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<b>Title</b>	<i>Breast Cancer: Causes and Prevention</i>
<b>Description</b>	Dr Valerie Beral talks about her research into the causes of breast cancer, looking into the history of the cancer as well as offering ways of reducing the risk of contracting breast cancer
<b>Presenter(s)</b>	Valerie Beral
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**Valerie Beral** Good morning. I'm Valerie Beral. As you can probably guess and I've got a very serious topic for discussion this morning and I realised I gave this title quite a while ago and when I looked at the day today and I thought about it I actually wondered if anyone would want to come on such a beautiful day when there's lots to do outside.

So thank you for coming and I am going to talk about breast cancer, about causes and prevention, what we know now. I'm an epidemiologist here in Oxford and I'm going to give not only an epidemiological perspective, an historical perspective too about what people have thought really over the decades about breast cancer and what causes it. Anyway the bottom line, as you'll see, is that ideas people had a long time ago have turned out to be true and we've been misled over the last few decades. But I'll get to that.

For some of you I'm sure you've got different reasons why you're here and I would presume that some of you have breast cancer or have relatives with breast cancer and have particular questions and I'm very happy to answer the questions either generally or later.

But if any of you are here because of nostalgia for epidemiology or for your time at medical school or something here in Oxford, I do want to just start to remind you that Richard Doll was the Regis Professor of Medicine here during the 1970s. And he really was responsible for a lot of the development of just medical research and biomedical research in Oxford in that capacity as Regis Professor.

And I now work in the Richard Doll building which is a new building that went up in 2005 near the Churchill hospital. There's now quite a big biomedical centre there, there's a Wellcome Trust, there's a huge sort of cancer biology here, this is the sort of epidemiology building, there's a genetics building just opposite.

Now epidemiology for those of you who don't know what it means, its origin is from the word epidemic, the epi part comes from the idea of epidemic; epi means upon and dermis is the people. And epidemiology as a discipline started with the study of infection diseases and epidemics. And a lot of the research over many centuries was really concerned with the epidemics of the Plague and so forth and people started analysing statistics to do so.

And it was really after the Second World War that people started looking at – not entirely but largely at non-infectious diseases and trying to understand them. And Richard, as I think many of you know, was one of the really key figures in showing by epidemiological methods that smoking

caused lung cancer. And he did this work – I’m just going to show you although it’s not really related to what I’m talking about, but just to show that he did his original work in 1950.

He actually died in 2005 and he saw over - this is in the UK, death rates smoking related cancers from 1950 to 2005. And you can see the huge – that actually when he did his original research, it was largely lung cancer contributed rates were going up, but not entirely lung cancer, much lower in women but rates were going up.

But since about 1970 look at this huge drop and in women rates went up and they dropped more recently. And this huge drop is almost entirely due to people stopping smoking, not young people not starting and so it really shows how important it is for people who smoke to give up. And to think that over his lifetime he saw what was just a sort of growing epidemic disappear. So disease rates are not constant over time, you can do things about them.

Another interesting sort of historical fact is he did his first original research in 1950 and it wasn’t until 1970, which is twenty years later, that people really took it seriously and the Government started saying people shouldn’t smoke. And there’s quite a long lag between first really quite serious, quite convincing results and someone taking note of it. And it must have been - and I know it was frustrating because at that time he was very attacked for his work obviously by tobacco companies but by other scientists too. Took a long time to accept these results. But he lived long enough to actually see this huge benefit and it really is quite phenomenal.

Now I’m just going to go back to breast cancer now which is what I’m going to talk about. And the reason why I’m talking about breast cancer, well for many reasons, but breast cancer is now the most common cancer and these pie charts don’t show how many cases but in developed countries breast cancer, the red there, is the most common cancer amongst women in developed countries and it’s 600,000 cases a year, something like that. And I think probably everyone in the room would know that. Lung cancer is number three and is still going up in many places.

