# Epidemiology of Carcinoma in Situ of the Cervix

## Current Research in Obstetrics and Gynaecology

**Discussed by Mr Geoffrey Chamberlain and Mr Joseph Jordan, University of Birmingham.**

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**Black-and-white**
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**<Opening titles>**

**<Chamberlain and Jordan seated for discussion with display board set between them>**

**<Chamberlain to camera>**

Good day. Welcome once again to another programme in our series on current research in obstetrics and gynaecology. These programmes are being made by the Blair Bell Research Society in conjunction with the Audio-Visual Unit of the University of London and we have discussed a variety of subjects so far. Today, we're going to talk about carcinoma in situ, not so much the clinical side of carcinoma in situ but the

epidemiology behind the mathematical scenes of carcinoma in situ for here is a subject which is ill understood by many of us in the clinical field. For this we're fortunate to have with us Mr Joe Jordan who has made a study of this and will lead us through the subject. He is the gynaecologist to the Birmingham Woman's Hospital, but as well as that, he is also President of the Pan American Cancer Cytology Society and President of the International Federation of Cervical Pathology and of Colposcopy. In addition to that, he's a member of the Blair Bell Research Society. And so Mr Joe Jordan will take us through.

Joe, would you take us through and tell us what are the problems with carcinoma in situ in this country?

**<Jordan to camera>**

Well, the problem must be related to death from cervical cancer. And I can give you figures and so on, but I think a broad way of getting the problem home to you very quickly is simply to say that about 1.4 % of women in England and Wales will develop invasive squamous carcinoma of the cervix, and about 1 % of women in England and Wales will die from squamous carcinoma of the cervix.

**<Chamberlain off camera>**

And if that sort of figure is of invasive carcinoma, what sort of figure would it be for those who get carcinoma in situ?

**<Jordan>**

Well, we have to look at whether we're talking about prevalence or incidence rates and again let's not get too bogged down in that, let us simply say that about 3 women in every 100 will develop carcinoma in situ and a few more will develop, no doubt, even before that, the dysplastic lesion.

**<Chamberlain>**

Yes, so, let's take those round figures of instance at the moment of 3 % developing in situ and in conjunction with the 1.2 developing carcinoma invasive; that would imply a sort of 2 to 1 ratio of the two. We'll come back to that in a moment, I think, if we may. How would you define carcinoma in situ?

**<Jordan>**

Well, it's interesting that we're sitting here talking in London and it was here in London in 1886 that the first description of the lesion we now refer to as carcinoma in situ was made by Sir John Williams. He was giving the Harvey lectures on tumours of the uterus, and as purely an incidental finding to one of the tumours he removed, he found that there was a lesion on the cervix which was pre-cancerous. In fact, it was an early invasive carcinoma, but he stressed the fact that this was, well in his words, 'cancer in its earliest identifiable form'. And he stressed the point that the patient had been examined by him before surgery and she had no pain, no bleeding, no discharge and the cervix looked the same as anyone else's cervix, and that's the nub of the problem. They were dealing with a lesion which is precancerous and it's called carcinoma in situ because the epithelial part of the lesion demonstrates the cytological changes which we associate with cancer, but yet there is no invasion of the underlying stroma. And that's what carcinoma in situ is – it's a precancerous change.

**<Chamberlain>**

Is the basement membrane still an important anatomical barrier in this subject?

**<Jordan>**

Well, I think it's an important barrier. Whether, in fact, it's an anatomical barrier to invasion taking place is still not yet known. In fact, until very recently, there was debate as to whether or not there was a basement membrane, but, in fact, there is – electron microscopy has confirmed this. But, there is a very clear line, therefore, the

basement membrane, and it must have some function and presumably it helps to prevent something …<voice *fades*>

**<Chamberlain>**

So, you would say, Joe, that carcinoma in situ is a microscopic, cellular change, which is bounded by the basement membrane, would you?

**<Jordan>**

That's correct, yes.

**<Chamberlain off camera>**

And that's Feger's definition, is it not?

**<Jordan>**

Yes, it is.

**<Chamberlain>**

And that's stage nought.

**<Jordan>**

That is stage nought.

**00:04:51:10**

**<Chamberlain>**

Now, just to clear our lines a little, what is stage 1a then?

