

# An introduction to viruses and cancer

Cancer affects around one in three people in Western societies, where, along with heart disease and stroke, it is one of the major killers. Cancer results from the uncontrolled growth of a single cell that eventually forms a clone of tumour cells which may then metastasize (be disseminated) to other sites in the body. Over the years researchers have identified many factors which increase the risk of developing certain types of cancer, such as smoking for lung cancer and sunlight for skin cancer. But since not everyone exposed to these risks develops the cancer, additional factors must be required for the outgrowth of a tumour.

We now know that for a healthy cell to transform into a cancer cell a series of changes must occur which slowly release the cell from the multiple checks and balances which control its normal growth. This chain of events, which involves both genetic changes and environmental factors, explains why cancer may take many years to develop after exposure to a single risk factor and is therefore generally a disease of middle and old age.

Viruses are associated with up to 20% of cancers. **Dorothy H. Crawford** describes how the links were made between viruses and cancer and how current research is leading to the development of vaccines.

## The link between viruses and cancer was one of the pivotal discoveries in cancer research

Because cancer development requires several 'assaults' on an individual cell, at the cellular level it is very rare. Each of us has around  $10^{14}$  cells in our bodies with the potential to become a cancerous clone, but only one cell in one third of the population will turn cancerous. So the chance of an individual cell becoming a cancer cell is a vanishingly small  $1$  in  $3 \times 10^{14}$ .

### Linking viruses with cancer

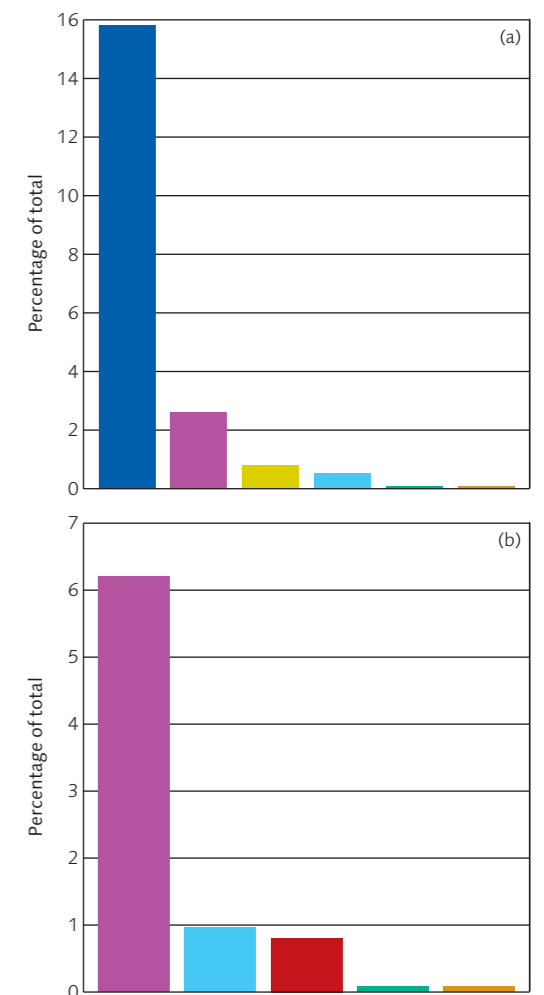
The link between viruses and cancer was one of the pivotal discoveries in cancer research. These days it is generally agreed that viruses are involved in 10–20% of all cancers (Fig. 1). But acceptance of this association took a long time, probably because viruses were perceived as infectious and transmissible whereas cancers were not. As long ago as 1908 two Danish scientists, Wilhelm Ellermann and Oluf Bang showed that leukaemia in chickens was caused by a filterable agent (a virus) which could transmit the disease. And just 3 years later, Peyton Rous, working at the Rockefeller Institute in New York, discovered a virus which caused sarcoma in chickens. Their findings were virtually ignored at the time, although 50 years later (in 1966) Rous received a Nobel prize. By that time several other animal tumour viruses had been discovered and the importance of his early work was finally recognized.

### Viruses and human cancers

Following the success of the animal tumour virus field, scientists turned their attention to human tumours, but progress was painfully slow. It was not until the early 1960s that Anthony Epstein, while working on *Rous sarcoma virus* at the Middlesex Hospital,

London, attended a seminar in which Denis Burkitt, a British surgeon working in Uganda, described a tumour of the jaw in African children. Although previously unrecognized, this was, and still is, the commonest childhood tumour in central Africa. Burkitt noticed that the tumour had an unusual geographical distribution and set about mapping its incidence throughout Africa. He found that it occurred in a belt across central Africa, mimicking holoendemic malaria (that is, malaria occurring all the year round independent of seasons). The tumour was restricted to lowland areas where the temperature was always above 16 °C and annual rainfall exceeded 55 cm. These are the exact climatic conditions required by the mosquito vector of the malaria parasite for breeding, so based on these findings Burkitt postulated that the tumour (now known as Burkitt's lymphoma; BL) was caused by an infectious agent which was spread by the mosquito.

