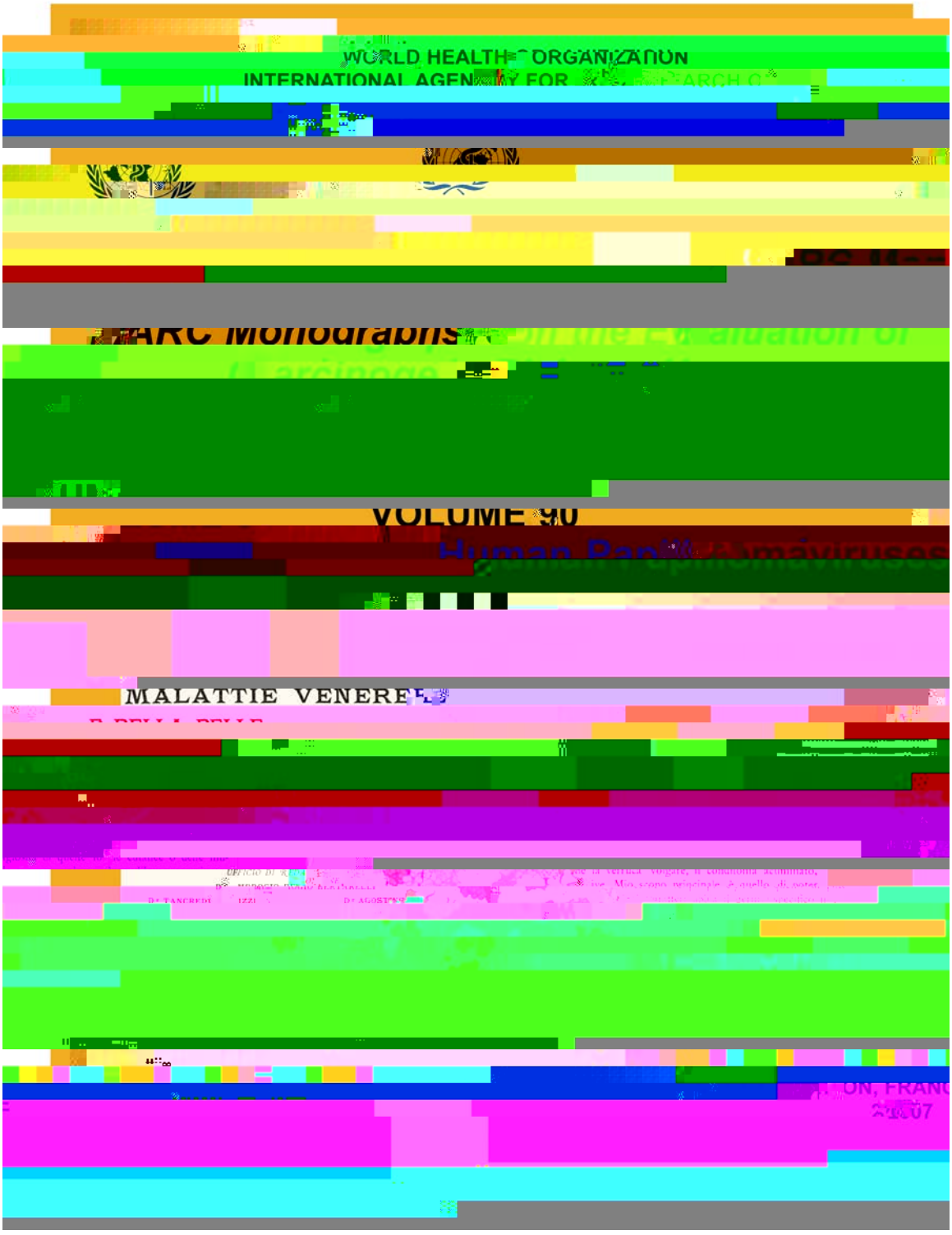
WORLD HEALTH ORGANIZATION
IARC Monographs
VOLUME 90
MALATTIE VENEREE

IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures, life-style factors and biological and physical agents, as well as those in specific occupations.

Cover Legend:

The cover shows the first page of a publication by Ciuffo (1907) who demonstrated — by auto-inoculation — that a cell-free extract of common warts contains an infectious agent, later to be identified as human papillomavirus (see text below).

Superimposed on this text is a molecular structural model of the HPV6 major capsid protein L1, with surface-exposed loops that contain highly antigenic epitopes (Oroczo *et al*, 2005; reproduced with permission; see also Section 2.2.1). Virus-like particles containing these epitopes have now been successfully used to develop prophylactic vaccines against several high-risk HPVs.

[cover design: Georges Mollon]

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PREAMBLE

plasms may in some circumstances (see p. 19) contribute to the judgement that the exposure is carcinogenic. The terms ‘neoplasm’ and ‘tumour’ are used interchangeably.

Some epidemiological and experimental studies indicate that different agents may act at different stages in the carcinogenic process, and several mechanisms may be involved. The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms. Information on mechanisms may, however, be used in making the overall evaluation (IARC, 1991a; Vainio *et al.*, 1992; see also pp. 25–27).

The *Monographs* may assist national and international authorities in making risk assessments and in formulating decisions concerning any necessary preventive measures. The evaluations of IARC working groups are scientific, qualitative judgements about the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which regulatory measures may be based. Other components of regulatory decisions vary from one situation to another and from country to country, responding to different socioeconomic and national priorities. **Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments and/or other international organizations.**

The

1998 gave recommendations as to which agents should be evaluated in the IARC Monographs series (IARC, 1984, 1989, 1991b, 1993, 1998a,b).

collected by the Carcinogen Identification and Evaluation Unit of IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems

agents present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with time and place. For biological agents, the epidemiology of infection is described.

Statements concerning regulations and guidelines (e.g., pesticide registrations, maximal levels permitted in foods, occupational exposure limits) are included for some countries as indications of potential exposures, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccines and therapy, are described.

8. STUDIES OF CANCER IN HUMANS

(*a*) *Types of studies considered*

Three types of epidemiological studies of cancer contribute to the assessment of carcinogenicity in humans — cohort studies, case–control studies and correlation (or ecological) studies. Rarely, results from randomized trials may be available. Case series

(*b*) *Quality of studies considered*

The Monographs are not intended to summarize all published studies. Those that are judged to be inadequate or irrelevant to the evaluation are genecevay omitted. They may be mentioned briefly, particulac24 hhen the information is considered to be a useful

and mixtures that cause cancer in experimental animals also cause cancer in humans, nevertheless, **in the absence of adequate data on humans, it is biologically plausible and prudent to regard agents and mixtures for which there is *sufficient evidence* (see**

(*c*) *Statistical analysis of long-term experiments in animals*

Factors considered by the Working Group include the adequacy of the information given for each treatment group: (i) the number of animals studied and the number examined histologically, (ii) the number of animals with a given tumour type and

organ toxicity, increased cell proliferation, immunotoxicity and endocrine effects. The presence and toxicological significance of cellular receptors is described. Effects on reproduction, teratogenicity, fetotoxicity and embryotoxicity are also summarized briefly.

Tests of genetic and related effects are described in view of the relevance of gene mutation and chromosomal damage to carcinogenesis (Vainio *et al.*, 1992; McGregor *et al.*, 1999). The adequacy of the reporting of sample characterization is considered and, where necessary, commented upon; with regard to complex mixtures, such comments are similar to those described for animal carcinogenicity tests on p. 18. The available data are interpreted critically by phylogenetic group according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micro-

may lead to misleading results in short-term tests have been discussed in detail elsewhere (Montesano *et al.*, 1986).

When available, data relevant to mechanisms of carcinogeot7n2.0hat do notin volvestructural hanige

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ions inc ranT*18.0001 0350.00871s in mtissuesrecombody fluids. Qurelit/Relrble, leotgReln wh[(V

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Group 2

This category includes agents, mixtures and exposure circumstances for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents, mixtures and exposure circumstances are assigned to either group 2A (probably carcinogenic to humans) or group 2B (possibly carcinogenic to humans) on the basis of epidemiological and experimental evidence of carcinogenicity and other relevant data.

Vol. 7. Some Volatile Halogenated Hydrocarbons (IARC Scientific Publications No. 68). Edited by L. Fishbein & I.K. O'Neill (1985)

Vol. 8. Some Metals: As, Be, Cd, Cr, Ni, Pb, Se, Zn (IARC Scientific Publications No. 71). Edited by I.K. O'Neill, P. Schuller & L. Fishbein (1986)

Vol. 9. Passive Smoking (IARC Scientific Publications No. 81). Edited by I.K. O'Neill, K.D. Brunnemann, B. Dodet & D. Hoffmann (1987)

*Vol. 10. Benzene and Alkylated Benzenes (*IARC Scientific Publications No. 85). Edited by L. Fishbein & I.K. O'Neill (1988)

Vol. 11. Polychlorinated Dioxins and Dibenzofurans (IARC Scientific Publications No. 108). Edited by C. Rappe, H.R. Buser, B. Dodet & I.K. O'Neill (1991)

Vol. 12. Indoor Air (IARC Scientific Publications No. 109). Edited by B. Seifert, H. van de Wiel, B. Dodet & I.K. O'Neill (1993)

IARC (1979) *Criteria to Select Chemicals for* IARC Monographs (IARC intern. tech. Rep. No. 79/003)

IARC (1982) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to*

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 frequen025 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)

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 beillticipated among their children (Arbyn & Dillner, 2007). As a consequence, it is llticipated that a

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

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 *Int.* , **13**, human *J.* 6

zur Hausen, H., Gissmann, L., Steiner, W., Dippold, W. & Dreger, I. (1975) Human papilloma viruses *Bibl.* , **43**, and *Haematol.* 569–57

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

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

MONOGRAPH ON
HUMAN PAPILLOMAVIRUSES

HUMAN PAPILLOMAVIRUSES

1. Human Papillomavirus (HPV) Infection

1.1 Evolution, structure and molecular biology

P

i

cervical cancer lead to the selective expression of *E6* and *E7* (Schwarz *et al.*, 1985; Yee *et al.*, 1985), which is a hallmark of cervical cancers. Whether viral integration alters cellular gene expression in any biologically relevant manner remains unclear. In a recent

to the taxonomic groupings, which today are widely accepted. Phylogenetic assemblages

‘species’ is biologically useful, as these are natural taxa based on the close phylogenetic relationship of certain types and because such species typically assemble papillomavirus types that have common biological and pathological properties, a requirement of the

Table 1 (contd)

Genus	Species	Type species
		Otherpillomav

Table 1 (contd)

Genus	Species

there is only one type in that taxon. Table 1 is an important reference that groups together (with the type species in many type-rich taxa) all those HPV types that belong to the same species and will presumably have properties similar or identical to the type species, but cannot be studied (for purposes of basic research, drug development and vaccination) as intensely as the type species. As an example, species No. 9 groups — with the type species HPV 16 — the HPV types 31, 33, 35, 52, 58 and 67, which have been studied to a lesser extent (with the exception of HPV 31) but which probably have similar biological and pathological properties as HPV 16.

