GENERAL REMARKS

This ninetieth volume of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* considers human papillomaviruses (HPVs), which were evaluated by a previous Working Group (IARC, 1995). The monograph in the present volume incorporates new data that have become available during the past decade.

HPVs represent the most common infectious agents that are transmitted sexually throughout the world; the major risk factors are behaviours associated with sexual activity. Although most infections are asymptomatic and are cleared within a period of 2 years, genital HPV infection can lead to clinical disease, including anogenital warts, cervical neoplasia, cervical cancer and other anogenital cancers. The risk for persistence of infection and progression of the more than 40 genital HPV types to grade 3 cervical intraepithelial neoplasia (CIN3) and cancer differs widely. Persistent infection with carcinogenic HPVs occurs in virtually all cases of cervical cancer.

Previous evaluations of HPVs have classified types 16 and 18 as *carcinogenic to humans (Group 1)*, types 31 and 33 as *probably carcinogenic to humans (Group 2A)* and some types other than 16, 18, 31 and 33 as *possibly carcinogenic to humans (Group 2B)*. At that time, the evaluation of types 16 and 18 was based on the strong association between infection with these HPVs and cervical cancer. For types 31 and 33, the association was less strong.

The new epidemiological data reviewed in the present volume strongly support and further confirm the previous evaluation of types 16 and 18, and provide new evidence for other HPVs. This information, which includes strong evidence of carcinogenicity at sites other than the cervix, supports new evaluations for several other HPV types in addition to those mentioned above.

A brief history of research on papillomaviruses

Research on papillomas and papillomaviruses began more than 100 years ago. Probably the earliest work was carried out in England in 1896 by McFadyean and Hobday who demonstrated cell-free transmission of canine warts (McFadyean & Hobday, 1898). This finding was followed by the more frequently quoted cell-free transmission of human warts reported by Ciuffo (1907) in Italy. However, warts were not considered to be authentic tumours at that time, and it is therefore not surprising that the subsequent reports

of cell-free transmission of chicken leukaemia by Ellermann and Bang (1908) in Copenhagen and of chicken sarcoma by Rous (1911) in New York received much more attention from the scientific community.

In spite of a limited number of studies on papillomas and their viral etiology in subsequent decades, it was almost 80 more years later when this area of research engendered broad interest, particularly in the field of medicine. This resulted from the demonstration of a relationship between specific HPV infections and cancer of the cervix, one of the most frequent cancers in women. However, the recent surge in activities in papillomavirus research basically has four (initially relatively independent) historical roots: (*a*) studies on the development of papillomas in cattle; (*b*) those on the development of papillomas in rabbits; (*c*) studies on a rare human hereditary condition (epidermodysplasia verruciformis), which is characterized by extensive verrucosis and the subsequent development of skin cancer in warts that are located at sites exposed to sunlight; and (*d*) investigations on the viral etiology of cancer of the cervix. Although they were initiated by different primary observations, all four types of study played a role in the subsequent progress and stimulated specific experimental approaches. A brief outline of the pioneer work performed in the four areas and some of the early major advances made in these fields are summarized below.

The infectious origin of bovine warts was initially demonstrated in Brazil (Magelhaes, 1920). Interest in these types of frequently giant papillomas developed from the studies of Olson and Crook (1951), who showed that transmission of these viruses to another species (horses) resulted in the induction of sarcoids. These invasive but non-metastasizing tumours are also observed in domestic horses under natural conditions. Thus, their experimental induction suggested that they originated from trans-species transmission of bovine papillomavirus (BPV), which was proven much later by molecular analyses (Lancaster & Olson, 1978). This group made another striking observation, namely the induction of bladder tumours in cattle by BPV infection (Olson *et al.*, 1959). Four years later, two additional reports by Black *et al*. (1963) and Thomas *et al*. (1963) described the transforming activity of BPV preparations in bovine and murine cells. This was the first time that tissue culture studies were used in papillomavirus research and they profoundly influenced progress in subsequent years.

The development of molecular biology and DNA-cloning techniques in the 1970s and the application of this technology to the BPV system characterized parts of the BPV genome as the elements responsible for transformation in tissue cultures (Lowy *et al*., 1980). Shortly thereafter, BPV-1 was the first type of papillomavirus to be fully sequenced (Chen *et al*., 1982).