**<Jordan>**

Stage 1 cervical cancer is cancer which is confined to the cervix. It's cancer, it's gone beyond carcinoma in situ, but because there are different types of stage 1, it's very important to recognise the difference. Stage 1a is the stage 1 cancer we refer to as microinvasive carcinoma, where just a few cells have broached the basement membrane and they rarely progress beyond about 3 or 4 millimetres. And then we have stage 1b where there is actual cancer, where it may be involving the lymphatics and the vascular channels. And stage 1b, we divide into two: one is stage 1b clinical, where it is obvious clinically to the gynaecologist, and there is stage 1b occult, which is diagnosed purely by chance, usually by screening programmes.

**<Chamberlain>**

Or of a specimen that's been removed – a uterus that's been removed …

**<Jordan>**

Yes.

**<Chamberlain>**

… seen retrospectively. Yes, I see. So, we'll talk about stage nought for the rest of our discussion together, which has not gone through the basement membrane. Now tell me, how do you see a progression from stage nought, carcinoma in situ, to frank division. Is there a link between them and, if so, how does it progress?

**<Jordan>**

Well, can we go back one step further and just look at how we believe carcinoma in situ develops?

**<Chamberlain>**

Yes, of course.

**<Jordan>**

Look at this chart.

**<Jordan refers to chart and narrates over it>**

In the black here, going down the left side of this chart, we begin with normal columnar epithelium, which is usually confined to the endocervix and part of the ectocervix. Now, in every single woman some of this columnar epithelium, by process of metaplasia, is changed from columnar down to normal squamous epithelium so that we have this change from columnar down to squamous; and the name we use for that, many have been used in the past, but the name which we use specifically today is this one, metaplasia.

Now then, we believe that the metaplasia cells, the cells undergoing change from columnar to squamous, are particularly susceptible to a carcinogen. And the carcinogen, we don't know yet really what it is, but it's certainly something which is transmitted by intercourse and by definition therefore squamous carcinoma of the cervix is a venereal disease. So what is it? We accept that it is a coitally transmitted mutagen. The first one which we've looked at was herpes virus type II and there is a considerable amount of evidence now to suggest that it is in some way incriminated in the development of abnormal epithelium. There is sperm and there are obviously other things we haven't even thought about yet or found. So that we start off with metaplasia and if we have a coitally transmitted carcinogen, we may end up, not necessarily, but we may end up here with an atypical type of metaplasia, which produces an atypical squamous epithelium, which then may go back here at this level to produce normal squamous, but what we think happens is that it goes on to dysplasia which is the very earliest abnormal change, which in turn has the ability to backtrack and go along to normal squamous epithelium. But some of these progress

to carcinoma in situ and that too has the ability, under certain circumstances, to revert to normal, but, nevertheless, we believe that many of them progress that way to produce invasive carcinoma.

So that we start off with a normal process, every woman undergoes metaplasia at some time or another, and if it goes wrong, this is the chain of events which may follow.

**<Chamberlain>**

But if, as you told us, something like 3 % get this and 1.2 % get that, then those two lines are almost to the same weight <*indicates pathways of dysplasia and carcinoma in situ*>.

**<Jordan>**

Not quite, because if we look at, if we follow a patient through a lifetime, and we haven't been able to do this yet – I say we, I'm talking about we in very general terms – that some patients who still have carcinoma in situ will progress in years to come.

**<Chamberlain>**

Yes, I see. Well, let's go into that for a moment if we may? What sort of numbers do you think progress because all of us have read various studies which seem to vary from 0 % in one study I read from the Antipodes to 3 % in some colposcopy studies to as much as 35 % in, I think, Peterson's classical study. What is the real progression rate, do you think?

**<Jordan>**

Well, nobody knows. On the one end of the scale, we have someone saying there is no progression or very rarely progression. Others will say that all, or almost all, will progress if you give them time. And, as usual, the answer lies somewhere in

between. What I can tell you is that the largest study of precancer of the cervix was in Vancouver in British Columbia. And they have estimated that at least 15 or 16 % of patients will progress over a period of years. Now, in October 1978, at the last World Congress of Colposcopy and Cervical Pathology, a Japanese professor, Professor Kurihara, estimated that in the study he had conducted over a period of over 20 years – he began in 1954 – he estimated that just over 60 % of patients with carcinomas in situ in his group progressed to invasive carcinoma. And that is the highest really documented one. At the same meeting, someone else from New Zealand, Dr McKendall, estimated that over a period of 18 years, 16.6 % of his patients had progressed to invasive carcinoma. So what we, there is great variation, what we do know is that some undoubtedly do progress.