Several hundred papillomavirus types have been partially identified in the form of short DNA fragments, but interest in isolating full-length genomes appears to be declining. The number of HPV types isolated and fully characterized now exceeds 100. A regulated taxonomic description of non-human papillomaviruses is particularly necessary because it is extremely probable that only a tiny fraction of all animal papillomavirus types have been identified or isolated. The present methodology used for the detection of papillomavirus types is very limiting, as it is based on the information available from known types. Hopefully, future efforts will be directed towards identifying additional types that are very distantly related to the known genera. An example of the large diversity of animal papillomaviruses are the two recently described types from birds, both of which lack traditional E6 and E7 ORFs (Tachezy *et al.*, 2002a,b; Terai *et al.*, 2002) and are less closely related to any mammalian papillomavirus type than they are to one another. Several of the papillomavirus types that presently appear as single species within a genus have in the past been identified only because of the availability of lesions that harbour

(*a*)

(African) branch and all of the German and most of the Singaporean variants were assigned to the other (Eurasian) branch. While some German and Singaporean variants were identical, each group also contained variants that formed unique branches. In contrast to the internal homogeneity within the groups of the Singaporean, German and Tanzanian variants, the Brazilian variants were clearly divided between the two branches. Exceptions to this were the seven Singaporean isolates with mutational patterns typical of

variants from Amazonian Indians are the closest relatives to those from Japanese and Chinese patients and suggest that a single point mutation in the phylogenetically evaluated

terminal domain is essential for regulation of transcription and viral DNA replication through the interaction with E1 protein (Desaintes & Demeret, 1996).

The majority of studies have demonstrated that expression of HPV E2 protein at various levels in human cells results in the repression of transcription from the viral promoter. In one study, low levels of HPV 16 E2 were shown to activate transcription in primary human epithelial cells, but repression occurred at high levels (Bouvard *et al.*, 1994a). One of the proposed mechanisms for repression by E2 is that it binds to the E2-BS adjacent to the TATA box of the LCR and thus interferes sterically with the binding of the TATA-binding protein (TBP) to the same site as has been shown for BPV-1 E2 (Dostatni *et al.*, 1991) and HPV 18 E2 (Steger & Corbach, 1997). In support of this

HPV 11-infected genital epithelium is abnormal and more fragile than that of uninfected tissue (its thickness is ~65% that of uninfected epithelium) and its association with this compromised CCE suggests that E4 could interfere with the normal assembly of CCE and aid the release of progeny virus (Brown & Bryan, 2000).

(iii) *E4 and mitochondria*

In epitheliimet3 86fi2f p E4 calso bindsmitochondria

(iv) *E4 and nuclearetdomain10*

Nuclearetdomain(ND) 10e tre nucleareisre/uures that -contai numeeros proteins,

tional co-activators, proteins involved in cell polarity and motility, tumour suppressors and inducers of apoptosis, and DNA replication and repair factors. Several proteins belong to more than one class.

Proteins that belong to the first class are p300 (Patel *et al.*, 1999; Zimmermann *et al.*, 1999), myc (Gross-Mesilaty *et al.*, 1998) and interferon regulatory factor 3 (Ronco *et al.*,

transcription factor, activator protein 1 (AP-1) (Antinore *et al.*, 1996), insulin-like growth factor binding protein 3 (Mannhardt *et al.*, 2000), TBP (Massimi *et al.*, 1997; Phillips & Vousden, 1997), TBP-associated factor-110 (Mazzarelli *et al.*, 1995) and a novel human DnaJ protein, hTid-1 (Schilling *et al.*, 1998).

Another important aspect of the biw[biw[b6763g

by HPV-infected patients mostly recognize conformational epitopes on the surface of the virus (Galloway, 1992, 1994).

bodies (Christensen *et al.*, 1991; Campo *et al.*, 1997b; Kawana *et al.*, 1999, Roden *et al.*,

(Fisher *et al.*, 1996; Baay *et al.*, 1995, 1997). This has led to the hypothesis that antibodies

wide range of estimated sensitivities and specificities have been reported; although all studies showed sensitivities of more than 60%, most reported relatively low specificities and positive predictive values. However, all of them reported high negative predictive values, which has important implications for national screening programmes. One very large (n > 50 000) study compared VILI with VIA (Sankaranarayanan *et al.*, 2004a,b; IARC, 2005) and found that VILI was more sensitive than VIA and equally specific.

For low-resource countries, DVI has several potential advantages, the most important of which are the simplicity of the test, its low cost, the fact that primary health care providers can be trained to perform the test in a relatively short period of time and that an immediate result is provided, which avoids the inevitable loss to follow-up that occurs when the results of the test or treatment of lesions is delayed (Sankaranarayanan *et al*., 1998, 1999; Denny *et al*., 2002; Sankaranarayanan *et al*., 2004a).

A disadvantage of DVI is the difficulty of standardizing quality control, which is

(LSIL) versus HSIL and cancer on colposcopy, the corresponding results were 85%, 69% and 82%. This suggests that, independent of prevalence and compared with low-grade lesions, high-grade lesions and cancer are diagnosed with higher sensitivity. Olaniyan

Since HPV infections supersede cell cycle controls, the immune detection of cell

HUMAN PAPILLOMAVIRUSES

achieved by hybridization with type-specific probes that can be performed in different formats and analysis of restriction-fragment length polymorphism by gel electrophoresis (Bernard *et al.*, 1994a), dot-blot hybridization (Bauer *et al.*, 1991), line-strip assays (Gravitt *et al.*, 1998) and microtitre-plate assays (Jacobs *et al.*, 1997; Kornegay *et al.*, 2001) which can be automated. Another pair of consensus primers is available that amplifies a smaller fragment of the L1 gene (65 bp compared with 150 bp for the GP primers and 450 bp for MY09/11). This short PCR fragment (SPF)-PCR is designed to discriminate between a broad spectrum of HPVs in an ELISA format (Kleter

or in reverse line-blot hybridiz

The SPF and GP5+/6+ syster

in detecting very high frequencies of known as well as new EV-HPV types in cutaneous lesions of renal transplant recipients.

An alternative PCR approach (primers FAP59/64) that is targeted to cutaneous HPV amplifies a broad spectrum of these HPV types from clinical samples, including new types, such as HPV 92 (Forslund *et al.*, 1999, 2003a,b).

(*b*) *Commercial nucleic acid hybridization methods (Hybrid Capture™)*

This is the only commercially available assay for the detection of HPV DNA that has been approved by the Food and Drug Administration in the USA. The two previous versions that had a low sensitivity have now been replaced by Hybrid Capture 2, one of the most extensively used HPV tests in both epidemiological settings and clinics.

Hybrid Capture 2 is based on hybridization in solution of long synthetic RNA probes

molecules and therefore cannot be carried out on all biological specimens, particularly not those derived from fixed tissues in which degradation of DNA is often observed. They are also technically cumbersome and are not suitable for large-scale population studies.

In these techniques, high-molecular-weight, highly purified DNA is digested with

fixed and submitted to hybridization with specific HPV probes. Depending on the label incorporated in the probes, different signal detection systems can be used. To increase the sensitivity of the test, radioactively labelled probes are commonly used, which limits the application of southern blot to certain laboratory conditions. Despite the stringent requirements, southern blot is considered to be the golden standard for the evaluation of HPV genomes, since ittion identify HPV genomes in a specimen accurately and specifically; moreover, it determines the physical status of the genomes (episomal or integrated) and gives a semiquantitative measure of viral load.

Table 9 (contd)

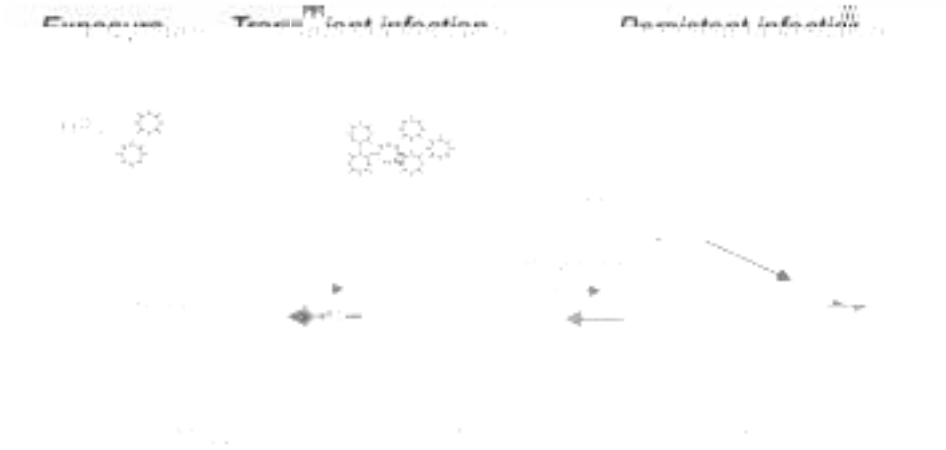
Reference	No. of samples	Type] 7 Tm

et al., 1998, Yuan *et al.*, 2001). To circumvent the tedious procedures of production and purification and the varying yields and quality of VLPs from different HPV types, an alternative ELISA for HPV capsid antibody has been developed based on the affinity of GST–L1 fusion proteins purified on glutathione-coated plastic surfaces. It has been shown

assays (Wideroff *et al.*, 1995). Human anti-capsid antibody responses were found to be directed against epitopes on the Ll protein, because addition of L2 protein did not augment

a very large number of experimental studies on immunological cross-reactivity of Jensonf 1980;

Figure 8. Natural history of preclinical abnormalities of the cervix



From IARC (2005)
[a] Classical histological features of CIN1 are uncommon among women who have transient infections.
[b] This entity is not as well defined as CIN3.

The major steps known to be necessary for cervical carcinogenesis include HPV infection, persistence of that infection, progression to precancerous lesions and eventually invasion. Provided that the latter step has not taken place, this process is reversible by the clearance of HPV infection and regression of precancer, which happen in many women who have ever experienced HPV infection. As discussed below, HPV infection might usefully be separated into low-viral load infections that engender no microscopically evident abnormalities and higher-viral load infections that do.

As described in Section 1.1, over 100 types of HPV exist, of which more than 40 are mucosotropic viruses that infect the anogenital and upper aerodigestive tracts (de Villiers *et al.*, 2004a). Among the latter, approximately 15 are considered to be high-risk types. The various HPV types do not all occur in different populations at the same rate; therefore, although much is known about the epidemiology and natural history of HPV infections, little is known about the long-term characteristics of infections at the type-specific level, e.g. the assessment of viral persistence. Most knowledge refers to HPV
frequently found in tumours in the general population, and is discussed separately below.

1.4.2 *Transmission and acquisition*

(*a*) *Horizontal transmission*

The most common mode of horizontal transmission of anogenital HPV is by sexual activity through contact with infected cervical, vaginal, vulvar, penile or anal epithelium. In the early 1950s, Barrett *et al.* (1954) reported that genital warts developed within 4–6

warts was identified by Sonnex *et al.* (1999); their findings supported the possibility of HPV transmission by digital–genital contact.

The non-sexual mode of transmission of genital HPV remains a controversial issue. Most studies among sexually inexperienced young women (Andersson-Ellström *et al.*, 1994; Dillner *et al.*, 1999) demonstrated that non-sexual transmission of HPV is uncommon. However, a number of studies (Pao *et al.*, 1992; Cason *et al.*, 1995; Winer *et al.*, 2003) reported that HPV might occasionally be transmitted through modes other than sexual activity. The possible non-sexual routes include vertical transmission, fomites and skin contact (Mindel & Tideman, 1999; Frega *et al.*, 2003).