The interest in studies of BPV continues and is mainly based on the ease with which some of the most prevalent BPV types (BPV-1 and -2) can be used in tissue culture studies to study the mechanisms of persistence of the viral genome, as well as the patterns of expression of specific viral genes. Oesophageal carcinomas that originate from BPV-4-positive papillomatosis of the oesophagus have added to this interest (Campo, 1987).

Moreover, the use of BPV DNA in shuttle vectors and the episomal persistence of this DNA greatly increased the number of studies on these types of virus.

Retrospectively, the impact of research on BPV to this field was mainly through the analysis of BPV-induced cell transformation, the dissection of the viral genome and the structural and functional characterization of individual viral genes and gene products. The data obtained particularly facilitated early studies on HPV infections.

A second root of papillomavirus research that substantially influenced cancer research in general was the identification of papillomas and their infectious origin in wild cottontail rabbits in the early 1930s (Shope, 1933). After successful transmission of this infection to domestic rabbits, Rous and Beard (1934) soon noted that the initial papillomas that developed in these animals frequently converted to squamous-cell carcinomas. Occasionally, malignant conversion also occurred in the natural host (the cottontail rabbit). In a number of ingenious studies by this group, synergistic effects of viral and chemical carcinogens were observed, and the concept of tumour initiation was developed through the analysis of this system (e.g. Rous & Kidd, 1938; Rous & Friedewald, 1944). Although Rous conceptually preceded his contemporaries by several decades, the importance of his work was only acknowledged in 1966, when he received the Nobel Prize. Ito and Evans (1961) showed that the purified DNA of the cottontail rabbit papillomavirus (CRPV) induced squamous-cell carcinomas in rabbits, and thus directly revealed the carcinogenicity of a viral genome.

The research by Peyton Rous was not specifically driven by his interest in the infectious agent of rabbit papillomas. He strove to understand the mechanisms of the induction of cancer. The frequent progression of rabbit papillomas to squamous-cell carcinomas provided a model with which to analyse the steps in cancer development and to understand the synergistic effects of different classes of carcinogen. Interestingly, the rabbit papillomavirus system drew comparatively little attention subsequently. The literature today contains comparatively few studies of CRPV in comparison with BPV, epidermodysplasia verruciformis and genital HPV infections.

The analysis of human papillomatous lesions and their relationship with viral infections and carcinogenesis began much more slowly. Because of their cell-free transmission, the infectious etiology of of human warts was clearly established. However, warts were mainly regarded as a cosmetic nuisance and were not considered to be of significant medical interest.

A gradual change from this view began with the description of a syndrome that was reported by Lewandowsky and Lutz (1922) in Basel. They described a hereditary condition that was characterized by an extensive verrucosis, and which they named epidermodysplasia verruciformis. At sites of these patients that were exposed to sunlight (the forehead, the face, the back of the hands and arms), some of these papillomatous lesions converted to squamous-cell carcinomas. Lutz (1946) and subsequently Jablonska and Millewsky (1957) proved the viral etiology of these warts in auto-inoculation experiments. Schellender and Fritsch (1970) and Ruiter and van Mullem (1970) were particularly intrigued by the restriction of the development of squamous-cell carcinomas to sites

exposed to the sun. It was largely the work of Stefania Jablonska in Warsaw, Poland, that pointed to the possible role of papillomavirus particles seen in these warts as causal factors for the subsequent development of squamous-cell cancers of the skin (Jablonska *et al.*, 1972). A collaboration between the group in Poland and the group of Gérard Orth in Paris successfully demonstrated the presence of novel types of HPV, most frequently HPV 5, within epidermodysplasia verruciformis lesions and within biopsies of squamous-cell carcinomas from these patients. (Orth *et al.*, 1977, 1978, 1979).

Although HPV 5 represents the first HPV that is regularly detected in cutaneous squamous-cell cancers of these patients, the rarity of the syndrome, the difficulties in obtaining sufficient clinical materials for extensive studies and the absence of tissue culture lines from these carcinomas were probably the reasons for the somewhat limited interest in this condition. More than 25 years after the initial discovery of HPV 5 and related viruses, most questions relating to their etiological role and to the mechanism of their interaction in infected host cells in the course of carcinogenesis still remain open. Only in more recent years has the study of cutaneous HPV infections and their relationship to non-melanoma skin cancer in immunosuppressed and immunocompetent patients found increasing attention.