Now what you may not know is in less developed regions now, 2002, breast cancer is now the most common cancer in developing countries too, India, many countries it’s now the most common cancer in women. It used to be cervix cancer which now there’s a vaccine for and that’s really very promising. And I will talk later about how the rates are increasing really very rapidly in less developed countries.

So breast cancer is now the most common cancer in women both in developed and developing countries but these are just proportions of cancers but there are far more women in less developed countries than in more developed.

And if you look at these incidence rates, rates per population if you like, around the world the red is the highest rates and you can see it’s in all the western countries basically, the developed countries. And then the rates go down, orange, yellow, light green and dark green are the lowest rates. And in this particular figure you can see it’s China, India, many parts of Africa, the rates are much lower. And there’s about a six, sevenfold variation between developed and developing countries.

And what I’m going to talk about today is, as an epidemiologist, I’m asking why are those differences and talking about why those differences exist. I’m not talking about what happens in cells or other because one can say well, you know, what are the changes in cells that lead to cancer. I’m not talking about that sort of thing. I’m talking about why we’ve got this difference. And this is in 2002 and as I’ve implied rates are increasing in these green countries and in the orange, most everywhere rates are increasing but particularly in the areas where rates have been low in the past.

And the way I’m going to talk about this, and it’s not too numerical though we do deal with numbers, is I’m going to talk about if you take those zoned World Health Organisation figures, these are from the International Agency of Research on Cancer which is a branch of World Health

Organisation. And if you take those figures and you actually look at the probability of having breast cancer by a particular age, and this is up to age 70, it's about 6% in developed countries.

Now you may have heard figures like 10% because this is often said in the media and so forth as 10% in developed countries. It is 10% if you go up to about 80 because you can see how breast cancer rates go up with age which is something a lot of people don't actually appreciate. If you went up to age 80 it would come to about 10% so it is true that by age 80 about 1 in 10 women would develop breast cancer. But I'm using 70 because the figures are not very reliable in sort of rural parts of Africa and Asia after age 70.

And I'm going to talk about why this gap exists and I'm going to keep coming back to this graph showing this gap and seeing how much of this difference can we explain by things we know. So this is the one figure I want you to remember, it's about six, seven times higher in developed countries than in rural Africa and Asia. So there's that sort of range of rates.

So let's go back. I said I'm going to go back through history. I mean you can go back to paintings in the Egyptian time and people have shown that you can see pictures of women were drawn with a sort of puckered breast as if they had breast cancer right back to thousands of years ago.

But the first description of a kind of cause if you like of breast cancer was Ramazzini who's very famous, who wrote really the first treatise on occupational disease, and he mostly talked about lung disease in miners and so forth, all the sort of classic occupations, really the first very thorough discussion of role of occupational disease.

But he actually mentioned at the time in 1743 that breast cancer was – and he called it an occupational disease of nuns, well he didn't it was in Italian but [[?? 0:10:24]]. And it was obviously in a way you could say it was something that was known about at that time but again there were no figures. But not long after that another Italian called Rigoni Stern who was the equivalent of the Minister of Health in Verona, had collected statistics on causes of death of men and women in Verona over an eighty year period, 1760 to 1839. And what his figures showed was that actually 2.7% of nuns and quite this large number, died of breast cancer compared with 0.4% of other women.

Now if you look at that that's a sevenfold difference and that's the same level of difference that was in Italy amongst Italian women, whether they were nuns or not nuns, that existed a few centuries ago. Because often one thinks oh there are so many differences between people in India or Africa and living in very rural, primitive conditions to us now, it could be infinite numbers of things, genetics, all sorts, and I'm going to talk about all of these. But this is in the same population if you like, nuns and others, there was about the same range of difference.

And then not much was done sort of statistical about breast cancer until the early 20th century when the League of Nations actually had a health organisation based in Geneva which was the forerunner of the World Health Organisation and in 1925 they set up a sub-committee on cancer and they were particularly interested in breast cancer and cancer of the uterus.

