probably one of the smallest living organisms. There's a bit of a debate about whether a virus is an organism, but without getting too sciencey, a virus has to have a host cell to replicate. So a bacteria is very small as well but that can live outside the human body. But the virus can't replicate without another cell. There is lots of different viruses, influenza, that is a virus obviously. Human papilloma virus is a virus. It can cause cancer, as I am sure all of you already know; and it is extremely common.

And I suppose part of talking about human papilloma virus, it is talking about carcinogens, which are things that can cause cancer. Really, that's what I want to try this morning, rather than panic people, is talk a bit about cancers and how they are caused and say to you that carcinogens are everywhere. If you look outside the window, there is a bright sunny day, and the biggest carcinogen in Australia is the sun. So excess exposure to sunlight, particularly if you have pale skin like me, will cause cancer. So the sun is a carcinogen. And it is all about balance. Bitumen is a carcinogen as well, which makes up the road outside; particularly when it's hot and getting laid. Not so much when it's dry like it is now.

Viruses can be carcinogens and we will talk about other viruses that can cause cancer. Bacteria can cause cancer as well. Some of you would have heard of Helicobacter, that causes stomach ulcers...by drinking a flask of it, and curing it with antibiotics. If you have stomach ulcerations for a long period of time, secondary to that bacteria, you can get gastric cancer, so that is one example.

Alcohol that we are all aware of is a carcinogen, cigarettes contain many different chemicals that are carcinogens. Radiation, so sun puts out solar radiation; and radiotherapy, itself, X-rays, CTs, they are all carcinogens as well. What we are trying to do is balance - trying to avoid excessive exposure to carcinogens. Don't think HPV is out there waiting to get us. The world is out there trying to get us. And we are trying to keep it all in perspective and not panic about one thing or another.

We are talking about HPV today. There are lots of viral viruses that can cause cancer in humans and HPV probably is the number one culprit, not just for head and neck cancer. It can cause cervical cancer and it's been a well-known cause of that for a long period of time, in women. But, also, the skin. A lot of cutaneous malignancies are caused by sun, various sites, like your toenails and fingernails, genitals, both male and female, and head and neck. Hepatitis B and C can cause liver cancer, Epstein-Barr Virus is implicated in nasopharyngeal cancer, which is a rare type of lymphoma, a few different cancers that are specific to AIDS and HIV is going down, world public health story is the control that we have over human immunodeficiency virus and there is Merkel cell cancer, which is rare.

HPV is probably not the only one, but the biggest cause, about 5 per cent of human cancer; so it is a big deal in terms of carcinogens.

If you want to put that in perspective, nearly every Australian Caucasian will get skin cancer at some stage in their lifetime. So still way up there on top of other things. Probably diminishing now as people get better with sun protection, but in terms of Basal Cell Carcinoma which is a cancer, of course, not like metastasized, easily treated with surgery, is very, very high if you are a Caucasian.

So what about HPV, probably up to 200 subtypes of human papilloma virus. Not all of them will give you cancer. Only a very small proportion of them will give you cancer. They are called human papilloma virus because they infect humans, obviously, but other animals have their own papilloma virus. There is rabbit papilloma virus, and the first cancers that were known to be caused by papilloma virus were in rabbits, they get weird looking horn things on their face and get a cutaneous malignancy from papilloma virus. They all have their own papilloma virus. Don't feel jealous of the rabbits, they only infect their host. And human papilloma viruses will infect humans.



It is clever in the way it spreads itself. Who has had a wart in the room on their skin? You have probably had papilloma virus already. And we will talk a bit more about different types and how common it is.

But it is quite clever in the way that it transmits itself because it's in the skin and it replicates in the basal layers of the skin. Most viruses will - not most, but a lot of viruses will kill the cell that they are in when they replicate enough, they fill the virus with virus particles and explode. That's how influenza spreads; it will infect your respiratory tract, kill off the cells and you sneeze and spread viral particles everywhere. If you have been sneezed on by a toddler, you get it everywhere and next thing you know you have got a virus. But that's how they spread. Human papilloma virus is not quite like that because your epithelial cells will constantly shed, mature and come off, and that's how the papilloma virus spreads; you are shedding the papilloma virus all the time as part of your cells/skin, or your mucosal, your actual evolution. It doesn't kill the cells that's in, it is part of your biology.