A fourth root of papillomavirus research resulted in the identification of specific HPV types as causative agents for cancer of the cervix, other anogenital cancers and a subset of oropharyngeal carcinomas. These investigations were initiated to investigate a viral etiology of cancer of the cervix. Techniques that were used for the detection of Epstein-Barr viral DNA in a 'virus-free' Burkitt lymphoma cell line (zur Hausen & Schulte-Holthausen, 1970) and in biopsies from Burkitt lymphomas and nasopharyngeal cancers (zur Hausen *et al*., 1970) were applied to cervical cancer in attempts to detect herpes simplex virus type 2 (HSV 2) DNA in these biopsies. By the end of the 1960s and the during the 1970s, serological studies had suggested a role of HSV 2 in this cancer (Rawls *et al*., 1968; Naib *et al*., 1969). The failure to find traces of HSV 2 DNA in these cancer biopsies prompted the search for other potential infectious candidates in the cause of this cancer, since its epidemiology provided good reasons to suspect an infectious etiology (zur Hausen, 1976).

A number of anecdotal reports of the malignant conversion of genital warts (condylomata acuminata) had appeared in the medical literature during the preceding 100 years and resulted in speculation on a possible causal role of HPV infections in cervical cancer that led to initial attempts to characterize the viral DNA in genital warts (zur Hausen *et al*., 1974, 1975; zur Hausen 1976, 1977). These and other studies led to the early discovery of the heterogeneity of the HPV family (Gissmann & zur Hausen, 1976; Orth *et al* 1977; Gissmann *et al*., 1977), which currently numbers more than 100 fully sequenced genotypes (de Villiers *et al*., 2004).

Meisels and Fortin (1976), Meisels *et al*. (1977) and Purola and Savia (1977) interpreted the koilocytotic lesions observed in what was considered to be a flat condyloma of the cervix as being the cytopathic effect of an HPV infection. At this time, they believed that these cellular modifications could be used to differentiate between 'benign'

virus-induced and premalignant 'virus-free' lesions. Della Torre *et al*. (1978) in Italy and Laverty *et al*. (1978) in Australia first demonstrated typical HPV particles in these condylomatous lesions of the cervix. In spite of their initial interpretation as markers for non-malignant progression of the respective lesions, these observations underlined the occurrence of HPV infections at cervical sites.

Although the eventual isolation of HPV DNA from genital warts (labelled as HPV 6; Gissmann & zur Hausen, 1980) and from laryngeal papillomas (HPV 11; Gissmann *et al.*, 1982) did not yield positive data for the causality of these viruses in cervical cancer, the use of their DNA in hybridization experiments, performed under conditions of reduced stringency, permitted the subsequent cloning of HPV 16 (Dürst *et al*., 1983) and HPV 18 (Boshart *et al*., 1984), the two HPV types most frequently found to date in cervical cancer. These findings led to a burst of activity in subsequent years. Among numerous other observations, these activities resulted in (*a*) the demonstration of a specific pattern of expression of the viral *E6* and *E7* genes in carcinoma tissues (Schwarz *et al*., 1985, Yee *et al*., 1985); (*b*) the finding that human keratinocytes are immortalized by high-risk HPVs that express the *E6* and *E7* genes (Dürst *et al*., 1987; Pirisi *et al*., 1987); (*c*) the discovery that E6 and E7 proteins interact with various cellular proteins, in particular with pRb and p53 initially (Dyson *et al*., 1989; Werness *et al*., 1990); (*d*) the direct demonstration that E6 and E7 proteins are responsible for the malignant phenotype of cervical carcinoma cells (von Knebel Doeberitz *et al*., 1992, 1994); and (*e*) large-scale epidemiological studies that identified high-risk HPV types as the major risk factor for cervical cancer (Muñoz *et al.*, 1992, 2003; Bosch *et al*., 1995).

Today, the practical consequences of these studies are increasingly apparent, since an increase of an order of magnitude in the quality of diagnostic approaches to validate early precursor lesions of cervical cancer and the development of preventive vaccines that can potentially prevent one of the major cancers in women are no longer unrealistic (reviewed in zur Hausen, 2002). The recent demonstration of the efficacy of virus-like particles in the prevention of persistent infection by HPV 16 in early precursor lesions of cervical cancer (Koutsky *et al*., 2002; Harper *et al*., 2004) has had a considerable impact on the development of prophylactic vaccines. Consequently, another cancer-preventive vaccine other than that for hepatitis B virus is now available (see Section 1.8).