Epstein and his team, with the facilities to hunt for a viral cause, spent the next 2 years scanning tumour biopsies under an electron microscope for viruses using material flown in from Uganda; but without success. The breakthrough eventually came when a biopsy was delayed in transit and arrived in an unfit state for electron microscopy. Epstein cultured the cells instead. Much to everyone's surprise the cells grew, and examination of the cultures under the electron microscope showed typical herpesvirus particles. This proved to be a 'new' type of herpesvirus – later called Epstein–Barr virus (EBV). But just finding a virus in a tumour is not enough to assume a causal association. Further work found



▲ Fig. 1. Virus-associated cancers in (a) females (worldwide incidence; 19.7% of total) and (b) males (worldwide incidence; 8.2% of total). ■, Cervix; ■, liver; ■, vulva; ■, penis; ■, nasopharynx; ■, Burkitt's lymphoma; ■, adult T-cell leukaemia. Dorothy Crawford

◀ Coloured transmission electron micrograph of Epstein–Barr viruses in Burkitt's lymphoma, seen as circles with central, dark-staining DNA (red). Dr Gopal Murti/Science Photo Library

Table 1. Viruses associated with cancer in humans

| Family                  | Virus                                   | Benign disease               | Tumour  |
|-------------------------|---|------------------------------|---|
| <i>Retroviridae</i>     | Human T-lymphotropic virus 1            | Tropical spastic paraparesis | Adult T-cell leukaemia/lymphoma   |
| <i>Papillomaviridae</i> | Human papillomaviruses                  | Benign warts                 | Cancer of cervix, skin, anus, penis   |
| <i>Hepadnaviridae</i>   | Hepatitis B virus                       | Hepatitis, cirrhosis         | Hepatocellular cancer   |
| <i>Flaviviridae</i>     | Hepatitis C virus                       | Hepatitis, cirrhosis         | Hepatocellular cancer, lymphoma   |
| <i>Herpesviridae</i>    | Kaposi's sarcoma-associated herpesvirus | Castleman's disease          | Kaposi's sarcoma, Body cavity lymphoma  |
|                         | Epstein-Barr virus                      | Infectious mononucleosis     | Burkitt's lymphoma, Hodgkin's lymphoma, B lymphoproliferative disease, Nasopharyngeal carcinoma |

the virus in almost 100 % of African BL, and more recently in other tumour types as well (Table 1). We now know a great deal about the way this virus transforms cells, but we still do not know the exact pathogenesis of BL. So Burkitt turned out to be right about the infectious agent causing BL, and although it is not spread by mosquitoes, holoendemic malaria remains an important cofactor for tumour development.

#### Further discoveries

Since the 1960s five more human tumour viruses have been identified (Table 1). They belong to five different virus families, but they are all viruses which can persist in the host after the initial infection. To do this they have evolved many sophisticated strategies for evading the immune response which would otherwise clear the infection.

In all cases infection with a tumour virus is much more common than the cancer it causes, so clearly virus infection alone is not enough to cause the cancer. This is not surprising because, as outlined above, individual cells require several 'hits' before becoming cancerous. So, for each virus-associated cancer there is a series of essential events in addition to virus infection. For example, integration of the viral genome into cellular DNA occurs regularly with retroviruses but not other viruses. However, this is an essential feature of human papillomavirus- and hepatitis B virus-associated tumours.

It is noticeable that the incidence of many virus-associated cancers shows a marked geographical variation. This may be due to geographical restriction of the virus, as in the case of human T-lymphotropic virus 1 which is only common in the Caribbean and Japan. Alternatively, geographical restriction may be caused by access to cofactors which are essential to tumour development. Here BL is a good example, since EBV infects over 90 % of the world's population, but the tumour is restricted to areas of the world where malaria is holoendemic.

#### Mechanisms of virus action

Broadly speaking there are two mechanisms by which viruses cause tumours – direct and indirect. The direct mechanism involves the virus infecting a cell and expressing its own

genes. These gene products then enhance the growth potential and/or survival of that cell. Next, over time, if other growth enhancing changes occur in the same cell it may grow into a cancer, for which the virus would be an essential element but insufficient on its own.

The indirect mechanism of tumourigenesis involves the virus acting as a cofactor for the tumour but not actually being present in the tumour cells. Human immunodeficiency virus (HIV) is a good example here, since by causing severe immunosuppression it allows other viruses, such as EBV and Kaposi's sarcoma-associated herpesvirus, to act opportunistically and cause uncontrolled cell growth in the absence of the normal immune control mechanisms.

#### Cancer treatment and prevention

The importance of the identification of an association between viruses and various types of cancer is that it opens up new possibilities for cancer prevention and treatment. Because virus-associated cancer cells express viral antigens, they can be recognized as 'foreign' by the immune system. So vaccines can be developed which induce an effective immune response to the virus and can thereby prevent infection and consequent tumour production. Vaccines for HBV and HPV are at present being tested in clinical trials and are giving encouraging results. Also, where tumours develop in the setting of immunosuppression, the key elements of the immune response controlling the virus infection, cytotoxic T cells, can be grown in the laboratory and given to patients to prevent or treat the tumour. With these various strategies, hopefully it will not be that long before the worldwide incidence of virus-associated cancers is dramatically reduced.

#### Dorothy H. Crawford

Professor of Medical Microbiology and Head of School of Biomedical & Clinical Laboratory Sciences, University of Edinburgh, Hugh Robson Building, George Square, Edinburgh EH8 9XD (t 0131 650 3142; f 0131 650 3711; e d.crawford@ed.ac.uk)