And they published these figures, this is taken from their 1925 report, showing – and it's a nice little graph, it looks a bit like one I showed you before but they showed – this is mortality rates not incidence rates for breast cancer by marital status. And you can see that single women had higher rates, married and widowed were rather similar but single women at every age had higher rates than married women.

And so this was a little step forward, saying well it's not just nuns but even just in the general population single women had higher rates than married and this fit with this idea that it was something to do with childbearing, because that idea was there and I'll come back to that in a minute. So that was extending the idea a little bit further.

And now I know this session is about women – when I was asked to speak, was something to do with women in science in Oxford so I'm just going to digress a little bit and talk about a woman

because there was a woman from the UK called Janet Lane-Claypon who was at that meeting in the Health Organisation in 1925 but in 1926 she published this report. She was in the Ministry of Health and she published a really absolutely beautiful report on breast cancer trying to look at the causes. She called it then 'Cancer of the Breast; a Further Report'. She'd done one on survival showing that if women got breast cancer how bad the survival was but she published a further report on cancer of the breast with special reference to antecedent conditions, in other words causes what came before.

And she studied 500 women of breast cancer in London and Glasgow and she picked controls, women in the same hospitals who didn't have breast cancer, and compared their characteristics. And she found that same thing, there were more single women with breast cancer, but even if she confined her analysis to women who were married the women with breast cancer had fewer children, 3.5 on average compared to 5, women who didn't have breast cancer. And she also found that women with children were less likely to breastfeed.

Now I'll return but I'll just tell you a little story about it because she published a number of absolutely beautiful reports for the Ministry of Health as was then called, not only for women's health but also on child health, on the facts of food supplementation and so forth. And one day her publications stopped and one of my colleagues was sort of interested in what happened to her and did a lot of research and it took a long time.

Anyway what was discovered was that she ended up marrying the person who was the sort of Chief Medical Officer or the equivalent who'd been widowed. And she married him and when at that time you married you could no longer be a civil servant. That's right. So someone like her who became Lady something or other, I can't remember what, who did absolutely stunning research, really groundbreaking in many ways, when she married she just disappeared from the face of research anyway.

And it's not that long ago that that was true. So anyway it just gives you pause and it's a sort of distraction but something we need to think about, how far we've come in actually quite a short time when you look at the timescale even of people thinking about breast cancer.

But anyway to just go back to the main point that really starting with Ramazzini and Lane-Claypon's results really sort of supported that, it was really thought that it was obvious almost that a major cause of breast cancer was if women didn't use their breasts for their natural purposes. And that was the sort of general view that was not rigorously tested but prevailing.

And what I'm going to show in the rest of my talk is that that's actually true and we've actually been misled for quite a while and still are. And I'm sure many of you in the audience have stories and I was speaking to someone before and in the meantime for reasons that I'll explain almost every hypothesis about anything has come forward and some people have championed it one way or the other. But the evidence is that this is largely true and then I'm going to talk a bit about what we should be doing about it.

But let's just go back. Now why did we get misled? We got misled, and this is very technical, for people who work in the field and even if you are vaguely interested in breast cancer it's hard to have escaped this idea of this concept of age at first birth. And it's a very funny word but it means age women were when they had their first child. And this is a result - if you remember, Lane-Claypon had a study of 500 women, well this was a study in 1970 published in the World Health Organisation bulletin - still French then, now it's all in English of course - of 5,000.

So it's bigger than the other study. It was in seven regions of the world and they decided something else. They said that it was an international study of breast cancer reproductive experience carried out in seven regions of the world but they said basically the age a woman is when she has her first child is what's relevant to breast cancer which is true, I'm not saying that's not true.

But they go on - and this is where we've gone wrong - they say births after the first, even if they occur at an early age, have no or very little protective effect. Now that's not true as I'm going to

show you. And then they go and the main thing that's really caught - the association with age at first birth requires different kinds of cause or hypothesis from those that have been evoked in the past to explain the association with breast cancer risk and reproductive experience.

