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Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens, MD EC-14
P.O.Box 12233
Research Triangle Park, NC 27709

June 20, 2000

Dear Dr. Jameson:

The American Academy of Dermatology [hereinafter referred to as "the Academy] submits these comments in response to the National Toxicology Program's recommendations to list ultraviolet radiation (UVR), nickel and nickel compounds, and human papillomaviruses (HPVs) in its tenth edition of the "Report on Carcinogens." The Academy supports the NTP's recommendations of inclusion of these materials on its list of known or suspected carcinogens.

Ultraviolet Radiation

Solar exposure is an environmental issue with profound effects for the majority of Americans. In this century, changes in attitudes of most Americans toward fashion and beauty as well as an increase in leisure activity outdoors has cost us dearly in terms of photodamage, photoaging, and photocarcinogenesis. In the last decade, however, public health education programs have been initiated to try to convince the American public of the error of its ways. This has been a public/private partnership with such entities as the Environmental Protection Agency, the National Institutes of Health, the Centers for Disease Control and Prevention, the American Academy of Dermatology, the American Cancer Society, The Skin Cancer Foundation and others providing educational materials in a variety of formats and media. We believe that adding UVR to the list of known carcinogens would be of great importance to our efforts to convince the public that unprotected sun exposure is dangerous and may lead to the development of melanoma and non-melanoma skin cancers, such as basal cell and squamous cell carcinoma.

This year, the American Academy of Dermatology estimates that 1.3 million Americans will be diagnosed with some form of skin cancer. The causal agent for the majority of these skin cancers is exposure to UVR. Genetic damage from UVR occurs in two general forms, mutations and chromosome damage. Both are important to the development of the majority

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of neoplasms seen on the skin – both benign and malignant lesions. Exposure to UVR leads to mutations in the DNA by at least two potential mechanisms. In general, mutations arise in the skin when UV-induced covalent damage is misrepaired, altering the base sequence from the original. Alternatively, undetected covalent damage that is not repaired prior to DNA replication could induce a misread by DNA polymerase, causing a base substitution that alters the original sequence.

Pyrimidine dimers and 6-4 photoproducts are two of the most important classes of direct DNA damage induced by UV. The peak wavelength for the formation of pyrimidine dimers and 6-4 photoproducts is 300 nm, so it is more than likely that UVB radiation is the major source of mutations in the human skin. In addition, most of the mutations seen in the p53 gene, an important tumor suppressor gene in human skin cancer are C→T and C→TT transitions. This is consistent with UVB-induced pyrimidine dimer formation as the initial effect. While UVB radiation can induce DNA damage directly through the formation of photoproducts, *in vitro* studies have shown that UVA requires an intermediate molecular target to generate the reactive oxygen species that are thought to be the primary mediators of UVA-induced damage.

UVB and UVA radiation can induce DNA damage indirectly, through the generation of reactive oxygen species, also known as free radicals. Products such as superoxide, singlet oxygen, hydrogen peroxide and hydroxyl radials – all generate from UV striking molecular targets in cells – can introduce DNA adducts or other covalent changes in the DNA. When covalent changes are unrecognized or unrepaired, they may be misread at the time of DNA replication prior to cell division, leading to permanent mutations in the DNA base sequences.

A characteristic change in DNA due to oxidative effects of UV radiation is the formation of 8-hydroxyguanine, a derivative of the purine base deoxyguanine. Base modifications characteristic of oxidative damage are produced by wavelengths throughout the UVA and UVB spectra, although the yield of pyrimidine dimers decreases exponentially above 315 nm – near the transition from UVB to UVA. In addition, there is a second peak of oxidative damage that occurs in the visible range between 400 and 450 nm. This suggests that blue light may also contribute to DNA damage. Support for the possibility that visible light may contribute to carcinogenesis comes from a fish model of melanoma, in which wavelengths in this range can trigger tumor development. More research, however, is needed in this area.