**<Chamberlain>**

Of course, the Japanese population has got a higher incidence, has it not, of carcinoma?

**<Jordan off screen>**

Of carcinoma generally.

**<Chamberlain>**

So could it possibly be some variation of definition of the earlier stages of dysplasia, of metaplasia and of carcinoma in situ, which makes these wide ranges.

**00:10:45:05**

**<Jordan>**

Well, as you well know, we have to look back only as far as our own Royal College of Obstetricians and Gynaecologists survey, and in the very famous Brudenell Cox study, they showed, they looked at several hundred patients diagnosed as having

pre-clinical disease of the cervix, and they distributed histological sections to a panel of pathologists and they were amazed at how many variations there were. For example, almost 10 %, between 9 and 10 %, of slides were totally inadequate for any diagnosis.

**<Chamberlain>**

Yes, and yet I seem to remember in that 9 or 10 % there had been many women who had been given a hysterectomy on just on the – which I think is over treatment anyway – just on the grounds of the slides. Is that right?

**<Jordan>**

Well, that's true. And I think that as clinicians, we tend to feel that the histologist is the final arbiter, and I think we must get away from this that the histologist – if you look at it a pathologist who is specialised, a gynaecological pathologist, then he will give you the best opinion, but many of us have to work with a pathologist who is a general pathologist; he looks at everything from brains to toenails and therefore he can't be expected to give the same attention to this detail.

**<Chamberlain>**

Yes but, Joe, it's all well for you at the Birmingham Women's and myself at the Chelsea Hospital, we can afford these luxuries, one can't have them everywhere.

**<Jordan off screen>**

Yes, yes.

**<Chamberlain>**

Let's come back to these numbers because it is interesting. You see to make a diagnosis of carcinoma in situ, you need a nibble of tissue, don't you, to look at?

**<Jordan off screen>**

Correct.

**<Chamberlain>**

Excluding Frost and a few who believe you can do it on smears, is there possibly any other way of making a diagnosis of carcinoma in situ without a nibble of tissue, is there any visual way?

**<Jordan>**

Yes, you can use a colposcope and a colposcope is a binocular microscope which was first described by Hinselmann in 1925. And this has developed; it's still, as Stanley Way refers to it, as a pair of binoculars on a stick with a light source, and that's all it is. There is nothing wrong with that *<laughs>*.

**<Chamberlain off screen>**

*<Laughs>*

**<Jordan>**

And it's a means whereby we can examine the epithelium of the cervix of the vagina by magnification. And by doing this, by looking at the vessel pattern, by using acetic acid, sometimes by using iodine, you can detect abnormal epithelium.

**<Chamberlain>**

Are you happy that you can give as good a veracity to a diagnosis down a colposcope as you can down a microscope or a piece of tissue removed of carcinoma in situ or dysplasia or carcinoma of frank malignancy?

**<Jordan>**

I think that if I speak, not personally, but I think an expert colposcopist would tell you that his assessment of the situation would be as good as a pathologist.

**<Chamberlain>**

Well, that's absolutely great and if you say that I'll believe you, Joe, I wouldn't believe it from some. The point being that, you see, all the other methods of looking at carcinoma in situ involve the removal of a piece of tissue, and in doing that, you might either, a) remove the only bit that might have gone on to become malignant thus muck up your study for later on or, b) you might, by your very surgery, interfere with the tissues left behind that they more rapidly progress to malignant change. So you're interfering with the biological situation.

Now, Joe Jordan's just told us of a method of colposcopy which does not interfere, as far as we can tell, or not interfere so much with the biological situation, that this would surely be a better way of following up the possible progress of carcinoma in situ than would be the invasive method of biopsy. Is this right?

**<Jordan>**

Yes and knowing your thirst for modern knowledge and progress, let me tell you there's one other way which we are currently using in Birmingham and that is to apply a very fine millefeuille[? indecipherable word] of filter paper to the abnormal epithelium and we can examine this with electron microscopy; it's relatively simple when the department's geared up to this. We can tell you within 24 hours whether or not the underlying tissue is in situ dysplasia or microinvasion. It's not 100 % nor are any of the other methods we've talked about today.