(*b*) *Vertical transmission*

Vertical transmission occurs when a parent conveys an infection to its unborn offspring, including a special form of vertical transmission — perinatal infection. Vertical transmission of HPV from mother to child was first suggested in the 1950s (Hajek, 1956) and was subsequently supported by several other studies (Cason *et al.*, 1995; Puranen *et al.*, 1997; Tseng

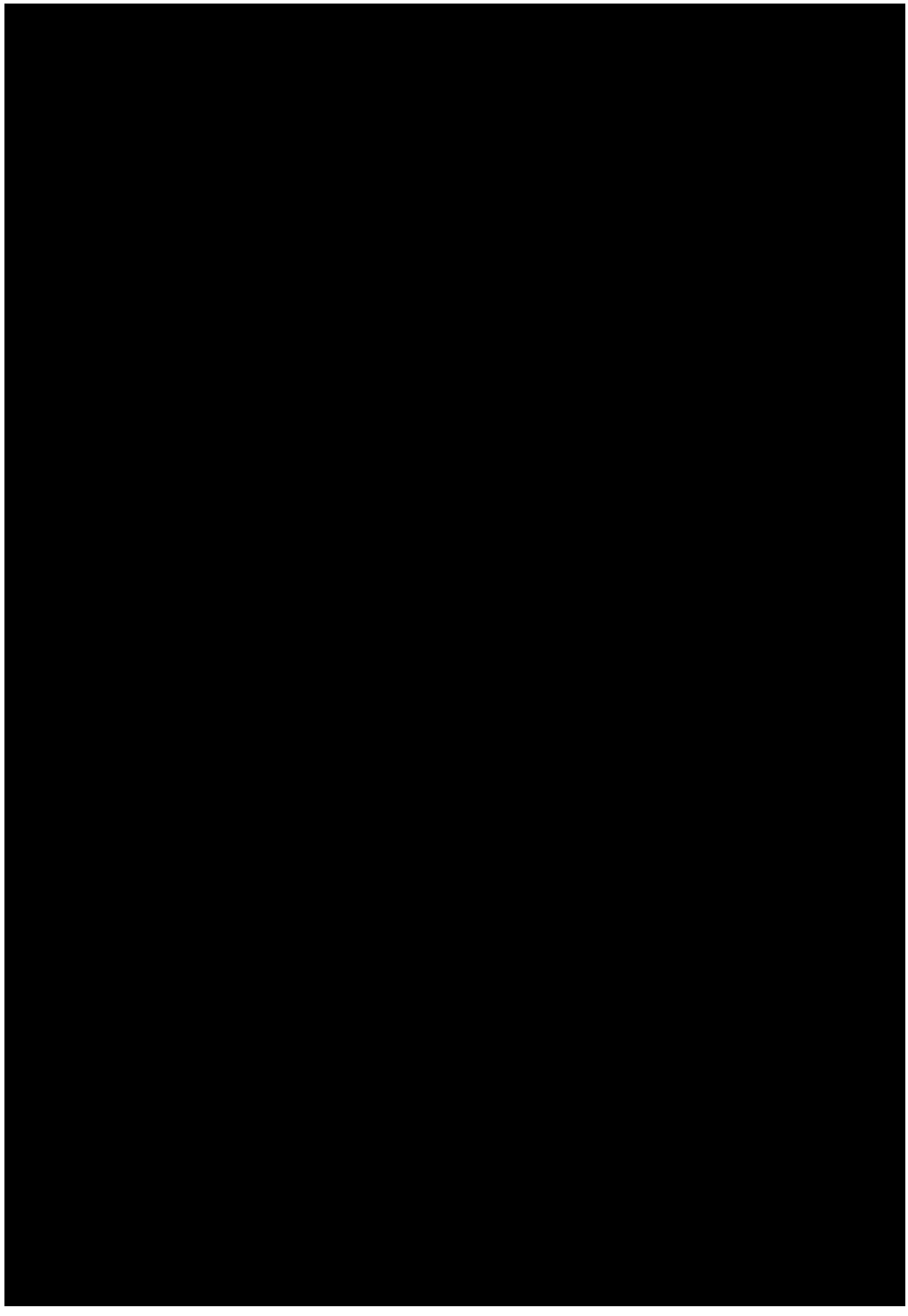


Table 11 lists the most relevant studies of the prevalence of HPV in cytologically negative women (also excluding atypical squamous cells of undetermined significance [ASCUS]; see the footnote for exceptions) for several populations worldwide with various age ranges. The restriction of surveys on the prevalence of type-specific HPV DNA to cytologically negative women was intended to minimize any influence of longer duration of lesions related to specific types. The selected studies were population–surveillance-

Table 11. Rates of detection of HPV DNA by polymerase chain reaction (PCR) amplification among women with cytologi-

Specific HPV type (%)

1.4.4 *Incidence, persistence and clearance*

Many prospective epidemiological studies published since the last evaluation (IARC, 1995) provide data on incident infection (although such events may represent latent infections that for some reason become detectable again) and duration of infections by different types. Tables 13 and 14 show the main characteristics of these studies and illustrate the estimates of incidence and duration by type, respectively.

Table 13 summarizes the incidence of type-specific HPV infection (infection per 100

Prevalence studies that address the oral mucosa in adults showed very diverse results that ranged from 0 to 60%. This was also true for the few studies among children. It has

In order to evaluate and update the 1991 Bethesda classification, the 2001 Bethesda system was established. The terminology used was agreed after a review process in which more than 400 cyto-/histopathologists, gynaecologists, cytotechnologists, epidemiologists, health physicians and lawyers were involved. The dichotomous division of SIL into LSIL and HSIL was based on virological, molecular and clinical observations that LSIL is more frequently a result of a transient HPV infection whereas HSIL is more frequently associated with viral persistence and high risk for progression. LSIL includes

gland-within-gland pattern. High-risk HPVs are found in nearly all adenocarcinomas *in situ* and in adenocarcinomas of the cervix. HPV 18 is more frequent in this disease than in squamous-cell carcinoma (Zielinski *et al.*, 2003).

(*e*)

more, in retrospective studies that analysed previous smears from women with cervical cancer for the presence of HPV and of abnormal cells, it was noted that (*a*) many women had smears with abnormal cells that had been overlooked by the cytopathologist/cytotechnician; and (*b*

et al., 1994; Williams *et al.*, 1994; Wright *et al.*, 1994; Cappiello *et al.*, 1997; Sun *et al.*, 1997; Cu-Uvin *et al.*, 1999; Ellerbrock *et al.*, 2000).

(iv) Patients in whom HPV-related lesions have been treated may have detectable HPV DNA despite normal cytological, colposcopical and histological findings. Such patients are at increased risk for recurrence compared with HPV DNA-negative controls (Koutsky *et al.*, 1992; Nobbenhuis *et al.*, 2001).

(*b*) *Low-grade CIN*

A number of studies reported that it was possible to distinguish between virus-containing flat condyloma and a true 'virus-free' CIN lesion (Meisels & Fortin, 1976). However, subsequent studies found that the distribution of HPV types in those lesions designated as flat condyloma and CIN was indistinguishable (Kadish *et*

& Munger, 2002). The characteristic koilocyte of low-grade CIN is generally absent or markedly attenuated in high-grade lesions.

One of the most important features that distinguishes high-grade CIN from low-grade

2004). Whereas SIL occurs on the squamous side of the cervical squamo-columnar junc-

well-differentiated. High-risk HPV types are found principally in the warty and basaloid types of VIN and are uncommon in the well-differentiated type (van Beurden *et al.*, 1995).

The basaloid type is composed generally of small, faim10uniform cwelsn tatd arehtypr-.

1.6.1 *Anogenital area*

The terms condyloma acuminatum and genital wart are synonyms. For many years, exophytic warts were the only recognized HPV-associated manifestations of HPV infection in the genital tract. Increasing attention to the lower female genital tract with the exten-

and are sometimes confused with cancer owing to a bizarre pattern of vessels (Coppleson,

Distal disease can develop and portends a poorer prognosis owing to its inaccessibility.

1.6.4 *Conjunctiva*

Conjunctival papilloma is a benign and common tumour of the stratified squamous epithelium of the conjunctiva (Santos & Gómez-Leal, 1994). Conjunctival papillomas are known to occur in both children and adults, but they are most common among peopl8 86.709 -378.8 al. mostTD1 126.61.2 -51njunctj/Fmmv25ur in ival86; McDonnell mostTD0.00017.7076 njunctiva

found by PCR in 74/112 (66%) warts of men who worked in meat-processing plants (abattoir workers and butchers) (Keefe *et al*., 1994).

Filiform or papillomatous common warts that are found most frequently on the face, lips, eyelids or nares contain HPV 1, 2 or 7 (Jablonska *et al*., 1985; Egawa *et al*., 1993a). HPV 7 was found in two individuals with generalized or extensive facial warts with filiform appearance (de Villiers *et al*., 1986a).

Flat or plane warts, which can appear at different locations on the body and can form a linear arrangement (i.e. Koebner warts), are associated with HPV 2, 3, 10, 26, 27, 28, 29 or 41 (Melton & Rasmussen, 1991).

Deep plantar warts, i.e. hyperkeratotic plaques or nodules on the plantar surface of the foot, are usually positnd inor HPV 1 or 4 (Rübben*et al*., 1993). HPV-associated epidermal cysts of the sole of the feet from 32 Japanese patient
1992; Egawa *et al*., 1994). HPV 1 and 63 were presen
wart (Egawa *et al*., 1993b).

Table 18. Efficacy of treatment regimens for HPV-related warts and neoplasia

Therapy (reference)	Type of application	Regien	Maximum duration	Clearance [a]

(Kourounis *et al*., 1999). In addition, large lesions may be treated and the depth of cryonecrosis is more suitably adapted (Scala *et al*., 2002).

Laser surgery

The carbon dioxide laser is a high-precision, non-blood-letting light scalpel used for the incision and excision of tissues and to seal small blood vessels. Healing occurs by granulation and the post-operative period is relatively painless for the patient. The risk for post-operative morbidity and complications is low (Bar-Am *et al*., 1993). Hyperthermia induced by a neodymium:yttrium–aluminium garnet (Nd:YAG) laser or a 585-nm pulsed dye laser has been used for the treatment of condylomata (Volz *et al*., 1994; El-Tonsy *et al.*, 1999; Kenton-Smith & TD0 sa2A-0.1(n, 1999).)]TJ/F5 1 Tf11 0 0 11 109.665 482.998 Tm(Photo

Excision techniques

Excision techniques that involve surgical removal (followed by histological analysis)

stage IIA disease, is approximately 40–50% for patients with stage IIB and stage III

Table 20. Options for the treatment2of cervical cancer

The aim of therapeutic vaccines is to eradicate infected cells or reduce their number. Initial strategies were targeted to eliminate residual malignant cells in patients with cervical cancer, although the prevention of progression of HSIL, LSIL or even cytologically normal HPV-infected cells are all possible end-points. Therapeutic vaccines have also been used as an approach to eradicate genital warts. Once HPV infection has been established, it is improbable that antibodies play a role in the eradication of infected cells. Cytotoxic T lymphoen es (CTL) are the primary effectors of tumour eradication. Many strategies for the generation of CTL involve the stimulation of antigen-presenting cells (to process the tumour or viral antigens, and present them in the context of the MHC receptor) and adhesion of co-stimulatory moleculec vacproduce anti-tumour lymphoen es. In many cases, HPV-associated tumours express only the E6 and E7rese in t of therapeuticticticti61ru inmostumour5 Tw68

As discussed in Section 1.8, chimeric VLPs that contain a linked segment of E7 have been developed, and have been shown to induce specific HLA T cells in humans after in-vitro vaccination (Kaufmann *et al.*, 2001).