It is probable that research on papillomaviruses will expand in the future; the role of these viral infections in at least some subsets of other anogenital and oropharyngeal cancers has become substantially more prominent over the past few years. In addition, the potential contribution to carcinogenesis (zur Hausen, 1999) of certain types of cutaneous HPV that prevent apoptosis in cells damaged by ultraviolet light (Thomas & Banks, 1998; Jackson *et al*., 2000) and/or target tumour-suppressor genes (Accardi *et al.*, 2006) has been hypothesized. Moreover, new perspectives have emerged for the prevention of these infections by the application of HPV testing technologies and vaccines.

Public health concerns

This volume of *IARC Monographs* provides a qualitative assessment of the carcinogenicity of HPVs and groups HPV types with regard to the strength of evidence of whether or not they cause cancer. However, there are evident and critically important differences in the absolute risk posed by individual HPV types within each class of carcinogen. Among the HPV viruses that have been classified as *carcinogenic to humans* (Group 1), the absolute risk for cancer associated with HPV 16 infection is of an order of magnitude higher than that for the weaker HPV types. Similar differences in risk are evident among the HPV types that have been classified as *probably* or *possibly carcinogenic to humans*. With regard to public health, it is important to comprehend that the term 'carcinogenic' is not uniform and must be interpreted carefully for each intended intervention. In the case of vaccination, it may be prudent to include all types of HPV that can be combined in an effective and affordable manner. However, in the case of screening, such a stratagem would have a seriously negative effect on clinical specificity and may mislead many women into believing that they are at high risk for cancers (Khan *et al.*, 2005; Schiffman *et al.*, 2005). When screening tests are applied to millions of women, a high ratio of false-:true-positive results is disconcerting: false-positive results in screening may lead to unnecessary colposcopies, biopsies and ablational/excisional treatments, which increases both health-care costs and morbidity (Sadler *et al.*, 2004).

Since the association between infection with HPV and the occurrence of cervical cancer has been well established, the sections in this monograph that cover cervical cancer are focused on an evaluation of the association between specific HPV types and this cancer. In these sections, a limited number of highly stringent techniques for the detection of HPV DNA were considered to be adequate to provide evidence of an association. For cancers at sites other than the cervix, the relationship with HPV infection was not so well established. Fewer studies have been conducted on the association between HPV infection and any of these cancers, and the number of cases reported is much smaller than that for cervical cancer. To enable a preliminary assessment of the association between HPV infection and cancers other than those of the uterine cervix, a wider variety of techniques and methods were considered to be acceptable for presentation in the respective sections.

Since the Working Group was convened in 2005, important innovations in HPV prophylaxis have occurered and these needed to be included in this volume (see Section 1.8). To date, two prophylactic vaccines have been developed and used in large multicentric trials (Harper *et al.*, 2004; Villa *et al.*, 2005; Harper *et al.*, 2006; FUTURE II Study Group, 2007; Garland *et al.*, 2007). One of the vaccines is Gardasil® (produced by Merck and Co.) that protects against HPV types 6, 11, 16 and 18 (quadrivalent) and another is Cervarix® (produced by GlaxoSmithKline) that protects against types 16 and 18 (bivalent). The quadrivalent vaccine was licensed in the USA by the Food and Drug Administration (US FDA, 2006) on 8 June 2006 for use in women aged 9–26 years; the European Medicines Agency (EMEA, 2006) gave official authorization for the marketing of this quadrivalent vaccine in the European Union on 20 September 2006. An application

has also been placed before this Agency to licence the bivalent vaccine. This prophylactic vaccination is expected to reduce the incidence of HPV-related genital diseases, including cervical, penile, vulvar, vaginal and anal cancer and precancerous lesions. In addition, a reduction in the incidence of the genital warts is observed among persons who receive the quadrivalent vaccine and a reduction in laryngeal papillomatosis can be anticipated among their children (Arbyn & Dillner, 2007). As a consequence, it is anticipated that a reduction in morbidity and mortality from HPV-related anogenital diseases will occur in populations who received the available prophylactic vaccines. However, the benefits of prophylactic vaccines in a broad public health perspective will be achieved only if such vaccines can be provided to those groups of women for whom access to cervical cancer screening services is most problematic. Therefore, the development of second-generation vaccines that are expected to be cheaper, easier to deliver and/or to provide T-cell response against pre-existing HPV infections is highly desirable.