**<Chamberlain>**

No, so that's a sort of specialised exfoliative cytology.

**<Jordan>**

It is but this, we believe, over a period of time will help to overcome the argument of removing tissue or not removing tissue.

**<Chamberlain>**

Yes, you see, I remember very well in Hopkins, Frost used to preach very firmly that he could diagnose carcinoma in situ and differentiate that from dysplasia on one way or [indecipherable word] to the other, on a smear, and no doubt in his hands it worked. Is there anyone in this country who believes that?

**<Jordan>**

Yes, I think that many of the better cytologists in this country will say that if you give them a good smear, and the operative word is a good smear, and it's well fixed and well assessed, then they will be able to give you a pretty good idea as to the underlying pathology. But, you know, there are pitfalls to this and it's a little better than an educated guess…

**<Chamberlain off screen>**

Yes.

**<Jordan>**

… but they can give you a trend.

**00:15:13:07**

**<Chamberlain>**

Well, let's go on if we may, Joe,  to the screening programmes now because, after all, most of the world depends upon cervical cytology in the conventional Ayre spatula to deal, to bring women in who are suspected of having changes. What are the better screening programmes going on at the moment?

**<Jordan>**

Well, the screening programme, of course, which we all quote is the David Boyes programme in Vancouver which was set up in 1948 by Agnew and Carter and that has been looking, as closely as these things ever can be looked at, by a number of people, including some statisticians from this country which the DHSS has sent over, and there over a period of, well, 31 years now have been trying to assess whether or not cervical cytology screening programmes really work. So that is, I think, the programme par excellence.

**<Chamberlain>**

And in this country?

**<Jordan>**

In Aberdeen, Elizabeth Macgregor's work, I think, is equally good.

**<Chamberlain>**

But not going on for so long I imagine.

**<Jordan>**

Not for so long, no.

**<Chamberlain>**

Yes, so the screening programme in Columbia, what sort of proportion of the population is it now covering?

**<Jordan>**

Well, they estimate that it's always impossible to get the ideal, which is what you and I would like which is 100 %; they estimate that they have screened over 90 % of the population at risk. They've not put a specific figure on it because they can't because of the changing populations.

**<Chamberlain>**

And this is with a yearly smear?

**<Jordan>**

They were doing it yearly initially, but now they've dropped down and they feel that if a patient has had 2 or 3 regular cervical, annual cervical, smears then you can drop down to every second or third year and certainly once the woman is passed the age of 50, then a smear every 4 to 5 years is probably all that is necessary.

**<Chamberlain>**

But you would go on, or they would recommend going on after 50 for how long?

**<Jordan>**

Almost certainly until the patient dies.

**<Chamberlain off camera>**

This would seem logical to me when you look at where the deaths occur in carcinoma of the cervix, but often people stop at the menopause, don't they?

**<Jordan>**

Yes, yes they do.

**<Chamberlain>**

And therefore, would you say that in a patient who's had 2 smears done early to pick up the ones you might have missed for false negative reasons, after that a 2 yearly smear in a fit woman who's got no high risk features will be adequate?

**<Jordan>**

Oh, I think that's reasonable, but let us not forget that the aim of a cytology programme is not purely to pick out carcinoma in situ, it's there to pick out the occult invasive carcinomas, and one of the mistakes which I think was made by the protagonists of cervical screening in the past was that: you have this regularly and this will eliminate death from cervical cancer, and, of course, it doesn't. Even people who are having regular smears, a very small proportion, nevertheless, a certain number will develop invasive carcinoma.

**<Chamberlain>**

Because they rush through disease at a quicker rate inside the interval of smears or because there was some condition, the condition was deeper and not spotted by the smear?

**<Jordan>**

A combination of both of those things. The most important is probably the fact that the disease developed very quickly while we think that most squamous carcinomas develop from in situ, carcinoma in situ, and develop over a period of years, there are some which obviously progress very quickly. But the other thing, and it's equally important, is the quality of the smear which is taken and it may be observer error.

**<Chamberlain>**

Yes. You as President of the Pan American Society must be aware of this very much, but is there any study on those who have got an invasive carcinoma, who have been smeared recently with an apparently normal smear, of the site of the carcinoma? Is up the canal a commoner site?