And this has really misled people and I'm going to show you why. Because remember this curve that I showed about rates in developed – this is the sort of cumulative rate in developed countries, six times higher than rural Asia and Africa. Now there's not much difference in the age women are when they have their first child in developing countries, particularly for women – these rates sort of relate to about 1990 or so.

And you see women who are 70 or 60 in 1990 were born in 1930, the ones who were 70 were born in 1920 and so when you think back – you have to remember that these rates by definition refer to people from quite a long time ago so in the 1920s and 1930s when these women were born or sort of soon after when they had children, we didn't have all the fancy contraceptive methods and life was very primitive if you like in rural Africa and Asia, pretty primitive in some developed countries too but nevertheless.

But anyway the average age that women had their first child was about 25 in developed countries and it was about 19 in rural Africa and Asia. So it was only about six years different, it wasn't that different. You know, things have changed now for these young people. I'm going to talk a bit about what's going on in these young ages later.

So the age wasn't different and we know roughly from a number of studies what percent breast cancers would be prevented, if you like, for each year younger at first birth and it's not that many. So one's left here saying "Well what if everyone in developed countries had their first birth at 19 instead of 25, what would the cumulative rates look like?" And the answer is not very different, would drop a bit if everyone in developed countries had their first child at 19 instead of 25 at that age.

You see so one's left with this huge gap, that difference still remains. And there've been since 1970 you name it – I mean this sounds very rude and I'm sorry – but there've been hypothesis after hypothesis after hypothesis: is it diet, is it chemicals, is it genes, everything you hear on the radio most days, you know, one of these is picked out and someone's found something on something.

Now the reason they were looking was because of this gap. Now this is where I come in, or people and myself and colleagues in Oxford, in that I had done work before I came here on the pill, not on breast cancer but on the pill. And when I came to Oxford almost 20 years ago now there was a huge argument in the literature and in the media too about whether the pill caused breast cancer and if any of you remember you don't hear it anymore and it's because of this group and the work that we did.

And one group claiming it did cause, the other – and people - even to the point where at scientific meetings, and it wasn't a meeting I was at but I've heard stories, just before I came to Oxford there was a big meeting where the different protagonists would actually pull microphones from each other and shout at each other, almost a punch up in sort of the meetings. So it was very emotive amongst scientific and the scientific community, epidemiologists doing the work.

So what we did is we – and I was quite neutral which helped set this up but I also had the help of Richard Doll and Sir Richard Peto, who you may have heard of, who does a lot of work now on smoking and lung cancer, Gillian Reeves, statistician. And the four of us set up this collaborative group on hormonal factors in breast cancer.

And the idea was to bring together the original worldwide data from all the studies in the world that looked at the pill and breast cancer to try and sort out what was going on. And we did sort it out and I'll just show you but it's a bit of distraction to this but I'll tell you the result anyway.

But once we had information together from a hundred studies and this time sort of 100,000 women with breast cancer and controls we could really look at other things in some detail as well.

And I'm just going to say the group meet every five years and this picture was in 2005 and this was taken actually in April of 2005 and Richard died in July after a very short illness and he was really well and very much participating in the meeting in April. And we all miss him and he really was a great man.

So we started off – and for sort of public health reasons, I'm just going to show one slide on the pill and hormonal replacement therapy which is what I do a lot of work on actually but I can answer questions about it later but this is all I'm saying about the pill and HRT.

And what we found – and it might be a bit complicated but don't worry too much, we basically found if this line here represents never users of the pill and this line is never users of HRT, this little block here and that little block here are people who are past users who'd stopped the pill or hormonal replacement therapy. And these points are how long they took it, this is less than a year, one to four years, five, this is ten years of use and this is the same, ten years of use.

And what we found surprisingly, both for the pill and HRT, was that when people stopped there was no increase of risk. Soon after people stopped both of them there was an increase, I'll go back, this is current users there was and I'll talk – but when people stopped there was no persistent effect. And this goes against a lot of ideas people had about how cancers are caused. People often think cancers are caused by something that happens one day and then you get a cancer 20 years, 30 years later.