References

Accardi, R., Dong, W., Smet, A., Cui, R., Hautefeuille, A., Gabet, A.S., Sylla, B.S., Gissmann, L., Hainaut, P. & Tommasino, M. (2006) Skin human papillomavirus type 38 alters p53 functions by accumulation of deltaNp73. *EMBO Rep.*, **7**, 334–340

Arbyn, M. & Dillner, J. (2007) Review of current knowledge on HPV vaccination: An appendix to the European Guidelines for Quality Assurance in Cervical Cancer Screening. *J. clin. Virol.*, **38**, 189–197

Black, P.H., Hartley, J.W., Rowe, W.P. & Huebner, R.J. (1963) Transformation of bovine tissue culture cells by bovine papilloma virus. *Nature*, **199**, 1016–1018

Bosch, F.X., Manos, M.M., Muñoz, N., Sherman, M., Jansen, A.M., Peto, J., Schiffman, M.H., Moreno, V., Kurman, R. & Shah, K.V. (1995) Prevalence of human papillomavirus in cervical cancer: A worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. *J. natl Cancer Inst.*, **87**, 796–802

Boshart, M., Gissmann, L., Ikenberg, H., Kleinheinz, A., Scheurlen, W. & zur Hausen, H. (1984) A new type of papillomavirus DNA, its presence in genital cancer biopsies and in cell lines derived from cervical cancer. *EMBO J.*, **3**, 1151–1157

Campo, M.S. (1987) Papillomas and cancer in cattle. *Cancer Surv.*, **6**, 39–54

Chen, E.Y., Howley, P.M., Levinson, A.D. & Seeburg, P.H. (1982) The primary structure and genetic organization of the bovine papillomavirus type 1 genome. *Nature*, **299**, 529–534

Ciuffo, G. (1907) Innesto positivo con filtrato di verruca volgare. *G. Ital. Mal. Ven. Pelle*, **48**, 12–17

Della Torre, G., Pilotti, S., de Palo, G. & Rilke, F. (1978) Viral particles in cervical condylomatous lesions. *Tumori*, **64**, 549–553

Dürst, M., Gissmann, L., Ikenberg, H. & zur Hausen, H. (1983) A papillomavirus DNA from a cervical carcinoma and its prevalence in cancer biopsy samples from different geographic regions. *Proc. natl Acad. Sci. USA*, **80**, 3812–3815

Dürst, M., Dzarlieva-Petrusevska, R.T., Boukamp, P., Fusenig, N.E. & Gissmann, L. (1987) Molecular and cytogenetic analysis of immortalized human primary keratinocytes obtained after transfection with human papillomavirus type 16 DNA. *Oncogene*, **1**, 251–256

Dyson, N., Howley, P.M., Münger, K. & Harlow, E. (1989) The human papilloma virus-16 E7 oncoprotein is able to bind to the retinoblastoma gene product. *Science*, **243**, 934–937

Ellermann, V. & Bang, O. (1908) [Experimentelle Leukämie bei Hühnern]. *Centralbl. F. Bakt. Abt. 1*, **46**, 595–609 (in German)

EMEA (2006) European Public Assessment Report for Authorised Medicinal Products for Human Use: Gardasil; European Medicines Agency (see http://www.emea.europa.eu/humandocs/Humans/EPAR/gardasil/gardasil.htm; accessed 04-09-2007)

FUTURE II Study Group (2007) Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N. Engl. J. Med.*, **356**, 1915–1927

Garland, S.M., Hernandez-Avila, M., Wheeler, C.M., Perez, G., Harper, D.M., Leodolter, S., Tang, G.W., Ferris, D.G., Steben, M., Bryan, J., Taddeo, F.J., Railkar, R., Esser, M.T., Sings, N.L., Nelson, M., Boslego, J., Sattler, C., Barr, E., Koutsky, L.A. & Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I Investigators (2007) Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N. Engl. Med.*, **356**, 1928–1943

Gissmann, L. & zur Hausen, H. (1976) Human papilloma viruses: Physical mapping and genetic heterogeneity. *Proc. natl Acad. Sci. USA*, **73**, 1310–1313

Gissmann, L. & zur Hausen, H. (1980) Partial characterization of viral DNA from human genital warts (condylomata acuminata). *Int. J. Cancer*, **25**, 605–609

Gissmann, L., Pfister, H. & zur Hausen, H. (1977) Human papilloma viruses (HPV): Characterization of four different isolates. *Virology*, **76**, 569–580

Gissmann, L., Diehl, V., Schultz-Coulon, H.J., & Zur Hausen, H. (1982) Molecular cloning and characterization of human papilloma virus DNA derived from a laryngeal papilloma. *J. Virol.*, **44**, 393–400