The use of viral vectors to introduce genes for vaccination is an effective way to stimulate many branches of the immune system. Recombinant vaccinia viruses, which have the advantage of being able to carry large inserts and not persisting in the host, have been widely used. The disadvantage of this method is that older individuals may have a pre-existing immunity to vaccinia virus which reduces the response; in addition, vaccinia virus may pose a risk to immunosuppressed recipients. A recombinant vaccinia virus that expresses the HPV 16 and 18 E6 plus E7 genes was created. In order to circumvent the potential problem of introducing oncogenes, the E6 and E7 proteins were mutated to block their binding to key tumour suppressors (Boursnell *et al.*, 1996). In an initial study, the vaccine was found to be safe when administered to nine patients with late-stage cervical bto 199; s fmst,of the iatients wire mmmunosuppressed ,oncy uoe peveloped,]TJT*00.01 5 Tv

1.8 Prophylaxis[1]

The discovery that the major capsid protein L1 can assemble into VLPs that are structurally and immunogenically indistinguishable from authentic virions and studies aimed at the characterization of HPV conformational epitopes that induce neutralizing antibodies that can block new infection have had a considerable impact on the development of prophylactic vaccines (see Section 1.2). This section highlights some important innovations in prophylaxis that have occurred since the Working Group was convened, in 2005.

To date, two prophylactic vaccines have been developed and tested 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). Both are based on the recombinant expression and self-assem-

The minor capsid structural viral protein L2 has been shown to elicit antibodies thatneutralize both h

Case–control designs typically rely on the assessment of HPV DNA at the time of diagnosis for cases and at a similar age for controls. Since persistence of HPV DNA is a

differentially in cases compared with controls, and thus overestimates the odds ratio for that specific type.

Serological data have yielded useful information for the assessment of exposure to HPV. HPV serology based on virus-like particles (VLPs) is a relatively type-specific but insensitive measure of exposure. Therefore, seropositive women appear to have been truly exposed to HPV, although the anatomical site of infection cannot be ascertained. Extremely large archives of serum specimens have permitted nested case–control studies of cervical cancer and CIN3 with an exceptional statistical power that is currently lacking in studies of DNA. Serology is included here to define HPV-exposed study populations for the consideration of etiological co-factors such as tobacco smoking or *Chlamydia trachomatis*e, serology isdiscussred withere(erecre to sites ther thnr the cervxo for)]TJ-4.778 -1.1818 TD0.255

2.2 Cancer of the cervix

2.2.1 *Historical perspective*

Table 24. Triage of LSIL: short-term outcome of ≥

(see Table 25). In HPV 16-positive women with ASCUS, the risk for ≥ CIN2 within 2 years was 16.1 (95% CI, 12.0–21.7) times higher than that in high-risk HPV-negative women. Positivity for other high-risk types was associated with a relative risk of 6.1 (95% CI, 4.5–8.3), which was similar to that associated with ASCUS that was unqualified by HPV. The relative risk associated with HPV positivity was lower in LSIL patients than

66 or 68, using PCR with GP5+/6+ primers). Sixty-nine (31.9%) of these high-risk HPV-

As the severity of cervical lesions increases, not only does the overall prevalence of HPV rise greatly, but the relative frequency of different HPV types also changes substan-

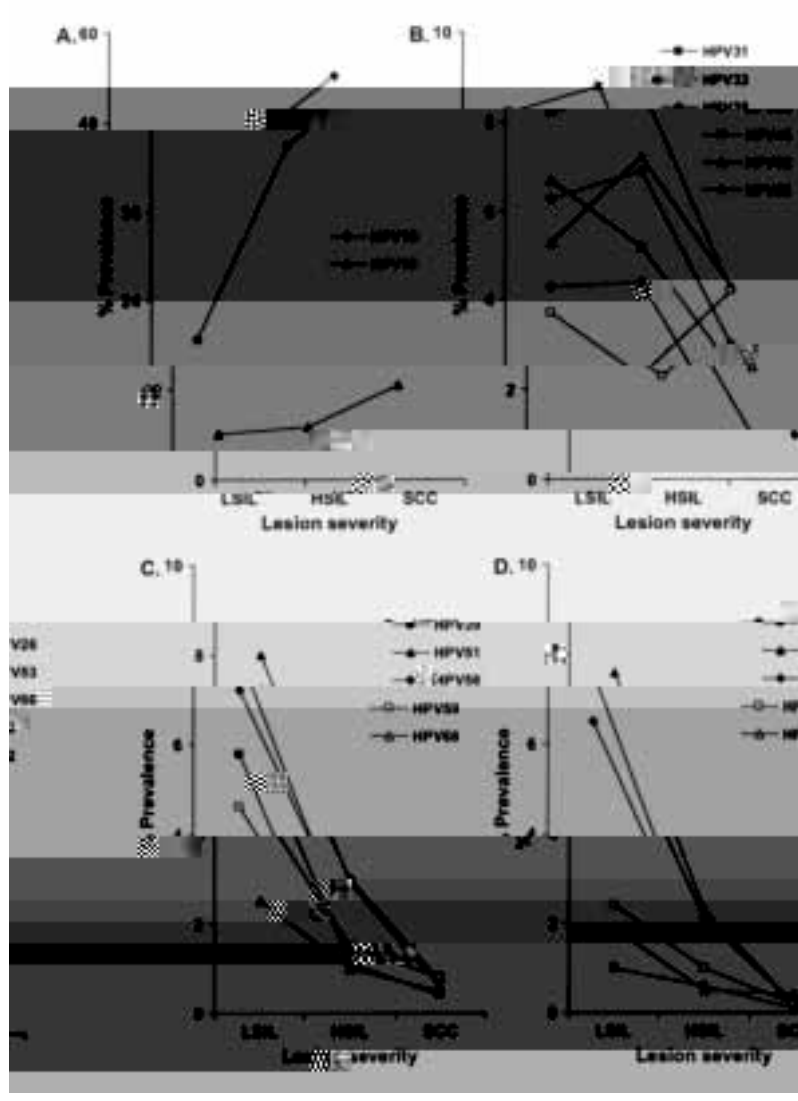
Table 26. Distribution of HPV types across cervical lesions of increasing severity

TSIL

common iu1TSIL than iu1squamous-cell carcinoma. A ratio of approximately 10 between TSIL and1squamous-cell carcinoma was also found1for low-risk types HPV 6, 11 and170. The type-specific findings1for adeno- or adenosquamous carcinoma were consistent with those observed1for squamous-cell carcinoma except1for the more marked1enrichment of HPV 18 from1TSIL to adeno- or adenosquamous than to squamous-cell carcinoma.

Comparisons of HPV distribution iu1international cross-sectional studies face several problems,1including differences iu1the accuracy iu1cytological/histological classification and1viral detection, as well as non-negligible heterogeneity iu1the distribution of HPV types across different populations.

Figure 12. Prevalence of HPV types in cervical lesions of increasing severity



Modified from Franceschi & Clifford (2005b)

Of particular note since the previous review (IARC, 1995), a high prevalence of HPV 35 has been reported in invasive cancer from previously unstudied regions in East Africa (19%) (Naucler *et al.*, 2004) and India (6%) (Castellsagué *et al.*, 2001; Franceschi & Clifford, 2005). Furthermore, a failure in the sensitivity of MY09/11 PCR primers to detect HPV 35 has also been identified, so that the prevalence of HPV 35 may have been underestimated in some of the previous case series (Iftner & Villa, 2003).

Nevertheless, the picture that emerges from the IARC systematic reviews suggests that: HPV 16 and 18 are substantially enriched in squamous-cell carcinoma compared with LSIL; some high-risk types are approximately equally represented (HPV 33 and 45) or moderately over-represented (HPV 31, 52 and 58) in LSIL than in squamous-cell carcinoma; and HPV 26, 53, 66, 73 and 82, which are not currently included in the DNA tests approved by the US Food and Drug Administration, are extremely rare in squamous-cell carcinoma, but this is also the case for some of the types that are currently included (e.g. HPV 39, 51 and 56).

In conclusion, the available evidence from cross-sectional comparisons of the distribution of HPV types in cervical lesions of increasing severity lends strong support to the notion that the risk that a woman will develop HSIL or cervical cancer varies substantially according to the specific HPV type with which she is infected.

(*b*) *Case–control studies*

Since the last review (IARC, 1995), a number of larger case–control studies have been completed that allow a more accurate evaluation of the type-specific risk of a number of additional HPV types. Only studies that reported HPV DNA results by type, as assessed by PCR, and by case and control status and included histologically confirmed end-points are reviewed and evaluated separately by disease end-point. Over the past 10 years, several specific and sensitive PCR-based methods of HPV detection have been used in epidemiological studies, and it is important to highlight that the various PCR systems differentially amplify different HPV types in disease and non-disease samples. Therefore, caution must be taken in interpreting the relative strength of the association between specific HPV types and risk for disease across studies. Due to the relative infrequency of some HPV types, smaller case–control studies have reported unstable risk estimates for certain HPV types. Greater emphasis is therefore given to larger studies and those that reported pooled data in relation to the risk associated with types other than HPV 16 and 18. As far as possible, the risk estimates presented here focus on those associated with single HPVinfections only.taken in int346 Tw

followed by PCR-based sequencing that detected several different HPV types. However, due to the rarity of most HPV types, risk estimates for disease could only be generated for

72.4% in cases and 14.0% in controls. The 168 women with HPV 16- and 18-positive cervical cancers were compared with 250 HPV-negative controls. The odds ratio for HPV 16 was 83 (95% CI, 39–232) for squamous-cell cancer and 24 (95% CI, 8.7–76) for

central laboratories using PCR-based assays. PCR primers for the *L1* gene, MY09/11, were used in the Colombian and Spanish studies and the GP5+/6+ general primer system

scrapings of archival cytology slides from the Swedish screening programme. A total of

Using quantitative PCR, van Duin *et al.* (2002) tested the viral load of archived HPV 16 DNA-positive specimens from a Dutch cohort that included 12 women who subsequently developed CIN2 or CIN3 and 47 controls who developed ≤

rily with an increased risk for squamous-cell carcinoma (odds ratio, 3.2; 95% CI, 1.7–6.2) while HPV 18 seropositivity tended to be associated with a higher risk for cervical adenocarcinomas (odds ratio, 3.4; 95% CI, 0.8–14.9). HPV 33 seropositivity was not significantly associated with either squamous-cell or adenocarcinoma (odds ratio, 1.6 and 1.7,

Shah

V-ttJT*0.251sC‰*0.0001 Tc.02409 Tw[ativ immunvit.,

Overall, the data indicate that HPV 16 is the predominant HPV type in VIN3 and vulvar cancer, particularly basaloid and warty cancer. In vulvar cancers, HPV 18, 45, 31 or 33 may play a smaller role.

2.3.2 *Cancer of the vagina*

(

Table 33. Prevalence of HPV DNA in case series of penile cancer (13 cases) and penile intraepithelial neoplasia (5 cases)

Table 33 (contd)

	Type-specific HPV positivity (%)

Table 34 (contd)

Table 35 (contd)

Reference, study location	Sites included	No. of cases	No. of controls	HPV prevalence (%)

mined in each study was small (< 105 cases), which may in part explain the large variability in the prevalence estimates.] A relatively low prevalence of overall HPV DNA, coupled with the high prevalence of HPV16 and the lack of other HPV types among HPV-positive laryngeal carcinomas, have been consistently reported in the more recent studies of HPV and laryngeal squamous-cell carcinoma.

Similar results were reported in a large systematic review of published studies that met the same inclusion criteria of adequate sample size and PCR-based HPV detection methods (Kreimer *et al.*, 2005). Of 1435 laryngeal and hypopharyngeal squamous-cell carcinomas,

Altogether, the evidence suggests that HPV may be involved in the development of some laryngeal cancers, but the associations documented to date are not as clear nor as strong as those observed at other upper aerodigestive sites, such as the tonsils and the oropharynx (Herrero, 2003). If HPV DNA causes a subset of laryngeal cancers, it is probably a smaller subset than that documented for other sites of the head and neck. However, HPV 16 predominates over other HPV types among HPV-associated laryngeal cancers.

has been found in non-melanoma skin cancers (Tables 42 and 43). However, HPV DNA is also frequently detected in specimens of normal skin and in plucked hairs (see Section 2.5.1(*b*)). A diverse spectrum of HPV types, including HPV 20, 38, 41 and 48, have been detected, and many new partial HPV DNA sequences (350–430 nucleotides from the L1 gene) have been identified. Most of them have been assigned to genera beta (including EV-associated HPV) and gamma (see Section 1.1.3) (Berkhout *et al.*, 1995; Shamanin *et al.*, 1996; Bens *et al.*, 1998; Forslund *et al.*, 2003a).