UV-induced chromosome damage is less well understood than UV-induced mutations, although there is abundant evidence that this is a major pathway for tumorigenesis. Chromosome translocations can inactivate tumor suppressor genes or up-regulate tumorigenic oncogenes. Non-random chromosome deletions are an important means of inactivation of function for tumor suppression genes, as control gene function is lost when a germ line defect combines with a somatic event or when two somatic events occur in both alleles.

In addition to skin cancers, there is strong epidemiological evidence linking UVR exposure to other malignancies. Data from the Swedish cancer registry indicates that UVR exposure may be an etiologic factor in non-Hodgkin's lymphoma. Much more research needs to be done in this area, but if these epidemiological observations are true, UVR may be a far more significant carcinogen than is currently appreciated.

Exposure to UVR has other deleterious health effects. Many of the cutaneous changes that we associate with aging are due primarily to exposure to UVR, and therefore are potentially preventable. Animal models have shown that both UVA and UVB contribute to photoaging. These cutaneous changes are caused by oxidative damage and stress, such as lipid peroxidation, as well as erythema. UVR effect on cytokine release and signal transduction pathways may alter the expression of enzymes that remodel the dermis. A photoaging-related effect of chronic exposure to UVR is solar elastosis, or the presence of abnormal elastin in the skin. Metalloproteinases, such as collagenase, can be up-regulated by UVB exposures equivalent to 1/6 of the minimal dose of UVB that produces erythema; this effect contributes to the development of cutaneous photoaging.

There are also a number of photosensitive disorders in which UVR plays a significant role. The two most studied are polymorphous light eruption (PMLE) and lupus erythematosis. PMLE is characterized by pruritic inflammatory skin eruptions seen primarily on the arms and upper trunk. PMLE is a relatively common disorder, affecting 10% of the general population. Individuals of Native American and Scandinavian ancestry are more at risk for these abnormal reactions to sunlight.

Lupus erythematosis is an autoimmune disorder characterized by the presence of inappropriate antibodies to self-antigens. Autoantibodies to DNA are highly characteristic of the disease. As with PMLE, UVB and UVA and perhaps visible light can play a role in the induction of lupus. This suggests that oxidative damage may play an important role in the disorder. Photosensitivity is a common manifestation of several forms of lupus, and tends to correlate with a less favorable prognosis and more organ involvement in systemic lupus and exacerbations of cutaneous lupus.

Nickel and Nickel Compounds

The Academy joins with our colleagues in the American Contact Dermatitis Society in supporting efforts that would reduce human exposure to nickel and nickel compounds. We ask that the NTP follow the lead of our European counterparts to reduce occupational and consumer exposure to nickel.

Currently, human exposure to nickel is common, as it is used widely in both industry and in consumer products. Experimental and epidemiological data have shown that sparingly soluble nickel compounds, and possibly also the soluble compounds, are carcinogenic in humans. Exposure to these metals has been linked to the development of lung and nasal cancers. The presumed route of exposure for carcinogenesis has been inhalation, although recently exposures from medical and dental devices have also been scrutinized. Furthermore, it has been hypothesized that certain paternal exposures to nickel may

increase the risk of cancer in progeny. The mechanism by which nickel induces carcinogenicity, however, still remains unclear, but may be caused by direct or indirect actions of nickel compounds on DNA, co-carcinogenicity by deregulating cellular proliferation, and/or tumor promotion. Much more research needs to be undertaken to determine which compounds are co-carcinogens and which act as tumor promoters.

In addition to its possible links to cancer, exposure to nickel causes another health effect of considerable morbidity - allergic contact dermatitis. Twenty years ago, epidemiological evidence showed that nearly 10% of the US population exhibited some sensitivity to nickel. Since that time, the incidence of nickel allergy has increased dramatically. In a recent study published in Norway, approximately 30% of women in two different regions of that country were found to be allergic to nickel, while the incidence rate among men was approximately 5%. Scientists postulate that gender differences in the incidence rates of nickel allergy maybe due primarily to the common practice of body piercing.