So it is not fatal for the cell that it's in. It is part of what happens in your skin; it sheds a superficial layer. Everyone has scaly bits on their hand, that is the way that your body works and then you are shedding those cells. If they have got HPV, and get on to someone else, particularly if you have a little abrasion, the cell gets into that, into the basal layers of your own skin or someone else's skin and you can spread the virus around.

So how common is HPV? Well, we have already discovered that nearly everyone in the room has had a wart. So you already know that human papilloma virus is extremely common. An infection with one of the types of HPV, and we said there's close to 200, is almost universal if you have had contact with another human-being. So that's the first thing to say; nearly everyone has had HPV. You can have more than one type at once. You can catch HPV, get rid of it and catch it again; and there's lots of numbers associated with this. I said before that there's about 200 different subtypes and all these numbers refer to a subtype. The common warts, the example that I showed you on the person's fingers are these non-high-risk subtypes, 2, 7, 22. Don't worry, you won't have to remember them all...the plantar warts that you get on your feet are a different subtype sometimes. So it is not just those ones.

Unfortunately, high-risk HPV, which is the ones that can give you cancer, are also extremely common. If you have been sexually active, then you have about an 80 per cent chance of having contracted a high-risk subtype of HPV of sometime in your life.

For women, it is usually about three years after commencement of sexual activity; and these are the numbers that are probably more important, 16, 18, 31, 33, 45. A lot of you have already heard HPV subtype 16, which is not the same as P16 which is a test that we do on cells to see if they have been turned into

cancer by HPV. Subtype 16 is one of the types that causes cancer; and genital warts are caused by those...and you can see how confusing it gets remembering a whole pile of different numbers. There's high/low risk. Low risk HPV, nearly everyone. High-risk HPV, you probably have caught it if you are sexually active adult. You can transmit the virus back and forth with your partners and there's all terrible things that we can talk about there.

So is it all bad news? I have an 80 per cent chance of contracting high-risk subtype HPV, unless I live in the monastery. But it is not bad news. We can get rid of it as well. You clear it out of your system. Your immune system discovers it, recognises that it is foreign and eradicates it. You can get it again, but then you would probably get rid of it again as well, which is why testing people for high-risk HPV is not really particularly useful, because the chance of you catching it, if you are going to clear it yourself, it doesn't make the test particularly worthwhile.

To get cancer from it, you have to have it for a long time and it has to persist. And it's probably about a ten-year lead-time from when you catch the virus and it persists in your body, cervix for example in cervical cancer, or your oropharynx, it has to be there for a long time before it develops into a malignancy.

How does it cause cancer? There is a little bit of science in here, so I will try not to dwell on it too much. The virus gets taken up into your cell; and the way virus works, they insert themselves into DNA and use your body cells to make copies of themselves. Fabricate themselves. Think like a Tesla factory, going to the Ford factory line and using the Ford factory for all the Teslas to make all themselves, and then they all get pumped out...a bad analogy but trying to make you understand.

There is a couple of proteins in HPV that help stop the cell from dying. That's what cancer is, a cell that's forgotten to die because normally cells will turn over or get wiped over by your body if they have problems and in cancer cells that doesn't happen. Which is part of the reason why immunotherapy, which is a therapeutic option that lets your body recognise cancer and kills them off when they resist them. So HPV keeps cells alive when they shouldn't be alive and they keep turning over; and so immortalises the cell, and it shouldn't be immortal particularly in of the skin mucosa, when it is normal for your skin to come off and shed itself and be constantly renewed. If something stays there forever, there's a greater chance of it turning into a nasty tumour.

