Wellcome Film Project

Epidemiology of Cancer

Uptodate: Cancer Research Today, Programme 6

A series of programmes from the Institute of Cancer Research.

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Black-and-white
Duration: 00:36:29:22

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<Opening titles>

<Hutt to camera>

In the first few talks of this series, attention was focused on the nature and biological behaviour of tumours and of the physical and chemical changes that take place in cells during carcinogenesis. In subsequent talks, emphasis will be placed on the diagnosis and management of patients with individual tumours. Today, we are going to consider the cancer problem in terms of its occurrence in various populations, that is to say, the epidemiology of cancer. In the wider sense, all tumours are due to the inter-reaction of exogenous and endogenous factors.

<Hutt narrates over slide>

The exogenous or environmental factors may be related to the geography, the socioeconomic, the cultural or the occupational background of the individual or population.

<Hutt to camera>

The endogenous factors may have a genetic background or may be related to hormonal or other chemical influences. The importance of environmental factors in determining the patterns of cancer can be shown by studying migrant populations.

<Hutt refers to charts and illustrations placed on display board beside him and narrates over them>

If, for example, we take the West African whose descendants are now present in large numbers in South America, the Caribbean and the United States, we will find that there are very considerable variations in the cancer pattern. <*Next illustration*> In this illustration, we see on the left an inhabitant of Nigeria. He has a low incidence of carcinoma of the colon, the stomach and the lung, and a high incidence of carcinoma of the liver and also a high incidence of Burkitt's lymphoma. After years of migration and residence in the United States, his cancer picture comes to resemble that of the American shown on the right, who has a high incidence of colon, stomach and lung cancer and has a low incidence of cancer of the liver and also of Burkitt's lymphoma.

On a more localised scale, both in terms of time and of distance, we can compare the incidence <*next illustration*> of the rural and the urban African. The rural African, shown on the right, has a cancer pattern similar to that that I have described in the Nigerian. The long-term inhabitant of a large urban city, such as Johannesburg, illustrated on the left, shows a changing pattern with an increase in the incidence of carcinoma of the colon and also of the bronchus and a decreasing incidence of carcinoma of the liver, suggesting that the latter is related to rural environmental factors.

<Hutt briefly to camera, then refers to further charts, illustrations and slides, and narrates over them>

Further information can be obtained by studying the effect of the age at which migration takes place. Inhabitants of Japan have a very high incidence of stomach cancer. The people who migrate from Japan to Hawaii or to America begin to have a lower rate. <*Next illustration*> Now, this is illustrated in this next picture. On the left, there is the inhabitant of Japan who lives there and has a very high risk. The first generation of migrants born in Japan but living in America have a moderately high risk, but the second generation who are born and brought up in America have a very much lower risk. <*Next slide*> This is shown in more detail in this next picture.

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The standard mortality rate of Japanese and Japanese migrants with stomach cancer are compared with those of the United States' citizens. If these standardised mortality rates for the Japanese are given as a 100, we will see that the Japanese-born living in the United States and migrating at various ages has a slight reduction in the incidence, but the Japanese in the next column who were born in the United States have a very much lower incidence, though it does not quite reach the very low rate seen in the US-born, the United States citizen born there, who has rates down to 17 and 18.

<Hutt to camera>

Probably, the age at which migration takes place is important. Somebody migrating at a very young age may well adopt the cultural patterns of the area to which he is going, whereas somebody migrating at an older age is unlikely to.

<Hutt refers to map and narrates over it>

Another interesting situation of migration and carcinoma of the stomach is shown by the cancer pattern in Colombia in South America. This is the outline of Colombia which is characterised by this high mountainous range that we see here. In this high mountainous area, there is a very high incidence of stomach cancer, whereas in the coastal region this is very much lower. People from both these areas migrate into this

major city of Cali and it is found that they maintain the high or the low incidence of the areas from which they come.

<Hutt to camera>

Dr Carrea and his colleagues, studying the pattern of stomach cancer in Colombia, have investigated the gastric mucosa of people coming to necropsy in Cali from both these areas. And they have found that in the people from the mountainous areas, there is an extremely high incidence of chronic atrophic gastritis, whereas in the people from the coastal areas this is comparatively low.