I could have a whole lecture about these hypotheses but there's certainly that not much evidence about whether just a single exposure at this point causes cancer a long time later. But actually curiously for both the pill and HRT there was no residual effect which is interesting biologically when I start talking because pregnancies are different as you may see where I'm heading, because a pregnancy when you're young actually does something – having just said there's not that much evidence, for pregnancies there is.

We know that a pregnancy at a certain age can prevent breast cancer when you're 70. And in fact one of the reasons I was very interested in the pill was because I expected the pill to produce a long term protection because I thought it was the same as a pregnancy but it's not. Taking the pill is not the same as being pregnant as far as breast cancer goes.

And that's quite important when I come to the end talking about what are we going to do, to see there's no persistent effects of either the pill or HRT. What we did find was that while people were taking the pill there was a small increase in risk, 20%, which didn't seem to relate to how long you take it, there was a small increase in risk. HRT we found there was a risk but it did go up the longer you'd been on HRT.

Now this quietened the argument on the pill and you really don't hear about it a lot. The HRT thing has grown a lot and there's a lot of people wanting to doubt this association. But I'm just going to show you what happened in the US because it's this residual effect for our purposes that's the most interesting.

And I'm sure you have heard that in the US there was a randomised trial because there was suspicion about a lot of the claims that were made about its benefit and showing really that the benefits claim were not right when you did a randomised trial. And use of HRT dropped considerably since 2001/2 when the trial was published.

And so the drop in HRT use in the States and it's happened - and these are just the first results to be published but now it's published in a dozen or so countries – HRT has dropped and breast cancer rates are dropping. This is the first time actually in the US they've ever seen a drop in breast cancer incidence and this followed the drop in HRT use.

And what's more HRT's associated with cancers that have oestrogen receptors on them, it was just the oestrogen receptor positive tumours that dropped not the oestrogen receptor negative. So that sort of supports in a way the idea that actually hormones, oestrogens' and progestogens, which are

the hormones in HRT and in the pill increase the risk of breast cancer and when you stop the risks go away. And that's not, again, what people generally think about hormones but there's really a lot of evidence to say that's the way hormones act.

But I'm just going to go back now to results from the collaborative group where we really had 100,000 women and we could look very carefully at all sorts of things. But we could look at the number of births a woman had, how many children in relation to breast cancer risk. This is one child and this is two, you can't adjust, this is holding age at first birth constants, a statistical reason, you can't hold it constant people who've had no children.

So, see one, two, three, four, five, see just goes down and down and there was a 9% reduction risk per child. And what we found too and I'm not showing here is it was only pregnancies that went on to a birth, miscarriages and induced abortions didn't have an effect. So something later in a pregnancy seemed to be protective.

Now it could be breastfeeding and it could be that all of that association was just breastfeeding but there are enough women in the study to actually just look at women who had children but who never breastfed. So this is to see whether it's the childbirth itself and the answer's yes. It's not as big, it's 7%, but even amongst just women who had never breastfed still each birth mattered. So that statement before that after the first, the additional births don't matter isn't true as you can see.

And then we could look at also duration of breastfeeding. How long in a lifetime and holding the number of children constant. And again you've really got to get to quite long lifetime durations, years before you start getting substantial reductions in risk, it takes a while but there's again a clear reduction in risk. And you see a lot of studies, particularly in the US, had been saying that the breastfeeding had no effect. In the US the average duration of breastfeeding is about three months you see so comparing this line unfortunately three months doesn't do very much you see, that against that, and so you've got to breastfeed for a long time.

But this was true in developed and developing countries, so this is not just because they're all – this is adjusting for – this is carefully just comparing women within a single study within a single country, within a single study exactly the same age, exactly the same number of children, having their first age exactly the same. So this isn't due to other things, because it's such large numbers we could really hold all that constant.