So if it goes on and on and it's there and it's alive and it shouldn't be alive, there's a potential for it to make further genetic mistakes, that lets it spread somewhere else, invade, or grow or become a worse type of malignancy. In most of us, the body works out that it's foreign, it shouldn't be there and those cells are killed and disposed of. Or they make enough mistakes, to become a cancer; so they are immortal but not malignant and don't do anything else. But in a small proportion



of people over a long period of time with persistent infection, then cancer can occur.

So I am sure a lot of you will want to know, can you be tested for HPV? And the answer is, yes, but...

So you can have cells taken from wherever you are concerned about, either a smear or a scrape or an oral rinse; and a pathology lab in Queensland will perform an automated test, using PCR, polymerised chain reaction, and it can tell you if you have one of 14 different types of HPV, including the high-risk subtype. You can't grow HPV in a lab. And serology or a blood test doesn't always work because lots of people have been exposed to it. Serology will only tell you whether you have been exposed to it or not. So it tests your body's reaction to the cancer, not the cancer, itself. Whether a smear or swap, you can send it to one of the labs, testing for all these different types.

As a consequence, there's been a big change to cervical screening. I am sure the Cancer Council people will be aware of that. It used to be every two years, for every woman aged 18 to 69 but now it's changed. Because the link between HPV and cervical cancer is so strong - they don't do a smear and look at the cells and say, "Are they cancer cells?" They do a smear and say, "Are the cells infected with high-risk HPV?" If they are not, you don't have to come back for five years; and the reason for that, even if you catch HPV the next day after your test, we know there's a long lead-time of up to ten years, before they can be malignant, so don't need to be tested for another five years and it reduces the burden of testing...

If you are positive for HPV in your cervical smear/swap, then you get tested again in 12 months; and lots of people will clear it. So if you clear it, it's not there in 12 months' time, you go down the five-year plan; if it's there, you go down other investigations/options. It's really changed cervical cancer screening, but we don't know quite as well what that means for head and neck cancer. So we haven't really got the information to say, "Should we give everyone an oral rinse; see if they have got HPV?" We don't know exactly what to do with that, which is the reason that we don't do widespread screening for head and neck cancer. The other reason really is that head and neck cancer is - obviously not in this room, but in the community it is a rare condition. When you talk about something like breast cancer, for example, that's in one in 8/10 women, a head and neck cancer is far less, and prostate, 8 per cent of people have prostate cancer in their 80s. So it is extremely common but not part of a national screening program. It doesn't mean that you will get cancer even if you are tested positive for HPV. So it's all a little bit confusing in terms of what the testing does.

I think the other thing that's important to remember is that screening doesn't change the instance of a disease. If you screen the whole population, it doesn't make cancer more or less common. All it will do, means you will detect it earlier.

That is obviously a good thing if cancer is treatable, but screening has some potentially negative consequences as well. If you screen a whole lot of men and they have prostate cancer and they all get treatment for that prostate cancer, if that cancer wasn't going to cause them a problem, they are getting unnecessary treatment. That is not the same for head and neck cancer...

But I suppose the point of this is to say: screening won't change the amount of disease in a population, but vaccination will change the amount of disease in a population. You can never get HPV, then the incident of HPV cancer is going to decline - it's not rocket science.

So this is - I know Annika Antonsson came and talked to the group, and I am pinching her data. She tested 700 people and had about 12 per cent - this is oral, not cervical, using the HPV PCR testing - and there are high rates if you have been engaging in kissing, giving and receiving oral sex, and having sexual partners.

What about vaccination? Has anyone in the room been vaccinated against HPV? Quite a few people. So that's good. It used to be - it was commenced in 2007, with four subtypes and a Brisbane inventor, Ian Frazer - you can see the high risks, 6, 11, 16, and now there's nine different subtypes across here, 6, 11.... those two, 18, 31, are the most common. It was originally only girls but then it was worked out that boys would go overseas and meet girls from other countries, so they get vaccinated now, at aged 12/13. And started in 2007.