Now, these facts about migration, both for the Japanese and for the Colombians, suggest that the aetiological factors act over a very long period of time and that they cause chronic atrophic gastritis, which is, in a sense, a precancerous condition. Whether or not another carcinogenic factor is necessary is not clear, but chronic atrophic gastritis in other parts of the world has also shown to be precancerous. Now, this is an interesting example of the effect of geography and I'd now like to consider some other geographical factors in the aetiology of cancer.

One of the clear-cut examples of this is the effect of solar irradiation on the development of skin cancer, particularly of fair-haired Europeans. The fair-haired Europeans living in the tropics or the subtropics, and particularly those living and working outside, have a great risk of developing solar keratosis with subsequent development of basal or squamous cell carcinomas. The African living in these areas is completely protected from this by virtue of his skin pigmentation. There is, however, one area or surface of the African which does not get this protection and this is the conjunctiva. And there is a high incidence comparatively of squamous cell carcinoma of the conjunctiva in Africans, particularly those living in high altitude areas.

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One of the most interesting examples of the geographical studies in cancer is Burkitt's lymphoma.

<Hutt narrates over photograph of face of boy with Burkitt's lymphoma>

This is a very typical case, as seen and described by Burkitt, and later defined as a clinicopathological entity.

<Hutt to camera then narrates over map of Burkitt's tumour distribution>

He found that such cases occurred everywhere in Uganda except in the Southwest, which was high mountainous country, and because of this curious negative area, he started a series of safaris which took him all over Africa, and as a result of this he produced the map of Burkitt tumour distribution we see here. Each of these individual black or white points represents a case of Burkitt's lymphoma. And, as you can see, there is a belt across Africa excluding North and South Africa. Within this belt, as I've already indicated, there are tumour-free areas. Examination of this geographical pattern led to the suggestion that there might be an association with a vector, such as the tsetse fly or the anopheline mosquito as shown in the left hand side of this map.

<Hutt briefly to camera and then narrates over slide>

And out of this came the hypothesis that the tumour might be due to a virus which was carried by a specific vector. However, further evidence became available which suggested that the geographical distribution might be due to endemic malaria. One reason for considering this was that the tumour virtually never occurred in malaria controlled areas. Now, how might the malaria work? It's now clear that malaria alters the immunological responses of an individual in a very considerable way. And it seems reasonable that this altered immunology might affect the susceptibility of the individual to a possible oncogenic virus, perhaps, in the case of Burkitt's lymphoma, EB virus. It has certainly been shown experimentally that the induction of malaria in

an animal will enhance the yield of tumours in animals subsequently given an oncogenic virus.

<Hutt to camera>

And it seems reasonable at the moment to suggest that geography is due to the malaria which makes the host susceptible to a virus.

Now, I would like to turn to cultural factors in the causation of tumours. One of the obvious examples of this is the very high incidence of oral cancer in most of the Indian subcontinent. This is clearly related to the cultural habit of betel nut chewing and is probably due to a direct carcinogenic effect of the betel nut and its associated constituents on the inside of the mouth.

Nearer home, the cultural cancer of this country, we might say, is carcinoma of the bronchus. And the classical epidemiological work of Doll and Hill have shown this very clearly. There is a rapid increase in the rate of carcinoma of the bronchus, first occurring in men and later in women.

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<Hutt refers to charts and slides and narrates over them, interspersed with talk to camera>

And if we look at the death rate per million from cancer of the bronchus in a series of different countries, and we relate them to the cigarette consumption from figures taken 20 years before, we will find that there is a very close relationship. <*To camera*> Now, of course, this does not prove cause and effect. Case control studies show a very much higher incidence of heavy smoking amongst cases than amongst controls, but often prospective or cohort studies are more useful. <*Next slide*> And we'll see in these next figures, taken from a study on British physicians, that in those who are non-smokers the annual death rate was very much less than in those who smoked 25 or more cigarettes a day.