The need for highly sensitive detection techniques can be explained by the very small amounts of HPV DNA present in skin tumours. When HPV DNA was determined by quantitative, type-specific real-time PCR in precancerous actinic keratoses and non-melanoma skin cancers that were positive in nested PCR, viral loads ranged from 1 HPV DNA copy per 14 200 cell equivalents to 50 HPV DNA copies per 1 cell equivalent (Weissenborn *et al.*, 2005). The HPV DNA load was significantly higher in actinic keratoses than in squamous-cell carcinomas and Bowen disease. In most m1%und srobably not every tumour cell harbours an HPV genome, which is supported by in-situ hybridization that shows only a few HPV DNA-positive cell nuclei per section.

The genus- and species-specific PCRs used differ in sensitivity towards individual types, i17 ious ifsecy the spectrum of HPV typen identifie kin coseskin which(DNA)-01.4(l evlsy)]TJT*-0. ORF),n HPVDNA was detected in55%t ofbaseal-cell carcinoma8, 6%g squamous-cell carcinomatsand10%t ofhreathya skinsamplves Caldevirt

O 248 I O V 0

Table 47. Prevalence of HPV DNA in case series of periungual and palmoplantar Bowen disease of the skin

Reference, study location	Method of detection and types tested	No. and type of lesions	Type-specific HPV positivity (no. positive/ total)

junctival specimens from the same patients or from five age-matched control subjects ($p < 0.001$). In contrast to these findings, other studies detected HPV not only in epithelial neoplasms but also in non-neoplastic lesions as well as in apparently healthy conjunctiva. In one study, HPV 16 DNA was found by PCR with consensus primers and dot blot hybridization using 28 type-specific probes, in two of 10 invasive cancers of the conjunctiva, and in the normal muscosa of one of 30 age- and sex-matched controls (Palazzi *et al.*, 2000). In another study, HPV 16 infection was found by PCR in seven of 20 samples from carcinomas (35%) and in two of six samples from conjunctivitis (Waddell *et al.*, 1996). Karcioglu and Issa (1997) identified HPV 16 and 18 DNA by PCR in eight of 14 (57%) in-situ squamous-cell carcinomas, in 17 of 31 (55%) invasive squamous-cell carcinomas, in four of 20 (20%) samples of climatic droplet keratopathy, in 11 of 31 (35%) samples of scarred corneas and in six of 19 (32%) samples of normal conjunctival tissue obtained during routine cataract extractions. HPV DNA was not detected by PCR with MY09/11 primers in any of 28 pathological specimens that ranged from intraepithelial neoplasia to invasive squamous-cell carcinoma or in 23 disease-free, age- and sex-matched patients (Tulvatana *et al.*, 2003).

F6 zlak association between infections with genital HPV types and carcinoma of the conjunctiva is supplemented by the lack of a statistically significant association between anti-HPV 16 antibody status and the risk for conjunctival neoplasia (Newton *et al.*, 2002; Waddell *et al.*, 2003).

In a pilot study of 21 squamous-cell carcinomas of the conjunctiva and 22 conjunctival samples of control subjects from Uganda, broad-spectrum and EV-specific PCR-based assays detected EV-HPV types in 86% of the cases and in 36% of controls (odds ratio after adjustment for exposure to the sun, 22.7; 95% CI, 1.7–312) (Ateenyi-Agaba *et al.*, 2004). No mucosal HPV types were found in either cases or controls by genus

and three squamous-cell carcinomas that extended to several sites of the nasal cavity and paranasal sinuses by indirect immunoperoxidase staining (Syrjänen *et al*., 1987b). Seven of the 25 papilloma biopsies analysed expressed HPV antigens. By in-situ hybridization with probes for HPV 6, 11 and 16, nine lesions in seven patients were shown to contain HPV 11 DNA. The three carcinomas tested were positive for HPV 16 DNA. If DNdther study that used only in-situ hybridization to detect HPV 6 and 11, a high prevalence of bdth HPV 6 and 11 was Ndted in the 21 inverted papillomas analysed (Weber *et al*., 1988).

Table 48. Prevalence of HPV DNA in case series of lung cancer detected by the polymerase chain reaction (PCR) method

In summary, with the exception of the studies in Taiwan, China, there is a paucity of data in non-cancer lung specimens, which greatly limits the interpretation of the large number of studies that have been reported to date. In those studies that did test non-cancer lung specimens, the high prevalence of HPV DNA reported was unexpected. [Simultaneous testing of normal human tissues, for which there is broad agreement that the prevalence of HPV is very low (in addition to cancer and non-cancer lung specimens), is

been associated with HPV, have an increased risk for developing subsequent prostatic cancer (Rabkin *et al.*, 1992).

Table 49 presents case series of cancer of the prostate and benign prostatic hypertrophy in association with HPV prevalence. A few studies found an association of HPV with prostatic cancer (McNicol & Dodd, 1990a; Anwar *et al.*, 1992a; Serth *et al.*, 1999; Carozzi *et al.*, 2004). In three of these studies, specimens of non-cancerous prostate were also found to have a substantial, although lower, prevalence or copy number of HPV DNA (McNicol & Dodd, 1990a; Serth *et al.*, 1999; Carozzi *et al.*, 2004). Other studies reported that HPV DNA was equally prevalent in cancers, benign prostatic hypertrophy and normal prostatic tissue (McNicol & Dodd, 1990b, 1991; Ibrahim *et al.*, 1992; Dodd *et al.*, 1993; [illegible] 196b4).

Table 50 (contd)

Type-specific HPV positivity (%)

from the most recent Pap smear. A significant approximately twofold increase in risk for carcinoma *in situ was observed for both former and current smokers compared with those who had never smoked.*

Among women who participated in a study in Västerbotten County, Sweden, ever

(2002a) observed a longer duration of high-risk HPV infections and a lower probability

Table 53 (contd)

Table 54. Prospective studies of oral contraceptive (OC) use restricted to HPV-positive women

Reference,

significant interaction was detected, there appeared to be a higher risk among women with high parity and young age at first full-term pregnancy, and high parity and 5 or more years of oral contraceptive use. A significant increase in risk for adenocarcinoma was also detected among women with one to two full-term pregnancies, although this did not increase linearly with increasing parity.

In a study of women residing along the USA–Mexico border by Giuliano *et al*. (2004), no significant association between SIL and parity was observed.

(ii) *Prospective studies* (Table 56)

The number of prospective studies that have evaluated the association between parity and risk for cervical cancer among HPV-positive women is limited. Deacon *et al*. (2000)

Table 56. Prospective studies of parity and pre-invasive cervical cancer restricted to HPV-positive women

Reference, study location	Parent cohort	No. anpe of cases	No. anpe of controls	Number of full term pregnancies	Odds ratio (95% CI)	Detection method and comments

HUMAN PAPILLOMAVIRUSES

Table 57 (contd)

Reference, study location	No. and type of cases	No. and type of controls

these associations reached statistical significance. Among women resident in Chennai, India, Rajkumar *et al*. (2003) observed a non-significant inverse association between consumption of vegetables and fruit and the risk for invasive cervical 86.7r.

Serum retinol has been examined in two studies that restricted their analyses to HPV-positive women. Ho *et al*. (1998b,c) did not observe significant associations between serum retinol and CIN1–3 among women in the USA. This was the only study that examined the association between serum carotenoids, α-tocopherols and vitamin C concentrations and risk for CIN1–3 combined or considered separately. Only serum vitamin C was significantly associated with a reduced risk for disease (odds ratio, 0.41 for ≥ 0.8 mg/dL versus < 0.8 mg/dL), and the association was limited to the comparison between women with CIN1–3 and those with normal ytology. Among women infected with HIV in the USA, French *et al*

lycopene (odds ratio, 0.44) (Sedjo *et al.*, 2002a,b). In the same study, the authors reported an approximately threefold higher probability of oncogenic HPV clearance among women in the highest compared tertile of both *trans*- and *cis*-lycopene concentrations (Sedjo *et al.*, 2003a).

Increasing levels of dietary vegetables decreased the risk for persistent HPV infection (Sedjo *et al.*, 2002b). Giuliano *et al*. (2003) assessed the association between dietary nutrient intake and risk for HPV persistence among women who participated in the Ludwig-McGill HPV Natural History Study in Sao Paolo, Brazil. Dietary intakes of β-cryptoxanthin, lutein/zeaxanthin and vitamin C were significantly inversely associated with risk for persistent type-specific HPV infection. In addition, consumption of papaya was inversely associated with persistent HPV infection in this population.

(iii) Brazil (Sao Paulo) (Sedjo

[redacted]

[redacted] method of [redacted] end-point	Dose	Duration	Results
Folic acid [redacted]			

regression. In Arizona, USA, Childers *et al*. (1995) similarly found that 5 mg folic acid per day had no significant effect on cervical lesions after 6 months of treatment. Again, the majority of participants entered the study with CIN1 lesions.

β-Carotene trials

Five phase II/IIII trials of β-carotene supplements have been conducted, none of which demonstrated an increase in regression or a decrease in progression of any preneoplastic lesion. De Vet *et al*. (1991) found no effect of treatment with 10 mg per day β-carotene for 3 months among women in The Netherlands. A longer duration of treatment (9–24 months) with higher doses (30 mg) was also ineffective in altering rates of regression of lesions in studies conducted by Fairley *et al*. (1996) in Australia, Romney *et al*. (1997) in the USA, Mackerras *et al*. (1999) in Australia and Keefe *et al.* (2001) in the USA.

Retinoic acid trials

Three trials tested diffe3Romney

surface, which may confer susceptibility or resistance to HPV infection and neoplastic progression. Malignant transformation and regression of cottontail rabbit papillomavirus-induced lesions were clearly shown to be associated with class II DR and DQ genes (Han *et al.*, 1992).

The results of several selected studies are summarized in Table 60.

The first associations between HLA class II genes and cervical cancer were reported with *DR5*, *DR6* and *DQ3* (Wank & Thomssen, 1991). A second report on the same samples employed HLA typing using DNA-based methods and assigned the increase in risk to *DQB1*0301/0303* (Wank *et al.*, 1993). A number of studies that used different ethnic populations confirmed this association (Helland *et al.*, 1992; Gregoire *et al.*, 1994; Nawa *et al.*, 1995; Duggan-Keen *et al.*, 1996) but others did not find statistically significant associations for these alleles (Glew *et al.*, 1992; Apple *et al.*, 1994; Allen *et al.*, 1996; Lin *et al.*, 2001).