Because of the increasing rate of nickel sensitization, the Danish Ministry of the Environment recently issued a statutory order limiting the permissible release of nickel from objects intended for close contact with the skin to $\leq 0.5\ \mu g/cm^2$. These items include earrings, eyeglass frames, and buttons. This level was based on a number of studies that indicated the relative lack of sensitization to nickel at concentrations at or below $0.5\ \mu g/cm^2$ per week. Since the adoption of these nickel restrictions, the frequency of nickel allergy among children decreased from a high of 24.8% prior to the enactment of the new standard to 9.2%.

Shortly, the European Community will enact the *Directives of the European Standards for the Analytical Methods* to be used on the nickel directive. This directive states that objects, which come into direct and prolonged contact with the skin, must not contain more than $0.5\ \mu g/cm^2$ of nickel. Although this new law will prevent new cases of nickel sensitization, it will unfortunately have little effect on those individuals already sensitive to the metal. However, given the growing incidence of nickel allergy, prevention is very important and I would urge that the NTP consider restricting nickel exposure through the adoption of the European standard.

Human Papillomaviruses

The Academy supports the listing Human papillomavirus (HPV) as a known human carcinogen. Historically, dermatologists have played a crucial role in the diagnosis and treatment of sexually transmitted diseases (STDs), because many of these infections present predominantly with cutaneous signs and symptoms. Given our experience in vast experience in treating this prevalent viral STD, it is our expert opinion that listing HPV as a known carcinogen will assist us in our efforts to educate the general public about the dangers of this disease, how it may be prevented, how it is diagnosed, and how it is treated.

There are over 70 distinct types of HPV. Nearly half, 30 types, are transmitted sexually by skin-to-skin contact and cause genital HPV. According to the American Social Health Association, 5.5 million new cases of sexually transmitted HPV occur each year, and 20 million Americans are thought to have an active HPV infection at any given time. This year, direct annual medical costs for treating the symptoms of HPV infection is expected to reach $6 billion.

While many forms of the virus are harmless, certain strains of HPV have been clearly linked to the development of cervical lesions and then to cervical cancers. Indeed, over 99% of cervical cancers are associated with HPV. Cervical cancer is the second most common cacer of women in the world. In 1999, 500,000 women in the United States were diagnosed with cervical cancer, and 200,000 died from it. As with skin cancers, the lag time between exposure and the development of the cervical cancer is often lengthy, sometimes between 10 and 20 years. In addition to cervical cancers, exposure to certain strains of HPV is linked to the development of other cancers such as carcinomas of the nasal septum, laryngeal and hypopharyngeal carcinoma, cancers of the upper digestive and respiratory tract, as well as other anogenital cancers.

Unfortunately, the majority of Americans are unaware of the linkage between certain strains of HPV and cervical and other cancers. According to an expert panel convened in 1999 by the Centers for Disease Control and Prevention, many health care providers were equally unaware of the risks of exposure to HPV and the development of cervical cancer as well as to the new screening techniques for HPV and treatment modalities for cervical cancer.

Listing HPV as a known carcinogen will bring a clarity to our public health messages concerning HPV. It will provide an impetus to clinicians to learn more about the dangers of this viral STD and will encourage those at risk to be tested.

In summary, the Academy supports the listing of UVR, nickel and nickel compounds, and HPV to the NTP's tenth edition of the "Report on Carcinogens." A comprehensive list of citations from peer-reviewed clinical journals and Academy reports is appended to this letter. If I can be of further assistance to you in your deliberations, please do not hesitate to contact me.

Sincerely,

Dick Scher

Richard Scher, M.D.
President

**PLEASE NOTE: Human Papillomavirus is being deferred for review until the 2001 review cycle.

Report on Carcinogens Group, NIEHS/NTP

Citations – Human Papillomavirus

PLEASE NOTE: Human Papillomavirus is being deferred for review until the 2001 review cycle.