<*To camera*> If cigarette smoking is the cause of cancer of the bronchus, it is, of course, very important from a public health point of view to know whether cessation of smoking has any effect. <*Next chart*> Here we see the death rate per 1000 of people continuing to smoke as compared with non-smokers. And here we see a graph showing the declining death rate in ex-smokers in years after stopping smoking. And it is clear that after 15 years of cessation of smoking, the death rate per 1000 is almost down to that of non-smokers.

Now, this lesson has at least been learnt by the doctors. <*Next chart*> Here we see the death rate per 100 000 over a period from 1954 up to 1965. This is the death rate for all men in this country and shows a steady rise of some 7%. This shows the death rate in male doctors and shows a decline of some 38%. This decline can be directly attributable to the fact that a large number of doctors have accepted the figures and have given up smoking.

<Hutt to camera>

Cultural factors may also play an important role in the genesis of carcinomas of the genital tract and of endocrine organs. And one of the tumours that has excited the interest of epidemiologists is carcinoma of the breast. It has been known for many years that carcinoma of the breast had a higher incidence in nuns. And it also has a higher incidence in nulliparous women than in multiparous women. In terms of the geography, carcinoma of the breast is very much less common in the developing countries such as Africa than in the United States or Europe. Various factors have been thought of to explain these differences: the age at the time of the first pregnancy, the amount of breastfeeding, the length of breastfeeding, and the parity of the individual have been considered.

<Hutt narrates over slide>

McMahon working in the States did a prospective study involving a large number of women and examining the relative role of these factors. And he has shown that there

is an association with parity but that this is secondary to an association with the age of the individual at the time of the first pregnancy.

<Hutt to camera>

There did not appear to be a clear-cut relationship with the length or amount of breastfeeding. The woman who has her first child under the age of 20 has a very considerably reduced risk of developing carcinoma of the breast than the woman who has her first child over the age of 30. We still do not know how this works, but it seems probable that it must operate through hormonal factors, and possibly the relative levels of various oestrogen factors and their effect on breast tissue may be important. However, it is clear that this is not the whole story and that a number of other aetiological factors will have to be taken into consideration. As in most cancers, the aetiology is multifactorial.

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I've mentioned geographical and cultural factors and I would like to end by turning to food and drink. These are influenced, of course, by social factors, economic factors, geographical factors and cultural factors. And it is clear that what we eat and drink may be of importance in relationship to carcinogenesis. And Dr Hill is going to describe his investigations into the epidemiology and cause of cancer of the large bowel.

<Hill to camera>

Thank you, Professor Hutt. Well, Professor Hutt has just given you a broad outline of the way in which epidemiology can give us leads into the aetiology of cancer, and the example of lung cancer is a very good one in showing how the initial epidemiological studies link the incidence of lung cancer to a given agent and how then this leads on to retrospective studies, followed by prospective studies, followed by or going on at the same time as laboratory studies into the actual mechanism of the tumour formation.

We're attempting to do the same sort of thing with colon cancer and we're some way behind the lung cancer people, but we think we're making some progress. Now, the incidence of colon cancer is high in Northwest Europe and North America, and is low in Africa, Asia and most of South America. These geographical differences are not due to racial differences as is illustrated here.

<Hill refers to chart on display board beside him and then narrates over it>

The migrants from Japan, an area with a low incidence of colon cancer, who go to California, an area where the incidence of colon cancer is high, either in the same generation or in the subsequent generation take on the incidence of the area to which they have moved. The first generation of Japanese in California have a high incidence of colon cancer, so the aetiology is obviously not racial. It isn't climate because the three racial groups in South Africa, the black, white and Indian population, have differing incidences in colon cancer despite the fact that they are all breathing the same air, living in the same climate.

<Hill to camera>

And there seems to be a general agreement that the major factor in the aetiology of colon cancer is diet. There is not a lot of agreement as to which factor of the diet is involved.

Now, this has led people to look in the diet for carcinogens and this is a very productive occupation. There is no shortage of carcinogens in the diet, but none of the carcinogens that have been found is able to explain this geographical variation in the incidence of colon cancer. And so we put forward the postulate that the actual carcinogen is produced in situ in the gut.