Harper, D.M., Franco, E.L., Wheeler, C., Ferris, D.G., Jenkins, D., Schuind, A., Zahaf, T., Innis, B., Naud, P., De Carvalho, N.S., Roteli-Martins, C.M., Teixeira, J., Blatter, M.M., Korn, A.P., Quint, W. & Dubin, G. (2004) Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: A randomised controlled trial. *Lancet*, **364**, 1757–1765

Harper, D.M., Franco, E.L., Wheeler, C.M., Moscicki, A.B., Romanowski, B., Roteli-Martins, C.M., Jenkins, D., Schuind, A., Costa Clemens, S.A., Dubin, G. & HPV Vaccine Study Group (2006) Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: Follow-up from a randomised control trial. *Lancet*, **367**, 1247–1255

zur Hausen, H. (1976) Condylomata acuminata and human genital cancer. *Cancer Res.*, **36**, 794

zur Hausen, H. (1977) Human papillomaviruses and their possible role in squamous cell carcinomas. *Curr. Top. Microbiol. Immunol.*, **78**, 1–30

zur Hausen, H. (1999) Immortalization of human cells and their malignant conversion by high risk human papillomavirus genotypes. *Semin. Cancer Biol.*, **9**, 405–411

zur Hausen, H. (2002) Papillomaviruses and cancer: From basic studies to clinical application. *Nat. Rev. Cancer*, **2**, 342–350

zur Hausen, H. & Schulte-Holthausen, H. (1970) Presence of EB virus nucleic acid homology in a 'virus-free' line of Burkitt tumor cells. *Nature*, **227**, 245–248

zur Hausen, H., Schulte-Holthausen, H., Klein, G., Henle, W., Henle, G., Clifford, P. & Santesson, L. (1970) EBV DNA in biopsies of Burkitt tumours and anaplastic carcinoma of the nasopharynx. *Nature*, **228**, 1056–1058

zur Hausen, H., Meinhof, W., Scheiber, W. & Bornkamm, G.W. (1974) Attempts to detect virus-specific DNA sequences in human tumors: I. Nucleic acid hybridizations with complementary RNA of human wart virus. *Int. J. Cancer*, **13**, 650–656

zur Hausen, H., Gissmann, L., Steiner, W., Dippold, W. & Dreger, I. (1975) Human papilloma viruses and cancer. *Bibl. Haematol.*, **43**, 569–571

IARC (1995) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 64, *Human Papillomaviruses*, Lyon

Ito, Y. & Evans, C.A. (1961) Induction of tumors in domestic rabbits with nucleic acid preparations from partially purified Shope papilloma virus and from extracts of the papillomas of domestic and cotton tail rabbits. *J. exp. Med.*, **114**, 485–491

Jablonska, S. & Millewski, B. (1957) [Zur Kenntnis der Epidermodysplasia verruciformis Lewandowsky-Lutz]. *Dermatologica*, **115**, 1–22 (in German)

Jablonska, S., Dabrowski, J. & Jakubowicz, K. (1972) Epidermodysplasia verruciformis as a model in studies on the role of papovaviruses in oncogenesis. *Cancer Res.*, **32**, 583–589

Jackson, S., Harwood, C., Thomas, M., Banks, L. & Storey, A. (2000) Role of Bak in UV-induced apoptosis in skin cancer and abrogation by HPV E6 proteins. *Genes Dev.*, **14**, 3065–3073

Khan, M.J., Castle, P.E., Lorincz, A.T., Wacholder, S., Sherman, M., Scott, D.R., Rush, B.B., Glass, A.G. & Schiffman, M. (2005) The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. *J. natl Cancer Inst.*, **97**, 1072–1079

von Knebel Doeberitz, M., Rittmüller, C., zur Hausen, H. & Dürst, M. (1992) Inhibition of tumorigenicity of cervical cancer cells in nude mice by HPV E6-E7 antisense RNA. *Int. J. Cancer*, **51**, 831–834

von Knebel Doeberitz, M., Rittmüller, C., Aengeneyndt, F., Jansen-Dürr, P. & Spitkovsky, D. (1994) Reversible repression of papillomavirus oncogene expression in cervical carcinoma cells: Consequences for the phenotype and E6-p53 and E7-pRB interactions. *J. Virol.*, **68**, 2811–2821