**<Jordan>**

Yes, you see the usual spatula is that which was designed by Ernest Ayre, or he first described it in 1948, and we all use this wooden Ayre's spatula…

**<Chamberlain>**

Excepting for those of us who use the plastic spatula because we've been told that the wooden one absorbs abnormal cells more readily. I'll come to that in a moment.

**<Jordan off camera>**

I didn't think you'd heard of that spatula.

**<Chamberlain>**

*<Laughs>*

**<Jordan>**

Mine's not on the market yet.

**<Chamberlain off camera>**

Yes, go on.

**<Jordan>**

But the wooden spatula is, I agree, is not quite as good as the plastic. But more important, you know that it's sort of Y-shaped like this *<holds up finger and thumb to demonstrate>* and that it's the short end of the Y that goes on the ectocervix and the long end of the Y is supposed to get into the canal. Well, you look at how wide that is and it doesn't get into the underside of the canal…

**<Chamberlain off camera>**

That's right, a quarter inch only.

**<Jordan>**

… so that a lesion which is in the endocervical canal can be missed in this way. Because let's also remember that when Papanicolaou first described cervical cytology, he collected cells from the posterior fornix, cells which had genuinely been exfoliated, whereas Ernest Ayre, when he described his biopsy, he said you must scrape it, and he designed his spatula to be what he called more of a surface biopsy than a technique for picking up exfoliated cells. And that's why you've got to give it a good firm scrape.

**<Chamberlain>**

And, of course, you get then living cells are then removed rather than those that just happen to fall off like the dead apples from the tree as opposed to the living apples from the tree.

**<Jordan off camera>**

Quite.

**00:20:03:11**

**<Chamberlain>**

Is there any study which correlates the posterior fornix, the pick-up, the pool with the scrape?

**<Jordan>**

Yes, there have been several studies and, as you can imagine, they give different results. But by and large, you will find, as you might expect, that a good firm scrape with a spatula similar to Ernest Ayre's spatula will give you much much better results than the exfoliated cells.

**<Chamberlain>**

But, of course, there are some women who don't like going into clinics and for them, I believe, the Johns Hopkins have invented the do-it-yourself pack, didn't they, which was used in the Appalachian study and then in the West Sussex study? If a girl will not come to a clinic, would you say it was better that she should have a do-it-yourself kit or is that a false security?

**<Jordan>**

I think that the do-it-yourself kits are super, it was the Davis cyto-pipette, and you know that you get a pipette <*demonstrates with a rod*> with a little cap on the top and the patient is given this with their pay slip or sent to her home, and she sits on the

loo, takes off the cap, puts it into the vagina, squeezes the fluid and releases, and then posts it back to the laboratory.

**<Chamberlain off camera>**

Yes.

**<Jordan>**

But she must take off the cap first.

**<Chamberlain >**

Yes, some don't. But, you would not object to that being used as a method in those who didn't want to go the labs?

**<Jordan off camera>**

Not at all, it works very well.

**<Chamberlain>**

Yes. Well now, let's go on. You hinted upon this a moment ago, but all these studies show a certain amount of false positive and false negative rates, that is, in people who've got a smear which appears to be grossly abnormal on which one might proceed to do some further procedure, they, in fact, haven't got carcinoma in situ, a false positive, and a false negative where you have a smear which is reported as being normal and yet later on, one finds that the patient actually has a lesion of the cervix. I consider the second is the more important and more serious – false negatives. Why do you get false negatives, Joe?

**<Jordan>**

We get false negatives because the clinician has taken a poor smear…

**<Chamberlain off camera>**

Wrong place?

**<Jordan>**

…he's taken it from the wrong place or he's just waved it somewhere on top of the vagina or, possibly, hasn't even seen the cervix, you know, and this happens.

**<Chamberlain off camera>**

Therefore, would you say, you've got to put in a speculum in order to do a smear?

**<Jordan>**

That's right. Certainly if you're using the Ayre spatula…

**<Chamberlain off camera>**

I was thinking…

**<Jordan>**

… then you must insert the speculum, expose the cervix properly, take a good firm smear, put on the glass slide and drop it immediately into fixative. We don't put it on the glass slide and then look around for the fixative because you will lose definition. It must then go to laboratory and when it's properly fixed, it's properly stained and looked at by an expert, and at each of these stages then errors can crop in, and it's not just the fact that the cytologist misses it.

**<Chamberlain>**

Yes. What would you say in a good laboratory, fed by reasonable facilities, is the false negative rate?