Other allele groups that have been reported to confer risk include

study (Bontkes *et al.*, 1998) and the *B*07–DQB1*0302*

active women in the general community, which can rise to 24% in high-risk populations (Burstein *et al*., 1998; Stamm, 1999; Burstein *et al*., 2001; Turner *et al*., 2002). Because 85–90% of *C. trachomatis* infections are asymptomatic, many remain undiagnosed (Turner *et al*., 2002) and untreated, and can persist for several months or even years (Stamm, 1999; Peipert, 2003; Stephens, 2003). *C. trachomatis* infection may also recur, or even possibly be reactivated, similarly to viral infections (Stephens, 2003; Hogan *et al*., 2004). Infection with *C. trachomatis* is associated with squamous metaplasia and hypertrophic ectopy and, when

a

T

R	Study design	N cases
study		
l		

transmission in an EV patient (Favre *et al*., 1998b). The same HPV types as those found W n2 irfW lesions of n2 imon2 r were detectable in 2 r amniotic fluid, placenta and genital scrapes. In contrast, EV-typeirfW warts nev r start to appear before 4–5 years of age and carcinomas dev lop much later. Majewrf and Jablonska (1997) observed EV patients withirfW autografts from n2 iuninvolved internal aspect of n2 iarm n2at cov red areas of n2 iforehead n2at had been excised for carcinomas. WithW n2 igrafted rfW, benigW lesions started to dev lop only sev ral years after transplantation. No carcinoma dev loped for up to 20 years of graft life, w2 reas premaligWant and maligWant changes appeared around n2 igrafts. This suggests n2at HPV-associated rfW carcinogenesis is a v ry slow process.

The high lev l of consanguinity in EV families suggests aW autosomal recessiveimode of in2 ritance (Lutzner, 1978; Tanigaf *et al*., 1986) but, in on ifamily, n2 iin2 ritance appeared to be X-linked (Androphy *et al*., 1985). *Genetic* [illegible] EVER1 and EVER2

after 9 years and 70% ter 9 s and 703r(Bouwes Bavinck a, 1996). These data suggest theain 9 play of UVligh

Table 65 (contd)

No. and % with HPV or lesion

Table 66 (contd)

	HPV type-specific positivity

et al., 1997) detected HPV DNA in more than 90% of skin warts (de Villiers

HUMAN PAPILLOMAVIRUSES

Table 69 (contd)

	HPV type-specific positivity

(*c*) *HPV infection and cancer at other sites in transplant patients*

(i) *Head and neck region*

Three cases of head and neck squamous-cell carcinoma were reported in patients who were 18, 29 and 53 years of age at the time of tumour diagnosis after renal, cardiac or

Table 70 (contd)

Table 70 (contd)

a
HPV prevalence
Cervical abnormality
T

among HIV-positive women with $CD4^+$ cell counts ≥ 200 and < 200 cells/μL ($p < 0.001$), respectively.

Ammatuna *et al*. (2000) studied the presence of HPV DNA in cervical scrapings from 110 HIV-positive women. Using PCR, HPV DNA was found in 60.9% of the samples. Using Hybrid Capture 2, low-risk HPV types were found in 19.4% of the patients, high-

95% CI, 2.0–31.5) were more likely to have HSIL or cervical cancer than HIV-negative women. This relationship was not detected among women without high-risk HPV infection. HIV-2-positive women were more likely to have HSIL (odds ratio, 3.3; 95% CI, 0.9–12.4) or cervical cancer (odds ratio, 7.9; 95% CI, 1.1–57) than HIV-1-positive women. The authors hypothesized that the increase in risk associated with HIV-2 infection may reflect the longer periods of mild immunosuppression than are typically seen with HIV-1, and this may be relevant to the effect of highly active antiretroviral therapy (HAART) on the natural history of CIN.

Baay *et al*. (2004) studied the prevalence of cervical HPV infection in a population of women from rural Zimbabwe. The prevalence of HPV was higher in HIV-positive (54%) than in HIV-negative women (27%) (odds ratio, 3.18; 95% CI, 1.67–6.10). The most common HPV types in HIV-positive women were 33 (5.2%), 35 (4.6%), 45 (4.6%) and 58 (4.6%); HPV 16 was found in only 3.4%. Among HIV-negative women, the most common types were HPV 35 (11.5%), 6 (9.8%) and 58 (8.2%); HPV 16 was found in only 3.3%.

Branca *et a.l*

Table 71 (contd)

	HPV prevalence	Cervical abnormality

40%; $p = 0.04$) and to have more visits at which multiple HPV DNA types were detected (18% versus 0%; $p = 0.02$) than HIV-negative women.

La Ruche *et al*. (1999) performed a short-term prospective study of CIN in Abidjan, Cote d'Ivoire. Of 94 women with a cytological diagnosis of SIL, 36 were infected with HIV-1 and two with HIV-2. The average follow-up period after the initial smear was 5 months. HIV-positive women had a higher percentage of persistent CIN (76%) than HIV-negative women (18%) (relative risk, 4.3; 95% CI, 2.4–7.7). Progression to high-grade

incidence rate among the high-risk types (2.61 per 100 person–years) but low-risk HPV 53 had the highest incidence rate overall (6.23 per 100 person–years).

Calore *et al*. (2001) studied cytological specimens from 1587 HIV-positive women in Brazil: 12.6% had SIL or cervical cancer in at least one specimen; 24 women progressed from normal to LSIL within 3 years and 11 progressed from normal to HSIL within 3 years.

Cohn *et al*. (2001) studied the 1-year incidence of CIN in 103 women who parti-

(LSIL, 20.2%; HSIL, 6.2%). The women were followed every 6 months for a mean observation time of 15.4 months (range, 6–24 months). Although $CD4^+$ cell counts increased

rate ratio for cervical cancer was 1.87 (95% CI, 0.77–4.56), which indicated that there had been no significant change in the incidence of cervical cancer since the introduction of HAART.

Dorrucci

Table 73 (contd)

Reference,

Palefsky *et al*. (1997a) characterized the prevalence of anal HPV infection and anal HIV disease..(d)0

in the anal canal of 57% of the study participants. The prevalence of anal HPV infection did not change with age or geographical location. In a multivariate analysis, anal HPV infection was associated with receptive anal intercourse during the preceding 6 months (odds ratio, 2.0; 95% CI, 1.5–2.8; $p < 0.0001$) and with having 6–30 sexual partners during the preceding 6 months (odds ratio, 1.4; 95% CI, 1.1–1.9), and more than 30 partners (odds ratio, 2.3; 95% CI, 1.5–3.6).

(ii) *Natural history of anal HPV infection and anal SIL*

Table 74 (contd)

Reference, study location

of follow-up is high in HIV-positive homosexual or bisexual men and lower in HIV-

multivariate analysis, women were at increased risk if they had a baseline $CD4^+$ cell count

intravenous drug use, heterosexual contact and unknown/other factors resulted in significantly increased SIRs for rectal, rectosigmoid and anal cancer as well as cervical cancer.

Newton *et al*

from 3.7 cases per 100 000 in 1973–78 and 8.6 cases per 100 000 in 1984–90 to 20.6 cases

3. Studies of Animal Papillomaviruses

Due to the species specificity 173papillomaviruses, infection 173experimental animals with human3papillomavirus (HPV) is not possible. However, understanding the natural history and carcinogenic potential 173HPVs is assisted by the study 173several animal papillomaviruses.

Whereas cancer is the end-point to assess carcinogenicity in the study 173HPV, benign tumours (warts and papillomas) are 17ten used as the end-point in the analysis 173the association 173papillomavirus with naturally 1ccurring or3experimentally induced neoplasia in animals. This is based on the grounds that: (*a*) the incidence 173warts is higher than that 173cancer and is therefore easier to monitor; (*b*) it is difficult to follow the course 17 disease in wild animals; (*c*) domestic animals, such as cattle, are usually killed before the 1nset 173malignancy; and (*d*) papillomavirus-associated3cancer ultimately derives from warts, and thus the presence 173warts can be considered as an indication 173possible incipient neoplastic progression.

For3each 173the animal papillomaviruses discussed below, naturally 1ccurring warts and their progression to cancer are considered primarily, followed by experimental reproduction in natural and heterologous hosts and tumour production in transgenic animals.

3.1 Non-human3primate papillomaviruses (Table 75)

Two different types of papillomavirus were isolated3from papillomas 173the colobus monkey (*Colobus guereza*): CgPV 13from a penile papilloma (O'Banion*et al.*, 1987) and CgPV 2 from a cutaneous papilloma (Kloster *et al*., 1988). CgPV 1 is a typical genital alpha-papillomavirus, whereas CgPVDue toom a cutanbet(alpha-papillomaviruses)]TJT*0.025 (Cher, S.Y

distinct regions for evidence of papillomavirus infection. By PCR, RhPV 1 DNA sequences were found in 12/59 (20.3%) animals from the three areas. The serological status of the animals was also investigated and 34/59 (57.6%) animals were positive for at least one RhPV antigen. There was concordance between viral DNA positivity and seropositivity in 10 cases. Histopathological analysis showed that the majority of the samples was clinically normal, with the occasional presence of mild-to-moderate chronic inflammation and focal squamous metaplasia. Four cases showed features of papillomavirus infection; of these, one was classified as CIN1 and another was the only case that concorded with seropositivity. All cases were RhPV DNA-negative. This situation parallels HPV infection in humans, in which most cases of infection are undetected clinically and the concordance between seropositivity and viral DNA positivity is not complete.

3.2 Bovine papillomavirus (BPV)

3.2.1 *Heterontieity of BPV* (Table 76)

BPVs are a heterontieous group of viruses that are distributed worldwide. They induce papillomatosis of the skin, the ntiital and parantiital area, the eye, the upper gastrointestinal tract and the urinary bladder. Six members (BPV 1–6) have been described in detail (Jarrett *et al*., 1984a,b; Jarrett, 1985), and a further 13 types were identified recently (Antonsson & Hansson, 2002; Ogawa *et al*., 2004), which more than trebles the heterontieity of BPVs (Table 76).

The six well-characterized BPVs were originally classified into two subgroups (A and B), based on their ntiomic structure and recognized pathology. Subgroup A comprised

3.2.3 *BPV 2*

BPV 2 induces classical skin warts (Campo *et al*., 1981) that are histologically similar to those induced by BPV 1 (Jarrett, 1985). It also induces fibropapillomas of the oesophagus and rumen, which, contrary to fibropapillomas of the skin, do not produce viruses and appear to be the result of abortive infection (Jarrett *et al.*, 1984a). In experiments in which BPV 2 is transmitted to the skin, the virus produces0286 Twin 100% of the animals (Jarrett, 1985).

(*a*) *BPV 2 and cancers of the urinary bladder* (Table 77)

In Scotland, 30% of cattle that had squamous-cell carcinoma of the upper gastrointestinal tract (see below) had concurrent bladder tumours (Jarrett *et al*., 1978a): haemangioendotheliomas (23%), transitional-cell carcinomas (8%), fibromas (4%) and adenocarcinomas (1%). The same histological types of tumour, including the Pagetoid variant of urothelial carcinoma, have been found in cattle in other p86 Twof the world and were associated with bracken fern in the diet, which contains highly immunosuppressive and mutagenic chemicals (Pamukcu, 1963; Rosenberger, 1971; Hirono, 1986; Borzacchiello *et al*., 2001).

InjectionTwof a 10% suspension of homogenized bovine0286 tissue, either alone0or in combination with 3-hydroxy-kynurenine0and/or 3-hydroxyanthranilic acid, into the wall of the urinary bladder of 2–3-month-old calves induced fibromas and polypTwin 13/15 animals examined cystoscopically at intervals st86 ing 14 days after inoculation. Simultaneous intradermal injectionTwof the same suspensions0or application on scarified skin in the same animals induced fibropapillomas in the skin of 12 calves in 33–83 days. No malignant tumours were observed in six calves examined histopathologically from 40 to 81 days after inoculation (Olson *et al*., 1959). In another experiment (Olson *et al*., 1965), suspensions0of six naturally occurring bladder tumours (two haemangiomas, one0haemangioma plus

Table 77. Bovine papillomavirus (BPV) in urinary bladder cancers

BPV type	Naturally occurring cancers (%)	Expeaaentally

papilloma, two papillomas, one papilloma plus adenocarcinoma plus squamous carcinoma — this latter case was accompanied by metastasis to the iliac node) were inoculated into the skin, vagina and urinary bladder of young calves. Of 17 inoculated calves, 10 developed skin fibropapillomas, seven developed fibropapillomas of the vagina and five developed polyps and fibromas of the urinary bladder. These experiments demonstrated both the presence of BPV in tumours of the urinary bladder and the ability of the virus to induce

similar to those that occur naturally; however, in contrast to natural sarcoids, experimental sarcoids regressed (Olson & Cook, 1951).