Koutsky, L.A., Ault, K.A., Wheeler, C.M., Brown, D.R., Barr, E., Alvarez, F.B., Chiacchierini, L.M. & Jansen, K.U. (2002) A controlled trial of a human papillomavirus type 16 vaccine. *N. Engl. J. Med.*, **347**, 1645–1651

Lancaster, W.D. & Olson, C. (1978) Demonstration of two distinct classes of bovine papilloma virus. *Virology*, **89**, 372–379

Laverty, C.R., Booth, N., Hills, E., Cossart, Y. & Wills, E.J. (1978) Noncondylomatous wart virus infection of the postmenopausal cervix. *Pathology*, **10**, 373–378

Lewandowsky, F. & Lutz, W. (1922) [Ein Fall einer bisher nicht beschriebenen Hauterkrankung (Epidermodysplasia verruciformis).] *Arch. Dermatol. Syph. (Berlin)*, **141**, 193–203

Lowy, D.R., Dvoretzky, I., Shober, R., Law, M.F., Engel, L. & Howley, P.M. (1980) In vitro tumorigenic transformation by a defined sub-genomic fragment of bovine papilloma virus DNA. *Nature*, **287**, 72–74

Lutz, W. (1946) [A propos de l'épidermodysplasie verruciforme.] *Dermatologica*, **92**, 30–43

Magelhaes (1920) Verruga dos bovideos. *Brasil-Medico*, **34**, 430–431

McFadyean, J. & Hobday, F. (1898) Note on the experimental 'transmission of warts in the dog'. *J. comp. Pathol. Ther.*, **11**, 341–344

Meisels, A. & Fortin, R. (1976) Condylomatous lesions of the cervix and vagina. I. Cytologic patterns. *Acta cytol.*, **20**, 505–509

Meisels, A., Fortin, R. & Roy, M. (1977) Condylomatous lesions of the cervix. II. Cytologic, colposcopic, and histopathologic study. *Acta Cytol.*, **21**, 379–390

Muñoz, N., Bosch, F.X., De Sanjose, S., Tafur, L., Izarzugaza, I., Gili, M., Viladiu, P., Navarro, C., Martos, C. & Ascunce, N. (1992) The causal link between human papillomavirus and invasive cervical cancer: A population-based case–control study in Colombia and Spain. *Int. J. Cancer*, **52**, 743–749

Muñoz, N., Bosch, F.X., De Sanjose, S., Herrero, R., Castellsague, X., Shah, K.V., Snijders, P.J., Meijer, C.J. & the International Agency for Research on Cancer Multicentric Cervical Cancer Study Group (2003) Epidemiologic classification of human papillomavirus types associated with cervical cancer. *New Engl. J. Med.*, **348**, 518–527

Naib, Z.M., Nahmias, A.J., Josey, W.E. & Kramer, J.H. (1969) Genital herpetic infection: Association with cervical dysplasia and carcinoma. *Cancer*, **23**, 940–945

Olson, C. & Cook, R.H. (1951) Cutaneous sarcoma-like lesions of the horse caused by the agent of bovine papilloma. *Proc. Soc. Exp. Biol.*, **27**, 281–284

Olson, C., Pamukcu, A.M., Brobst, D.F., Kowalczyk, T., Satter, E.J. & Price, J.M. (1959) A urinary bladder tumor induced by a bovine cutaneous papilloma agent. *Cancer Res.*, **19**, 779–783

Orth, G., Favre, M. & Croissant, O. (1977) Characterization of a new type of human papillomavirus that causes skin warts. *J. Virol.*, **24**, 108–120

Orth, G., Jablonska, S., Favre, M., Jarzabek-Chorzelska, M. & Rzesa, G. (1978) Characterization of two new types of HPV from lesions of epidermodysplasia verruciformis. *Proc. natl Acad. Sci. USA*, **75**, 1537–1541

Orth, G., Jablonska, S., Jarzabek-Chorzelska, M., Rzesa, G., Obalek, S., Favre, M. & Croissant, O. (1979) Characteristics of the lesions and risk of malignant conversion as related to the type of the human papillomavirus involved in epidermodysplasia verruciformis. *Cancer Res.*, **39**, 1074–1082

Pirisi, L., Yasumoto, S., Feller, M., Doniger, J., & Dipaolo, J.A. (1987) Transformation of human fibroblasts and keratinocytes with human papillomavirus type 16 DNA. *J. Virol.*, **61**, 1061–1066

Purola, E. & Savia, E. (1977) Cytology of gynaecologic condyloma acuminatum. *Acta Cytol.*, **21**, 26–31