<Hill refers to and narrates over 3 slides in turn >

And our postulate takes the form of three statements: the first of which is, the gut bacteria can synthesize carcinogens from dietary components or from intestinal secretions; the second that the composition of the gut flora is determined by the nature of the diet; and thirdly, since the diet controls both the substrate concentration and the flora acting on this substrate, it would determine the amount of carcinogen produced and therefore this would explain the link between diet and the incidence of colon cancer.

<Hill to camera>

Now, before we can test a postulate like that, we have to make an assumption regarding the actual substrate molecule because otherwise it's like looking for a needle in a haystack. So, we have taken as our first assumption that the substrate molecule is a bile acid and we've chosen bile acids for two reasons: first of all, because the concentration of bile acids in faeces is dependent on the diet in a way which will correlate with the world distribution in colon cancer, and secondly, because the bile acids bear a close structural relationship to the polycyclic aromatic hydrocarbons.

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<Hill refers to diagrams using indicator stick and narrates over them, interspersed with talk to camera>

Now, if you remove the peripheral substituents from this molecule and make it fully aromatic then this will be a polycyclic aromatic hydrocarbon belonging to a family of very potent carcinogens. Now, the problem is: how to get from the bile acid to the polycyclic aromatic hydrocarbon? Because this involves oxidative reactions, the insertion of double bonds into the nucleus, and the gut is a reducing environment. <*To camera*> The majority of the bacteria are very good at doing reducing reactions but not very good at doing oxidative reactions.

Well, we've postulated four mechanisms by which bacteria could insert double bonds into the nucleus and have then demonstrated these four mechanisms using gut bacteria. And using just these four types of reaction, we can produce a fully polycyclic aromatic hydrocarbon from the bile acid nucleus.

Now, I'll just go quickly through these four mechanisms. And we start off with the bile acid. R represents the bile acid side chain and the first step, the first necessary step is an oxidation of this 3-hydroxyl group to produce a keto group. And that's an easy reaction for bacteria to do. And then with that keto group in position, the first way in which bacteria can introduce a double bond into the steroid nucleus is to introduce it conjugated to that keto group. And the double bond can go there or else it can go in this position. The important thing about conjugation is you have an alternating double bond / single bond situation: double bond, single bond, double bond, and this is a stabilising influence on the double bond; it allows the action to go more easily and stabilises the product.

Now, the second type of reaction is the removal of this methyl group. Now, while the methyl group is present, there is no way in which ring A can be made aromatic because you need a double bond at this position and all four valencies are taken up. So removal of that methyl group is the second important step. This reaction, by the way, is only carried out by certain group of clostridia. Removal of this methyl group is also only carried out by the same clostridia and it occurs linked to a 1,2-dehydrogenation to give this 1,4-diene-3-one structure which, under normal pH conditions, rearranges. A hydrogen migrates from here to here and you end up with a phenolic ring A.

So, now we'll start on ring B. And the third type of reaction is a dehydration reaction removing the elements of water across this bond here; we remove an OH from the 7-position and hydrogen from the 6-position, leaving a double bond at the 6,7-positon. Now, this happens normally. The 7-dehydroxylation reaction is a common reaction and this is normal intermediate, but under normal conditions this would spontaneously reduce to give the saturated product, but when this double bond is introduced in the presence of an aromatic ring A, then it's stabilised in conjugation.

Again, conjugation is very important in the stabilisation of double bonds. So that's the third type of reaction and this is a very common reaction carried out by most of the anaerobic bacteria.

And the fourth type of reaction is a makeweight. It's the insertion of this double bond in the 8,9-position. Now, that's inserting a double bond conjugated to other double bonds. It's analogous to the insertion of a double bond conjugated to a keto group and it is a different type of reaction. Now, this fourth type of reaction is, again, only carried out by a certain group of clostridia, and it's the same group of clostridia that were able to do the 4-diene-3-one or remove the 10-methyl group.

And now using the same set of reactions, we can finish off the series. A dehydration reaction to give a double bond in the 11,12-position, once again in conjugation with the rest of the molecule. And then a demethylation reaction followed by a dehydrogenation to give the final fully aromatic – polycyclic aromatic hydrocarbon. And this is a family of compounds, the cyclopenta phenanthrenes which have been shown by Coombs in the Imperial Cancer Research Fund to be very carcinogenic.