**<Jordan>**

Somewhere between 8 and 15 %. The Vancouver people think about 8 %; here in the UK, we think that it's in round terms about 15 %.

**<Chamberlain off camera>**

That's Ewell's figures, is it, 15?

**<Jordan>**

Yes.

**<Chamberlain>**

Yes. Because it seems a very high figure, but you go on and ask your chemical pathologist what is the false negative rate of some other tests and bear that in mind. I think we're being very strict with ourselves here, but it is a serious problem. And because of this, therefore, the recommendation is often made to do 2 smears at the beginning. Isn't that right?

**<Jordan>**

Yes, and do one smear now and then another in 6 months to 12 months, and the hope being that with the second smear fairly quickly, you'll find the false negative.

**<Chamberlain>**

Yes, so if it was, shall we say, 15 %, it would then be 15 % off 15 % which would be down in the single figures?

**<Jordan off camera>**

Yes, it's not quite but I think it's near enough.

**<Chamberlain>**

Yes, and the false positive rates?

**<Jordan>**

Well, that's extremely low. The false positive rate again varies according to reports, but it's somewhere between 0.5 % and 2 %, but they're not really such a problem because, you see, I look upon cytology as being a means whereby a clinical problem can come to me as a clinician, and if it's a false positive, I don't really care.

**<Chamberlain>**

Yes, it would come to you and you then as a good colposcopist would probably colposcope the patient and go on from there. But unfortunately, it might come to other gynaecologists who don't use colposcopy, who would go then straight on to cone biopsy, or even to hysterectomy, or even as [indecipherable word] quoted Cox and Brudenell on to radical hysterectomies and radiotherapy even, which I think is a terribly overkill, isn't it?

**<Jordan>**

Yes, well, I think the only way round this is to say, well, you should have 2 positive smears, unless, of course, there was anything clinically obvious; if you make that working rule, then you realise that if the next one is negative, there's something wrong somewhere.

**<Chamberlain>**

Let's go on. The question is always being asked, and being asked more frequently now that screening has been going on for a long time, are we doing any good by all this screening. We're doing something in the region of 10 / 12 million smears a year, it's costing about 10 million pounds a year in the country. What good are we doing by screening, do you think?

**<Jordan>**

The government give us figures about numbers of smears per year, but this, of course, bears no relation to the number of women being screened. We estimate that there are perhaps 17 or 18 million women at risk in the United Kingdom, and if we're doing 7 or 8 million smears per year, the inference is, of course, well, we're smearing every woman every other year. It's not that at all; that each year, we only screen about 2 million women. And, unfortunately, the women who are particularly at risk tend to be the patients, the women, who do not come for screening.

**00:25:18:13**

**<Chamberlain>**

Yes. Are we altering the incidence of the condition?

**<Jordan>**

Yes, I think we are, but let me just show you this slide […]

**<Jordan narrates over slide, using indicator>**

[…] because this again is from Vancouver and I think highlights the end of over 30 years of work, that this is the incidence of invasive squamous carcinoma, or the rate of invasive squamous carcinoma related to the population in thousands in British Columbia, and here in black is the population, and you see that between the years of 1955 and 1974, the population has steadily increased.

**<Chamberlain off camera>**

That's the population screened?

**<Jordan narrating over diagram>**

That's the population screened, no, the total population…

**<Chamberlain off camera>**

The total population, I see.

**<Jordan narrating over diagram>**

... the total population in British Columbia. During the same period of time here in white, here, we have invasive squamous carcinoma rate per 100,000 head of population. And here you see that the rate from 1955 has steadily fallen right down here to 1974.

**<Chamberlain off camera>**

Yes, I must point out to our viewers that this <*indicates total population screened*> does not go down to nought whereas this does <*indicates rate of carcinoma*>, so if drawn on the same sort of scale it would not be quite so dramatic, would it?

**<Jordan>**

No quiet so dramatic, but it makes the point.

**<Chamberlain>**

Well, how about, that the incidence would appear to be going down, not quite so dramatic as that slide would show, but it is going down, how about, is there anything that shows on the ultimate result of all this – the death rate?

**<Jordan over diagram>**

Well, here again from Vancouver, we're comparing population in thousands, in black, just as we did before. This is from 1958 to 74. Again we see the increase in population over this period of time. And in white, we have the mortality rate per 100,000 population, mortality rate for squamous carcinoma of the cervix and you'll see how this has also fallen. So not only are we reducing the incidence of invasive carcinoma but we can also say that Vancouver, British Columbia, anyway is reducing the death rate.