And what's interesting about this and the pregnancies is this persists throughout life so it's not the same as the pill, it's not the same as the effects of the pill and HRT. In principle it's not like just when you take it or when you're pregnant something happens and then there's nothing subsequently. This is a persistent effect throughout life in contrast to the pill.

So when you then plug these things in in the same way that I did before for just saying that if you just take age at first birth there's no difference, but if you just take account of the larger families that were typical of women in this age contributing to this data set and the longer duration of breastfeeding – because the average duration of breastfeeding in developing countries in communities that have no contraception, in rather poor, rural communities is about two years.

So if you say well the more with typical larger family size, typical breastfeeding habits, breast cancer rates would be more than halved. It would go from 6.3% to 2.7%. It would almost half from those statistics which are a worldwide sort of summary really of the worldwide evidence, it's really quite a substantial effect.

Now we published this in 2002. I'm just going to tell you a funny story because this is – I mean it was known, you know, there are many statistics about developing countries showing that it's typical to breastfeed to about two, but also if you go back to some of these old maintaining of the time, you know, if you see all these Madonnas and child, the children are pretty big. And it was usual to see quite big children – you know this was sort of a typical scene if you like around that time. You saw women breastfeeding quite large children who could walk and talk probably.

And, you know, I was rung by a reporter about this when we published, I'll just tell you this, who said to me "Is it really true that women in developing countries breastfeed for two years?" and I said "Yes" and she said "Yuk". And it really illustrated - she'd been told to write this story and then no story appeared and it is very interesting that we've got to the point in society - you'll see I'm not suggesting this is the way forward but it is interesting that in much of western society now this is thought to be yuk like it couldn't be true.

And anyway a little aside but there you are, that's how attitudes change. But it's very hard the attitudes are now about - because the implications from some of these things are really quite striking. But before I go back to all the implications and I'm not suggesting people have more children or they breastfeed but these are reasons which people find hard to - but it's not the only reasons, I don't want to say it's the only explanation, there are other things too.

And I'm not going to go into them but a lot of things related to growth also affect breast cancer risk. And just to say that the earlier people are at puberty, the younger women - and all of these favour higher rates in developed countries than developing - the younger you are when you're at puberty, age at [ [?? 0:34:49] ] the higher the risk. Worse in developed than developing who tend to have later ages at puberty. The earlier the age at menopause - well put it the other way - so the later the age at menopause the higher the risk and again developed countries women have their menopause later than in developing.

The taller you are the higher the risk, again this is women in developed countries are taller. Now weight is a bit complicated, it's only obesity in post menopausal women, in pre-menopausal it doesn't matter, but that's when most of the breast cancers are. So basically weight or obesity are also - so these are all things that, as I say, are sort of related to being big and they're size and they're also nutritionally related.

There's another one as well which you can regard as nutritional or whatever you like but it's very clear that alcohol, number of drinks of alcohol that women have on average also is associated with risk. This is on average one drink a day, two drinks a day, three drinks a day; four is about a 20% increase in risk.

So again I have to say because we published this you get reporters ringing up and saying "Oh, you know, three drinks a day, you can't say that's, you know, that's bad." And again because a lot of the journalists certainly - and some of you may well be journalists - you know they think this is quite normal. And so I have to - and I said that to someone, these findings don't sit well with the sort of contemporary woman. So anyway when we go back - sorry to keep saying it but it is true.

So when you go back we've already talked about childbearing and breastfeeding, when you put in all those what I've called nutritional factors, they're not food, it's not food like fats or milk or something. People have looked at all these things and you'll find a study that's found almost everything, soya, there are all these claims of different things but actually it's just being bigger, eating more may give you earlier puberty, make you fatter, taller, all those things do affect risk.

So it brings it down to one 1.8, we're almost where we are in rural Africa, Asia. And we don't account - think that these are not measured very reliably, measurement error tends to underestimate it so it could just be - it's not like there's a gap, it's probably that really accounts for almost all the difference. And we've known all these - everything I've talked about, even the [ [?? 0:37:32] ] and the puberty, we've known these things for a long time. But the important message is that they're probably the main things.