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<Hill to camera>

Right so, we have our substrate molecule, the bile acids, and we have now, since three of these four reactions are only carried out by a certain specific group of clostridia, the nuclear dehydrogenating or NDH clostridia for short hand. Then we have a specific organism to look for. And to test this hypothesis, we investigated nine populations throughout the world, some with a high incidence of colon cancer, some with a low incidence and some with an intermediate incidence. And we looked for the faecal bile acid concentration and we looked at the numbers of the specific clostridia, these NDH clostridia, in faeces.

<Hill narrates over series of graphs>

And the first graph shows the relationship between the incidence of colon cancer within these populations and the mean faecal concentration of total acid steroids, bile acids. And you can see that there is a good correlation between a postulated substrate, concentration of postulated substrate, and the incidence of colon cancer within the population. <*Next graph*> This is of total acid storage; if we take one particular bile acid, deoxycholic, then the correlation is even better. Now, deoxycholic acid is the product of 7-dehydroxylation of cholic acid and you'll remember that the 7-dehydration reaction is one of our four nuclear dehydrogenation reactions, so this is probably a measure of one of our four reactions.

<*Next graph*> And then thirdly, we looked at the numbers of the particular clostridia that we infested in these NDH clostridia. And you can see that the two high-incidence populations that we studied, which were England and Scotland, had large numbers of these organisms compared with the relatively small proportion of organisms in the faeces of Ugandans and Indians.

<Hill to camera>

So that so far the data supports our postulate; in high-incidence populations, there is a high faecal concentration of our postulated substrate, and there are large numbers of the organisms which are postulated to convert the substrate into the carcinogen. So we were now in a position to apply our studies to individuals rather than populations. And the rationale behind the study is illustrated in the next slide.

<Hill narrates over series of slides>

You see a person who has a high faecal concentration of the bile acid substrate and large numbers of NDH clostridia should produce relatively large amounts of carcinogen and should therefore be at high risk of getting colon cancer. Now, if you only have the clostridia and only low concentrations of bile acid, or if you have large concentrations of bile acid but small numbers of clostridia, or if you have a shortage of both, then you should have a low incidence of colon cancer. And in order to test this, we analysed faecal samples from patients entering a gastroenterology ward.

<*Next slide*> The colon cancer patients were all freshly diagnosed and a stool sample was taken as soon as they were admitted to hospital. And the controls were the people who had entered the same gastroenterology ward with diseases other than colon cancer. Though in this slide, we have the same four groups and there were a total of 98 patients so far, of whom 28 were in group 1, the high-risk group, 10 in group 2, 30 in groups 3 and 4 each. And of the high-risk group of 28, 24 had colon cancer. Now, we would expect about a third, 32 of our 98 had colon cancer, so we would expect about a third of our 28 to have colon cancer, and the relative risk is the ratio between the number of cancer patients in the group and the number that we would expect from the overall population. And only our high-risk group had a high relative risk and our postulated low-risk groups, in fact, were found to have a low risk.

<*Next slide*> The next slide shows the same data presented differently. Here, we've divided them up into cancer patients and controls. And you can see that three quarters of our cancer patients belong to the high-risk group compared with less than 2% of our controls. So that at this stage, whether our postulate is right or not, we have what appears, at any rate, to be quite a good discriminant for retrospective studies.

<Hill to camera>

And we now have to apply this to prospective studies to see whether the same discriminant, in the presence of large amounts of substrate and of large numbers of clostridia, can, in fact, be used predicatively to determine who is going to get colon cancer and who is not. And then, of course, if this proves also to be true then one can postulate methods by which we can readily reduce the incidence of colon cancer. It would indicate that colon cancer is a preventable disease and can be prevented by modifying the diet.

Well, now to finish up with, I shall point out that there is no such thing as original research and this was all predicted way back by a non-scientist by Aldous Huxley; in his book *After Many a Summer* , his hero says, 'Cancer might be regarded, in the

final analysis, as a symptom of sterol poisoning'. And, I think he may well be right. Thank you.

<End credits>