**<Chamberlain>**

But, isn't it so that in many parts of the world, the death rate from carcinoma of the cervix with increased health is going down anyway? May I, I think this is a good example, is the Ontario figures because that's another state in Canada where they have a very low rate of screening, they haven't got a high intensive programme, and their figures are going down roughly in parallel, I seem to remember Cochrane telling us, as those of British Columbia.

**<Jordan>**

Yes, this is often quoted, and Saskatchewan is another, that all of the Canadian states have figures available. And on the face of it, it seems that their figures are as good as British Columbia, but, in fact, many of these states have, certainly the Vancouver people feel and the Walton Committee – remember that was the

committee from Ontario which reported only last year – that they believe that the incidence is falling, and that the incidence of cytology screening in these states, in fact, has been higher than what has been reported.

**<Chamberlain>**

Oh, I see, so it's a false positive of their own data.

**<Jordan>**

I think it's not quite as simple as that, but, nevertheless, there are several flaws in that argument which any statistician, if we had time, would be able to point out to you.

**<Chamberlain>**

And the only real way you could distinguish between these two would be to do a randomised control trial, I suppose.

**<Jordan off camera>**

Yes.

**<Chamberlain off camera>**

Which would be difficult to mount now.

**<Jordan>**

So even taking into consideration all of the figures from Canada, not just British Columbia, that when Walton, based in Ontario, published his report recently, he did say that cervical cytology was working.

**<Chamberlain off camera>**

That was his opinion?

**<Jordan>**

Well, that was his opinion and it was also the opinion, of course, of Elizabeth Macgregor from Aberdeen…

**<Chamberlain off camera>**

Yes, yes.

**<Jordan>**

… here in the UK.

**<Chamberlain>**

Are there any changes in trends of the disease?

**<Jordan narrates over diagram>**

Yes, here's another one look. On this slide, we have down here <*indicates y-axis*> the rate of preclinical carcinoma, here, rate per 1000 women screened as against the age of the woman from 25, 35 and so on right up to 75.

**<Chamberlain off camera>**

This is when first diagnosed, is it?

**<Jordan>**

Yes, and the white line shows the incidence of preclinical carcinoma here in various age groups, and that was in the 5 year period, 1958 to 62. The next 5 year period studied from 62 was 63 – well, it wasn't 5 year but it was an 8 year period – shows the rate per 1000. And you see that in this black line, it's moved to the left. And in every centre in the Western world which has been looking at the incidence of preclinical carcinoma, they will report that there has been a shift to the left. And what, in fact, has happened here, although it's not quite as obvious from this slide as it really is, is that the incidence of preclinical carcinoma in the third decade, that's from the age of 20 to 30, has increased by more than 2 times. It's more than doubled in the third decade.

**<Chamberlain>**

But your peak here is about 34, 35, isn't it?

**<Jordan narrating over diagram>**

Yes, in fact, it's running just below that. And recently the Vancouver people reported that their peak they thought was in the age group of about 28.

**00:30:13:14**

**<Chamberlain>**

Do you think this is related in any way to alterations in lifestyle, sexual habit, earlier intercourse or anything?

**<Jordan>**

Well, this trend was predicted in the early 1960s; it was predicted by many people that the change in sexual habits of young people in the Western world would lead to an increasing incidence of preclinical carcinoma of the cervix. And we've accepted, you see, that it's a venereal disease. And therefore if young people are having

intercourse at an earlier stage with more partners, who in turn have had more partners, then we would expect that for each individual woman, her risk of being exposed to what to her is a carcinogen will be increased. And this here now is an interesting slide.

**<Jordan narrates over graph>**

This was by Valerie Beral. And here in white on the top, we have standardised mortality rates for women born 1902, 12 and 22, you see. And you see this peak?

**<Chamberlain off camera>**

Standard mortality for carcinoma of the cervix, is it?

**<Jordan over graph>**

Yes. This peak here of women born in 1922; when these women were about 20, let's look at the incidence of gonorrhoea per 100,000…

**<Chamberlain off camera>**

That's elegant, yes.