Oh I'm going to talk about genetics, I wonder what time it is. I'm just going to say a few things about genetics because there's been a lot of advances in genetics recently too. And genetic differences do explain within a population there is a range of risks and what I'm trying to say is this is a sort of distribution if you knew people's genes because we do know now a lot.

So if this is the 6.3% developed countries and if we look at what we know about genetics which is a lot, two thirds of all women would range between about 5 and 7.5 so that most women let's



say in this country for sort of simplicity, even if we could type all the genes, and they're now like about a dozen we know about, we could put most women in this sort of range but they'd never go down to here. It's this kind of range. And so it is true that there is a variation between women because of their genes but it's about this much on this scale.

And interestingly because the genetic work has been done in Asia and the same genes have the same proportional effect in Asia and Africa, it's not that they don't but because the background rates are so low it's still two thirds have a risk but it's only between 0.8 and 1.2 so the genes act in the same way in all populations. But the thing is the background rates are lower here and they're higher there. So genes are important but they're not explaining any of this. And anyway when it comes to prevention which I'm talking about, you know, you can't do much about your genes.

Now I'm just going to say – again these are just commonly asked questions, so I'm just going to answer some of these. Because often when I speak someone says “Oh but why are the rates in Japan so low?” and actually someone's already – so it is this thing people say the rates in Japan are very low. Now they're low because if we went out to 70 up here we've still got a lot of Japanese women who had traditional almost developing country type reproductive patterns.

But if you just amplify up to 45 where modern women, if you like - I don't know if that's the right term but I'll say it – where the rates are not – and instead if 6% about 1% in women in developed countries will have breast cancer by the time they're 45 compared to 0.2% in rural Africa, Asia.

But look at these, you see, you've got – these obviously include, you know, Africa, China, India, but you see you've got right up at this extreme developed countries, well the statistics are on Japanese Americans, Chinese Americans, African Americans, and their rates are exactly the same as Caucasian so that in the US people of the same sort of genetic makeup as down here but living in the US have rates the same as white Caucasians.

But then you've got all this intermediate. You've got like Japanese in Osaka, Chinese in Shanghai are already up here, even though Chinese in rural China were down here. And you've got Japanese in Tokyo up here, Chinese in Hong Kong and Singapore. So even in areas that were more westernised you see you've got the range right from here to here.

And Osaka Cancer Registry has been going a long time and you can actually – these figures are for women who were born in 1945 but you can go from the Osaka registry, you can look at the cumulative risk to age 45 for different years of birth. And women born in 1930 the cumulative risk was 0.26, so they were down here. For women born in 1955 they were 0.61, up here.

So in one area that's collected statistics for a long time women who were young enough to have changed and these generations have changed a lot, you can see more than a twofold increase in risk. And the same is happening very much so in China and in India where the birth-rate has fallen a lot quite recently. You can see in young women rates going up quite fast.

So there's no – and that's what I sort of showed you also about even the cancer rates associated with smoking falling, there's no – the thing about statistics and national comparisons and things, things change over time, they change quite rapidly and you have to always be aware that in certain age groups things may be different and so forth. And that's, you know, why one can – anyway you have to just be aware of that.

So given that we've got about just over a million cases of breast cancer every year, now you can look at the trends and make – it's now the most common I said in both developed and less developed countries and you can look at the trends and very easily say – and you know I wouldn't want to be sort of quoted seriously – but in about 40 years time it's going to be two million and much of those two million are people from developing countries actually.

So breast cancer rates are going to keep going on and what are we doing about it? And that is outside – it's not outside my [ [?? 0:43:48] ], it's not something unfortunately epidemiologists can easily do. It was okay for smoking because it was easy to say stop smoking.

But for breast cancer it's really quite complicated – no it's not complicated but it's – well it is, you know, it is.