Lancaster *et al*. (1977) first detected BPV DNA in natural equine sarcoids in the USA. Neither natural nor experimental sarcoids contained virus or structural viral antigens. More recent analyses of these equine tumours throughout the world have confirmed the original findings (Table 78).

Trenfield *et al*

In all surveys but one (Carr *et al*., 2001a), BPV 1-like DNA has been found more often than BPV 2 DNA (Table 78). Furthermore, the absence in most surveys of BPV 1 or BPV 2 DNA sequences identical to those of the reference genomes suggests the existence of ‘equine-adapted’ variants of BPV that specifically infect horses.

The causal involvement of BPV in equine sarcoids has been confirmed by the

CRPV induces carcinomas on tarred skin. Rapid malignant progression was also observed

et al., 1992; Mietz *et al.*, 1992). E6 proteins from multiple human and animal papillomaviruses bind to cellular proteins other than p53 and E6-AP. These include (*a*) transcription factors such as p300 (Patel *et al.*, 1999; Zimmermann *et al.*, 1999), myc (Gross-Mesilaty *et al.*, 1998), interferon regulatory factor 3 (IRF3) (Ronco *et al.*

The ability of E6 to induce genomic instability probably reflects its ability to inhibit the function of p53 (Havre *et al.*, 1995), which leads to the disruption of normal DNA repair processes and a consequent accumulation of genetic change. The genomic instability induced by E7 may reflect its effect on centrosome biogenesis and the consequent defects in segregation of daughter chromosomes during cell division (Duensing *et al.*, 2000; Duensing & Münger, 2001; Duensing *et al.*, 2001a,b). However, the manner in

kinase as a substrate for phosphorylation (Chien *et al.*, 2000). E6 has also been shown to induce suprabasal DNA synthesis (Song *et al.*, 1999), a p83-independent activity that correlates with the ability of E6 to bind PDZ-domain proteins (Nguyen *et al.*, 2003).

transformation to the malignant phenotype has been demonstrated using various cell lines in these experimental models. Using an inducible promoter, it has been shown that con-

factors. However, detection of early gene transcripts by reverse-transcription PCR is more sensitive both in cancers (Park *et al.*, 1997) and in benign or dysplastic cervical swabs, in which the presence of integrated genomes has been shown to correlate with severity of disease, particularly for HPV 18 (Hudelist *et al.*, 2004). Recently, alternative methods for the accurate determination of the physical status of HPV genomes have been proposed (Klaes *et al.*, 1999; Luft *et al.*, 2001; see Section 1.3.3). In the study by Klaes *et al.* (1999), transcripts derived from integrated HPV were more frequently detected in high-grade lesions and cervical cancer than in norm inor low-grade dysplastic tissues. Integration of HPV 16 and 18 in high-grade lesions is often accompanied by chromosom inabnorm iities (Hopman *et al.*, 2004). This supports the potenti inuse of measurements of HPV integration as markers of progression in cervical cancer. In tonsillar cancers, the presence of extra-

The studies described above favour the concept that HPV genomes may interfere with critical cellular functions by insertional mutagenesis. However, this has not been confirmed

were found in high-grade lesions with integrated HPV DNA than in low-grade lesions (Alazawi *et al.*, 2004). ELhamidi *et al.*

(ii) MYC

HPVs have been shown to integrate in the proximity of *c-MYC*, which justifies the search for alterations of this proto-oncogene in HPV-associated lesions. However, the results have not been consistent. Recently, Abba *et al.* (2004) described *c-MYC* amplification in a high proportion of cervical cancers compared with benign and premalignant cervical lesions. Moreover, a significant association between *c-MYC* amplification and HPV 16 infection was observed. Elevated levels of *c-MYC* have been found in several HPV-positive cervical carcinoma cell lines (Dürst *et al.*, 1987b). More recently, Hukku *et al.* (2000) described genetic changes associated with progression to a malignant phenotype of a non-tumorigenic HPV 18-immortalized human prostate cancer cell line, which included amplification of *c-myc* that was considered to be central to this process. However, the significance of these events in HPV-mediated transformation is not clear. The involvement of the Myc protein in HPV-induced immortalization was recently addressed (Veldman *et al.*, 2003). High-risk HPV E6 was shown to associate with Myc addre21(-posiMad,T* p.1(els E6- is narvef) 1 Tf 1hTER)6ig HPVs et al.MYCC

4.1.5 *Interactions between HPV and environmental agents*

(*a*) *Effects of other infectious agents*

The proposed mechanisms through which infectious agents might act as co-factors in HPV-associated tumorigenesis include direct biological interactions, such as modification of HPV replication and transcription, and indirect effects, such as inflammation and damage to

Overall, the immune response to microbial infection (i.e. cervical inflammation) may play a role in HPV-associated tumorigenesis and help explain the possible associations of

(Meyers *et al.*, 2001) and, under certain culture conditions, AAV actually increased the tumorigenicity of papillomavirus (Hermonat *et al.*

anti-oxidants (in particular nutrient anti-oxidants) in the down-regulation of viral repli-

in-vitro study demonstrated that sequence-specific methylation of CpG sites in the constitutive enhancer region of the HPV 18 upstream regulatory region resulted in a down-regulation of transcriptional activity (Rösl *et al.*, 1993). Methylation of a novel transcription factor-binding site decreased the activity of the HPV 16 enhancer and suppressed viral transcription (List

In addition to its direct role in carcinogenesis, tobacco smoking has been associated with a generalized suppression of the immune system, including a significant decrease in NK cells and NK cell activity, in circulating levels of immunoglobulin (Ig)G and IgA (Ferson *et al.*, 1979))G ain Langerhans cells (Barton *et al.*, 1988; Poppe *et al.*, 1996). Langerhans cells are dendritic cells that are localized in the epithelium)G apresent antigen to T lymphocytes. A reduction in the number of Langerhans cells available to detect
antigens may facilitate the establishment an apersistence of local viral infection. Giuliano *et al.* (2002c)demonstrated that tobacco smoking was associated with an increased risk for persistence an aduration of high-risk HPV infection. The resultant viralapersistence may increase the probability of the development of virally induced neoplastic transformation.

(*e*) *Radiation*

(i) *Ionizing radiation*

Carcinomas in EV patients usually show very slow progression, are only destructive locally an ashow very low invasive an ametastatic potential. However, treatment of EV patients with ionizing radiation (γ-rays, X-rays)provokes rapi ametastasis, which is probably due to its co-carcinogenic effect (IARC, 2002))G /or the release of large amounts of TNFα (Jablonska & Orth, 1985; Jablonska & Majewski, 1994). These findings have led to strict regulations of the use of ionizing radiation in the therapeutic treatment of EV patients.

Similarly,

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(ii) *Ultraviolet radiation (UV)*

that encode cell-cycle inhibitory and apoptotic factors. However, the overall consequence to the cell of the induction of viral genes by UV radiation is not known.

Anti-apoptotic effect of viral protein E6

4.2 Immune mechanisms and HPV-associated neoplasia

4.2.1 *Immunosuppression*

Impaired immunity is a host factor that has been associated with increased numbers of

antigens — a late activation marker — but only a few express CD25 — an early activation marker (Coleman *et al.*, 1994), which indicates that they are probably activated at distant

et al., 1991; Feltkamp *et al.*, 1993; Tindle & Frazer, 1994). In these cases, the epitopes that

the cellular machinery that mediates antigen-specific responses. This section reviews studies that demonstrate that HPV gene products can modulate innate immune responses. For a more in-depth summary of the effects of HPVs on the host immune response the reader is referred to the review by O'Brien and Campo (2002).

are known as species, which are closely related phylogenetically; while members of the species have distinct genomes, they have identical or very similar biological or pathological

can provide a measure of past HPV infection. Taken together, these methods have contributed greatly to understanding the natural history of genital HPV infections.

Transmission of genital HPVs occurs primarily through sexual intercourse. Annual rates of incident infection in young women are approximately 5–15%, and infections by high-risk types, particularly HPV 16, are the most frequent. Overall HPV positivity in cytologically normal women ha372tatreporutedat leveles ofbetw2tat1.5%, and39%n. Tthe inco-

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The presence of HPV in some conjunctival squamous-cell carcinomas and the results

CRPV-induced papillomas progress to carcinomas at a much higher frequency in domestic rabbits than in cottontail rabbits, which implicates the genetic background of the host in the neoplastic process. Increased malignant progression of persistent warts is linked to alleles within the hypervariable region of class II DQ alpha genes.

The transforming proteins SE6, LE6 and E7 of CRPV are consistently expressed in all cancers. Experiments on overexpression in rodent cells also determined a transforming role for E8, which may represent an orthologue of the HPV E5 protein. Most genes, except for *E4* and *E5*, are necessary for the induction of papillomas in domestic rabbits.

Relevant biochemical propertsuc-encoded oncoopeteins E5, E6 and E7 includeRec, DNA-Rerepair and a

With regard to immunomodulation by HPVs, tissue culture-based studies suggest that E5 and E7 oncoproteins of high-risk HPVs can modulate the cell-surface levels of major histocompatibility complex class I and class II molecules and inhibit the function of transporters associated with antigen presentation, respectively. In human cervical cancers, major histocompatibility complex class I is down-regulated whereas class II is up-regulated. In addition, the E6 proteins of both high- and low-risk HPVs and the E7 protein of high-risk HPVs can modulate the activity of several factors that regulate interferon-responsive pathways, which mediate the innate immune response and modulate antigen-specific responses. Furthermore, the risk for cervical cancer could be affected by genetic polymorphisms in the major histocompatibility complex class I and II genes.