**<Jordan over graph>**

… so that that this woman born in this year <*indicates 1922*> would be 20 in 1942. Can you see this peak incidence here? And what, in fact, Valerie Beral did was to superimpose this chart on this one, and you see that if we accept that gonorrhoea is an indicator of, well, I still use the word promiscuity, I think we all know what we mean by the word promiscuity, if gonorrhoea is an indicator of promiscuity…

**<Chamberlain off camera>**

It's certainly an indicator of intercourse, isn't it? <*Both speakers laugh*>

**<Jordan over graph>**

… then you'll see there is a peak of promiscuity here when these women were twenty. And then you see how, interestingly enough, it peaks again in the early 1960s and late 1970s.

**<Chamberlain>**

That's a very adept presentation of putting the two time scales 20 years apart, that's very nice. Well, if then this is a sexually transmitted disease as you imply, what do you think there is about sexual intercourse that causes it? Is it smegma, is it sperm? What is it?

**<Jordan>**

Smegma was the first thing incriminated and the first report linking sexual activity with intercourse with cervical cancer was way back in 1842 by Rigoni-Stern. And many people looked for a factor after that time. And round about the year 1900, it was found that Jewesses had very low incidence of cervical cancer and they thought – Jewesses, male circumcised, and it was thought that circumcision in the male imposed some sort of immunity from the wife developing cervical cancer. But, in fact, this has been shown not to be true and circumcision really plays no part. But, nevertheless, we know that it is something to do with sexual activity. And two things top the list of possible aetiological factors: one is the herpes virus we've already spoken about, and the other is sperm. Now, why should this be so? Why should the epithelium be more susceptible to these than other types of epithelium? Well, look at this diagram here.

**<Jordan narrates over diagram>**

This is from the very elegant work of Bevan Reid and Albert Singer and Malcolm Coppelson. And this represents a normal cell. It's the funniest looking cell you've ever seen <*laughs*>, but let me explain what it is? This little spot in the middle is the nucleus, this line here represents the cell boundary. And these funny things coming out, in fact, represent little fibrils of nuclear material. The nucleus actually comes out here. Now that's a normal squamous cell. This one is meant to represent an abnormal cell. Remember we talked about metaplasia, well, the metaplastic cells are in a state of very great activity and they send out enormous numbers of these fibrils and each one of these, remember, contains some nuclear material. And this is a way in which we believe that the nucleus may send out feelers to see what's going on in the external environment. And this one represents sperm and what this H here represents, here and here, is histone. It's arginine-rich histone and it's thought that this may be very carcinogenic to these particular cells on the cervix, and what Reid and Singer and Coppelson are trying to show now is that some types of sperm are very, very rich in histone and this has led to their high risk male theory that if you have a man with sperm which has an enormous amount of histone, and this histone has the potential to get into these metaplastic cells and that's where the damage occurs. And in the same way, we believe that virus will probably work, and this is a very interesting theory that we believe, I certainly believe what they've said about this, although many still have to be convinced, but it fits in very nicely, and if sperm can, if sperm DNA can get into the genome of this nucleus, then so can virus, so can anything else.

**<Chamberlain>**

That's to allow herpes to get in or any passing infection, and that's coming back to our Jewish population who have very high standards of hygiene and they might be at a low level because of that.

**<Jordan off camera>**

Absolutely, yes.

**<Chamberlain>**

That's very interesting and I like the hypothesis there, difficult to prove but a nice hypothesis. Well look, finally, Joe, what do you think is the aim of a screening programme in a conventional carcinoma of the cervix?

**<Jordan>**

Well, let me quote David Boyes, who for many years has been in charge of the Vancouver programme, and he said, and he based this on World Health Organization statistics, 'the aim of a cytology screening programme is to reduce the morbidity and the mortality from squamous carcinoma of the cervix'. And as far as British Columbia Vancouver is concerned, and as far as Aberdeen and the UK is concerned, we believe that this aim has now been met.

**<Chamberlain>**

Thank you very much, Joe, and thank you for taking us through this subject in such a clear way. It is a subject which is changing all the time and some people find it a little difficult to keep up with it. I would recommend, and I can do this but the speaker can't, but there is a very good book, *The Cervix*, by Joe and by Albert Singer published last year. And I can say this because some of the chapters weren't written by Joe, they explain this problem very clearly and you may like to read that for background reading. I read it and enjoyed it and I'm sure you may. Thank you very much.

**<Jordan>**

Thank you.

**<End credits>**