Because you need to be rational about it and this is not so at the moment because – anyway let me just go on but it is hard because, first of all, we know it's the most common cancer in women who are white. Incidence is increasing rapidly, particularly in developing countries.

But we actually do know, we really do know the main potentially modifiable causes and we do know it counts for the most of the worldwide variation in breast cancer. But if we want to think about it it's not like a treatment, if we really want to prevent it it's in healthy women, it's in women who haven't got breast cancer, has to be accepted or it has to be without serious side effects.

There are lots of people advocating giving women all sorts of hormone blocking drugs for all their life but that's not really serious in my view because you can't expect someone to give – I mean still you could argue 10% of women get breast cancer by the time they're 80 but 90% don't. And to make 90% take a drug for life that might cause side effects doesn't actually sit very well.

And so you have to have something without side effects that's acceptable. Now we do know – and I'm just going back, what is easy to do. As I said for smoking it's easy if you just say stop smoking but – now in the UK there are about 45,000 cases a year. Now if no one drunk alcohol, no woman drank alcohol it could be 5,000 fewer. If no post-menopausal woman was obese it would be about 4,000 fewer and it would be a 1,000 fewer if no post-menopausal woman used HRT. I would have said five years ago it was 2,000 fewer but actually use has halved so now it's only a 1,000.

So all of that together is about 10,000 which is a bit over a quarter but they're pretty hard to achieve these things except the HRT. But anyway pretty hard to achieve, it's not like this is easygoing and it's not going to solve the problem anyway, it's going to reduce but not solve the problem.

But what about the thing that is actually staring us in the face that most people don't want to believe and I'm going to say that because it really is true. That the main cause has been known for centuries, it really has, and you know the worldwide evidence supports it. But it's really not an option. I mean we've all become nuns and that's really quite – and you know it's not like having no children or children late in life is disadvantageous, for many reasons it's advantageous in life. You know breast cancer isn't the only thing that one thinks about so it's not something that's sort of acceptable, or a likely change or sensible.

So I'm going to say it's an option to us to suggest women breastfeed for longer but even, as I said, three months, I'm not saying no but you've got to start breastfeeding each child for like two years to really – three years because we have so few children. And probably that's not an option but it's certainly something people could consider but it's really long term breastfeeding.

So what about mimicking the effects of childbearing? And this is – I've only got one or two slides to go but this is just a little picture to show that you that during pregnancy all sorts of hormonal changes happen, I'm not going to say what they are, I hope you can't read what it is, just to show that things happen.

Now we know from epidemiology that short term exposure in early adulthood to one or more of the hormones of pregnancy and lactation gives you lifelong protection against breast cancer. And we also know – you see when I give talks to an audience who are very much into hormones they all say well we know it's oestrogens and progestogens, the main hormones pregnancy produces in the body. And I used to think that that was so and because we knew pregnancies protect against breast cancer as I said before I always thought the bill was going to protect against breast cancer in the long term because I thought it was the same as pregnancy.

But the point is that there are lots of other hormones in pregnancy, particularly ones that affect the breast like something called prolactin. And it does make you think. It's very hard for me to avoid the idea that really why aren't we working out which of these hormones and forget – because it's

not oestrogen and progestogen, that's – you know most of the work I've done has been on the pill and HRT. These things increase the risk of the breast cancer in the short term and don't have a persistent protective effect. Must be one of these other hormones.

Very few people are working on it. But if we could work out which it was we should surely be able to work out something over a nine month period or a bit longer that's like a hormone vaccine that you give to young women and exposure for a short period would give, in theory, lifelong protection against breast cancer and maybe repeated exposures, you know, a couple of times. But it would be something over a relatively short period which should protect in the long term. And, you know, we've got the HPV vaccine, thank heaven, for cervical cancer and it's almost a kind of equivalent idea but it's not popular.

So I'm going to finish there and say thank you for listening and I'm very happy to answer questions.

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