5.5 Evaluation

There is *sufficient evidence*

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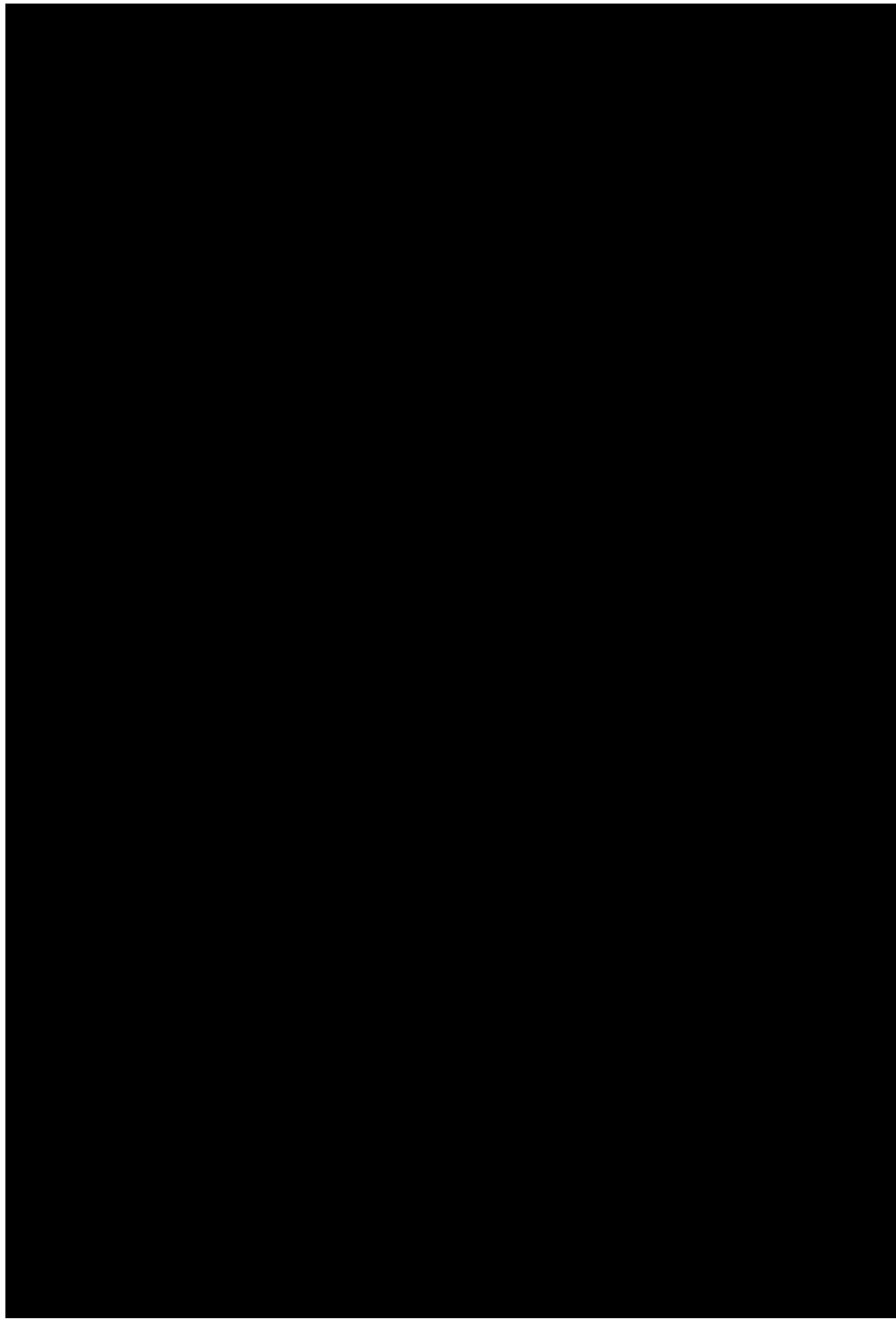

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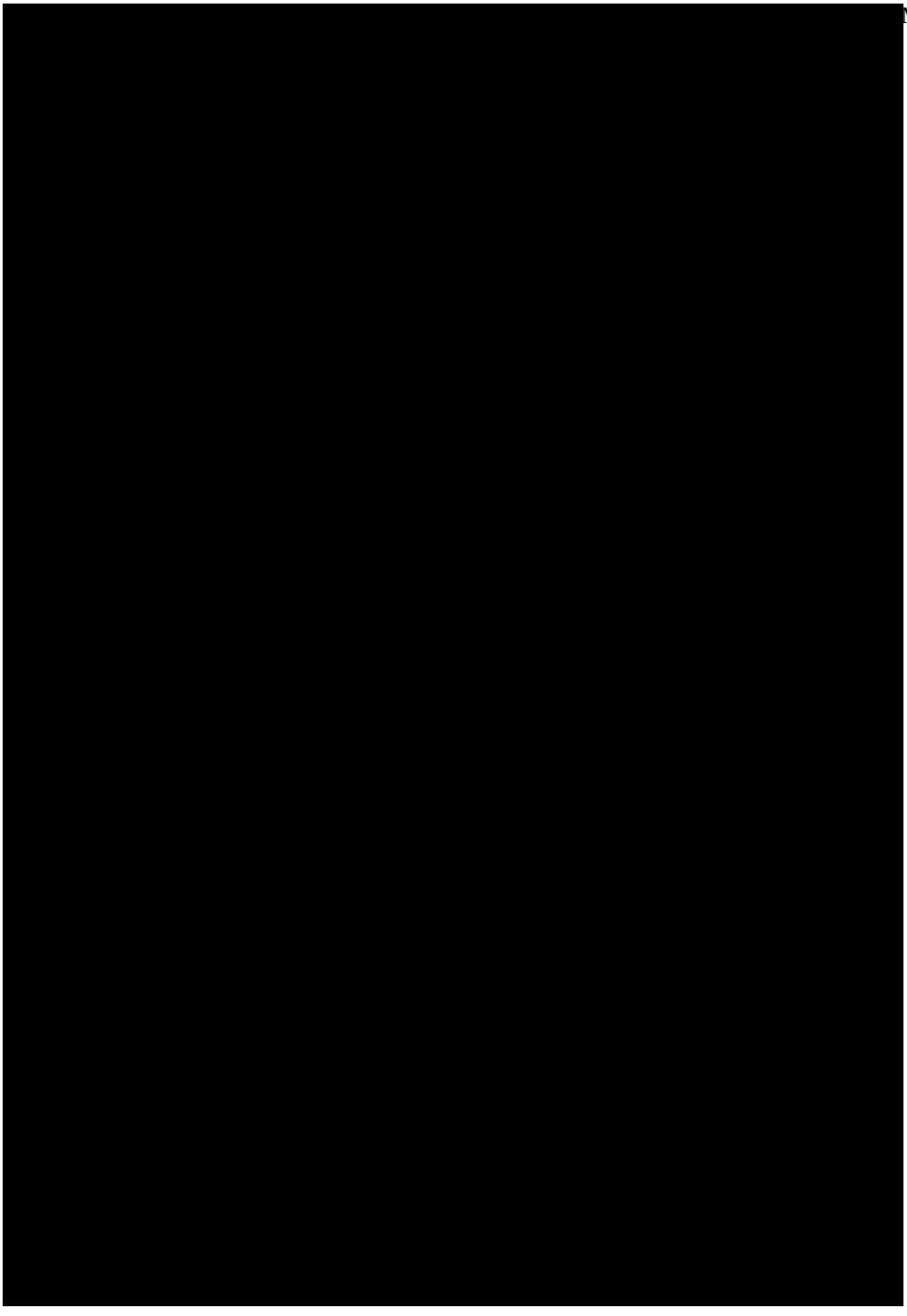

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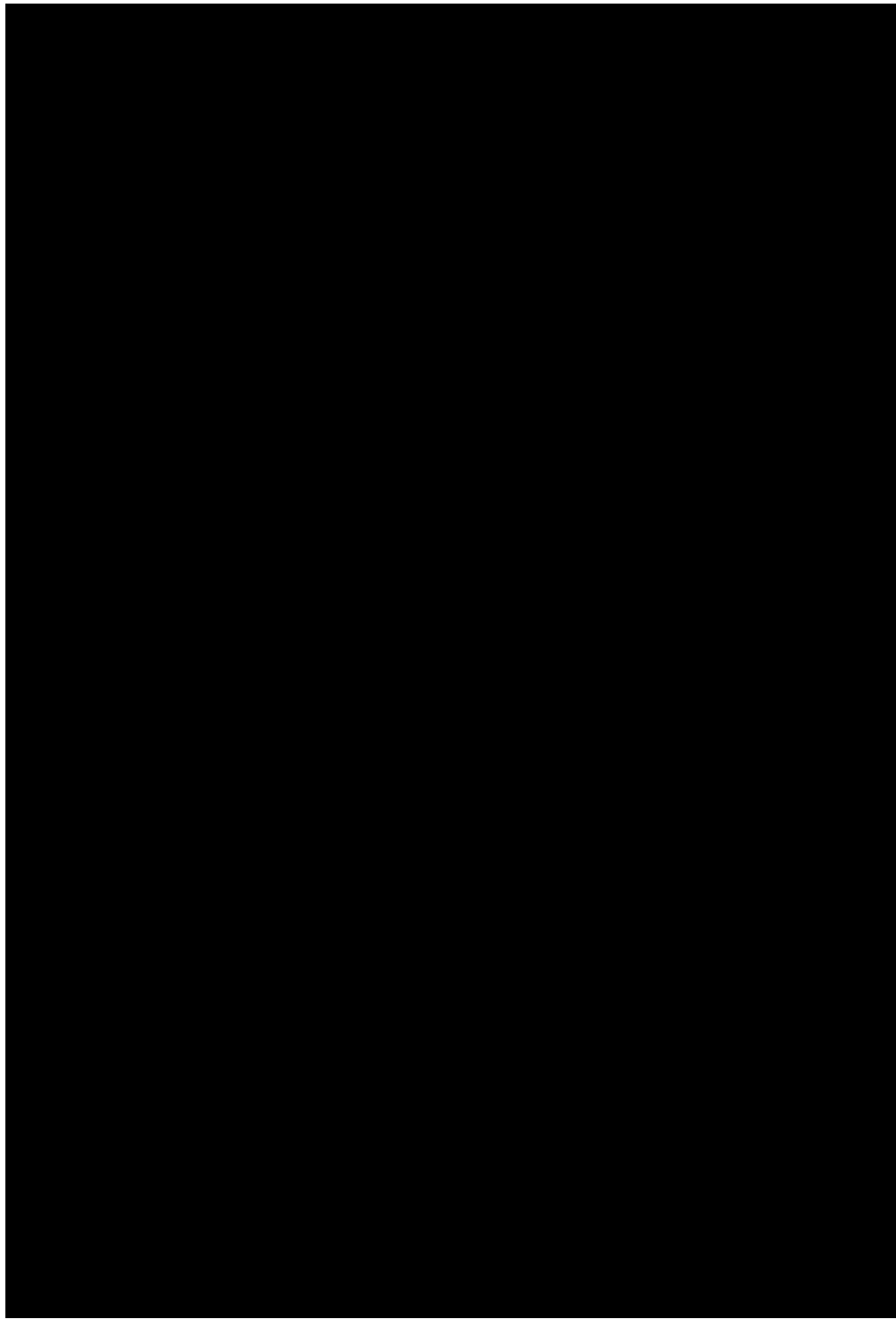

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EEPV	European elk papillomavirus
EGFR	Epidermal growth factor receptor

NASBA	Nucleic acid sequence-based amplification
Nd:YAG	Neodymium:yttrium–aluminium garnet
ND10	Nuclear domain 10
NES	Nuclear export sequence
NF-κB	Nuclear factor-κB
NK	Natural killer
NLS	Nuclear localization signal
NURD	Nuclease remodelling and deacetylase
OvPV	Ovine papillomavirus
ORFOpen-reading frame	
PI3K	Phosphatidylinositol-3′-kinase
Pap test	Papanicolaou test
PARP	Poly(ADP-ribose) polymerase
PCNA	Proliferating-cell nuclear antigen
PCPV	Pygmy chimpanzee papillomavirus
PCR	Polymerase chain reaction
PDGF	Platelet-derived growth factor
PDZ	PSD-95/Disc-large/ZO1 protein
PePV	*Psittacus erithacus timneh* (parrot) papillomavirus
PIN	Penile intraepithelial neoplasia
PML	Promyelocytic leukaemia protein
pRb	RsTc0obasitmav tumou-suppressorprotein
NPsV	

Aldrin *5*, 25 (1974); *Suppl. 7*

CUMULATIVE INDEX

2,4,5-Trimethylaniline	*27*, 177 (1982); *Suppl. 7*, 73 (1987)
2,4,6-Trimethylaniline	*27*, 178 (1982); *Suppl. 7*, 73 (1987)
4,5′,8-Trimethylpsoralen	*40*, 357 (1986); *Suppl. 7*, 366 (1987)
Trimustine hydrochloride (*see* Trichlormethine)	
2,4,6-Trinitrotoluene	*65*, 449 (1996)
Triphenylene	*32*, 447 (1983); *Suppl. 7*, 73 (1987)
Tris(aziridinyl)-*para*-benzoquinone	*9*, 6m4r6.-0.04;

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