Rawls, W.E., Tompkins, W.A., Figueroa, M.E. & Melnick, J.L. (1968) Herpesvirus type 2: Association with cancer of the cervix. *Science*, **161**, 1255–1256

Rous, P. (1911) A sarcoma of the fowl transmissible by agent separable from tumor cells. *J. exp. Med.*, **13**, 397–411

Rous, P. & Beard, J.W. (1934) Carcinomatous changes in virus-induced papillomas of the skin of the rabbit. *Proc. soc. exp. biol. Med.*, **32**, 578–580

Rous, P. & Friedewald, W.F. (1944) The effect of chemical carcinogens on virus-induced rabbit papillomas. *J. exp. Med.*, **79**, 511–537

Rous, P. & Kidd, J.G. (1938) The carcinogenic effect of a papillomavirus on the tarred skin of rabbits. I. Description of the phenomenon. *J. exp. Med.*, **67**, 399–422

Ruiter, M. & van Mullem, P.J. (1970) Behaviour of virus in malignant degeneration of skin lesions in epidermodysplasia verruciformis. *J. invest. Dermatol.*, **54**, 324–331

Sadler, L., Saftlas, A., Wang, W., Exeter, M., Whittaker, J. & McCowan, L. (2004) Treatment for cervical intraepithelial neoplasia and risk of preterm delivery. *J. Am. med. Assoc.*, **291**, 2100–2106

Schellender, F. & Fritsch, F. (1970) Epidermodysplasia verruciformis. Neue Aspekte zur Symptomatologie und Pathogenese. *Dermatologica*, **140**, 251–259

Schiffman, M., Khan, M.J., Solomon, D., Herrero, R., Wacholder, S., Hildesheim, A., Rodriguez, A.C., Bratti, M.C., Wheeler, C.M. & Burk, R.D. (2005) A study of the impact of adding HPV types to cervical cancer screening and triage tests. *J. natl Cancer Inst.*, **97**, 147–150

Schwarz, E., Freese, U.K., Gissmann, L., Mayer, W., Roggenbuck, B. & zur Hausen, H. (1985) Structure and transcription of human papillomavirus type 18 and 16 sequences in cervical carcinoma cells. *Nature*, **314**, 111–114

Shope, R.E. (1933) Infectious papillomatosis of rabbits. *J. exp. Med.*, **58**, 607–627

Thomas, M., Levy, J.-P., Tanzer, J., Boiron, M. & Bernard, J. (1963) Transformation in vitro de cellules de peau de veau embryonnaire sous l'action d'extraits acellulaires de papillomes bovins. *Compt. Rend. Acad. Sci. (Paris)*, **257**, 2155–2158

Thomas, M. & Banks, L. (1998) Inhibition of Bak-induced apoptosis by HPV-18 E6. *Oncogene*, **17**, 2943–2953

US FDA (2006) FDA Licenses New Vaccine for Prevention of Cervical Cancer and Other Diseases in Females Caused by Human Papillomavirus (see http://www.fda.gov/bbs/topics/NEWS/2006/NEW01385.html; accessed 04-09-2007)

Villa, L.L., Costa, R.L., Petta, C.A., Andrade, R.P., Ault, K.A., Giuliano, A.R., Wheeler, C.M., Koutsky, L.A., Malm, C., Lehtinen, M., Skjeldestad, F.E., Olsson, S.E., Steinwall, M., Brown, D.R., Kurman, R.J., Ronnett, B.M., Stoler, M.H., Ferenczy, A., Harper, D.M., Tamms, G.M., Yu, J., Lupinacci, L., Railkar, R., Taddeo, F.J., Jansen, K.U., Esser, M.T., Sings, H.L., Saah, A.J. & Barr, E. (2005) Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) virus-like particle vaccine in young women: A randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol.*, **6**, 271–278

de Villiers, E.-M., Fauquet, C., Broker, T.R., Bernard, H.-U. & zur Hausen, H. (2004) Classification of papillomaviruses. *Virology*, **324**, 17–27

Werness, B.A., Levine, A.J. & Howley, P.M. (1990) Association of human papillomavirus types 16 and 18 E6 proteins with p53. *Science*, **248**, 76–79

Yee, C., Krishnan-Hewlett, I., Baker, C.C., Schlegel, R. & Howley, P.M. (1985) Presence and expression of human papillomavirus sequences in human cervical carcinoma cell lines. *Am. J. Pathol.*, **119**, 361–366