So is it working? If we go back to that, and do a bit of semi-complicated Maths, "When is the cancer rate going to stop dropping because of the HPV vaccine?", which is probably a question that you guys want to know the answer to as well - if you think about it, there was a 13-year-old girl, for example, that was vaccinated in 2007, without talking about sexual activity in teenagers and when that might start or not start, and we know there's a lead-time of ten years, we are probably not going to see the incidents of cancer dropping for about another ten years; although that person that was vaccinated in 2007 potentially might be getting cancer about now. But most of the peak incidents of head and neck cancer of HPV are in the 40s to 60-year age group. So probably another ten years, before it goes down, because of the vaccination that occurred, or started ten years ago.

But we do know if you test young adults/teenagers who have been vaccinated, the chance of having high-risk HPV has diminished significantly, down by 75 per cent. If the virus causes cancer, then their chance of getting cancer is going to be less in the future; and the chance of having genital warts is down by 90 per cent as well.

I am going to wrap it up and say: it is probably the most common viral carcinogen in humans but don't panic about that but think that the world is going to end because we have been surrounded by carcinogens since time began; and

all we can do is try and manage it. With this one, fortunately, you can vaccinate against it. It's very common amongst healthy adults but the chance of catching cancer from it, for your friends/relatives that you are talking about to, is very low; and it is able to be prevented in terms of vaccine but not cured. You can't give someone an antiviral medication that will eradicate the virus. Thank you very much.

ANNA GORDON: We can take a couple of questions or can leave them for panel as well, because Martin will join us later in the panel.

PARTICIPANT: I remember reading something about Dr Ian Frazer working on a new vaccine at the moment for people who had HPV 16, et cetera, who can be vaccinated in the future. I'm not really clear-----

MARTIN BATSONE: So the question is: can you be vaccinated when you have already been exposed to HPV?

PARTICIPANT: Yes, but it's a different vaccine.

MARTIN BATSONE: Potentially. That's a good question. I would like to know the answer to that question for my own self-interests. I would like to be vaccinated. There was no vaccine when I was a young schoolboy. But the question about whether this vaccine works in someone if you have already been exposed to HPV, it probably does not; and I don't know whether or not the virus institute at the PA Hospital, that is working on a vaccine for people that's been exposed - obviously, a vaccine to prevent you catching it again is worthwhile. There's nine different subtypes in the latest vaccine and we probably haven't all been exposed to nine different subtypes, so even if you got the nine strain vaccine now, it would probably prevent you catching some of them.

PARTICIPANT: So you haven't heard of any progress with this new-----

MARTIN BATSONE: No, but I would certainly be interested in it. Obviously, the other thing that would be useful, is being able to help people clear the virus; and you can do that with surgery, by cutting it out, if you have a viral lesion/wart; you can cut the wart out and get rid of the virus; but that is not feasible if you don't know whether or not the wart is going to cause a problem or you screen the population and everyone's positive and you just can't field it all.

PARTICIPANT: Thank you.

PARTICIPANT: May I ask a question: going back to the information you had before about the HPV and the Epstein-Barr, et cetera, if you already have an underlying immune issue already, would that possibly increase with the HPV?

MARTIN BATSONE: The question is: if you have an immune suppression for some other reason? I don't know specifically about HPV. I think - an immune suppression condition, for example, if you have a kidney transplant, a lot of those people will have immune suppression, they are much more prone to cancer in general. So that means skin cancer, for example. That goes back to the role your immune system plays in recognising tumours and getting rid of them in your body; and that's why immunotherapy works but we already know that people who have suppressed immune system are more at-risk-----

PARTICIPANT: This is more probably talking about an underlying autoimmune disease-----

MARTIN BATSONE: An autoimmune disease is slightly different. Usually your body has a hyperactive immune system, rather than underactive. Medication you take for the autoimmune system, it will dial down the response; so it is a real balance. Probably no-one knows exactly where the balance lies in terms of your body getting rid of the virus and maybe your autoimmune condition flares up. It is probably too complex.