Report on Carcinogens Group, NIEHS/NTP

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References

1. zur Hausen, H. Papillomavirus infections - a major cause of human cancers, Biochimica et Biophysica Acta. *1288:* F55-F78, 1996.
2. Majewski, S. and Jablonska, S. Human papillomavirus-associated tumors of the skin and mucosa, Journal of American Academy of Dermatology. *36:* 659-685, 1997.
3. Villa, L. L. Human papillomaviruses and cervical cancer, Advances in Cancer Research. *71:* 321-341, 1997.
4. Scurry, J. and Wells, M. Viruses in anogenital cancer, Epithelial Cell Biology. *1:* 138-145, 1992.
5. Van Ranst, M., Kaplan, J. B., and Burk, R. D. Phylogenetic classification of human papillomaviruses: correlation with clinical manisfestation, Journal of General Virology. *73:* 2653-2660, 1992.
6. McKaig, R. G., Baric, R. S., and Olshan, A. F. Human papillomavirus and head and neck cancer: epidemiology and molecular biology, Head and Neck. *20:* 250-265, 1998.
7. Karcioglu, Z. A. and Issa, T. M. Human papilloma virus in neoplastic and non-neoplastic external eye, Br J Ophthalmol. *81:* 595-8, 1997.
8. Buchwald, C., Franzmann, M. B., Jacobsen, G. K., Juhl, B. R., and Lindeberg, H. Carcinomas occurring in papillomas of the nasal septum associated with human papilloma virus (HPV), Rhinology. *35:* 74-8, 1997.
9. Kiviat, N. B., Koutsky, L. A., Critchlow, C. W., Lorincz, A. T., Cullen, A. P., Brockway, J., and Holmes, K. K. Prevalence and cytologic manifestations of human papilloma virus (HPV) types 6, 11, 16, 18, 31, 33, 35, 42, 43, 44, 45, 51, 52, and 56 among 500

consecutive women, International Journal of Gynecological Pathology. *11:* 197-203, 1992.

10. zur Hausen, H. Human papillomaviruses in the pathogenesis of anogenital cancer, Virology. *184:* 9-13, 1991.

11. Schneider, A. Pathogenesis of genital HPV infection, Genitourinary Medicine. *69:* 165-173, 1993.

12. Troncone, G. and Gupta, P. K. Cytologic observations preceding high grade squamous intraepithelial lesions, Acta Cytol. *39:* 659-62, 1995.

13. Majewski, S. and Jablonska, S. Epidermodysplasia verruciformis as a model of human papillomavirus- induced genetic cancers: the role of local immunosurveillance, Am J Med Sci. *304:* 174-9, 1992.

14. Clayman, G. L., Stewart, M. G., Weber, R. S., El-Naggar, A. K., and Grimm, E. A. Human papillomavirus in laryngeal and hypopharyngeal carcinomas. Relationship to survival, Archives of Otolaryngology and Head and Neck Surgery. *120:* 743-748, 1994.

15. Gomez, M. A., Drut, R., Lojo, M. M., and Drut, R. M. Detection of human papillomavirus in juvenile laryngeal papillomatosis using polymerase chain reaction, Medicina. *55:* 213-7, 1995.

16. Chang, F., Syrjanen, S., Kellokoski, J., and Syrjanen, K. Human papillomavirus (HPV) infections and their associations with oral disease, Journal of Oral Pathology and Medicine. *20:* 305-317, 1991.

17. Snijders, P. J., van den Brule, A. J. C., Meijer, C. J. L. M., and Walboomers, J. M. M. Papillomaviruses and cancer of the upper digestive and respiratory tracts. *In:* H. zur Hausen (ed.) Human pathogenic papillomaviruses, pp. 177-198. Berlin, Heidelberg, New

York, London, Paris, Paris, Tokyo, Hong Kong, Barcelona, Budapest: Springer-Verlag, 1994.

18. Miller, C. S. and White, D. K. Human papillomavirus expression in oral mucosa, premalignant conditions, and squamous cell carcinoma, Oral Surger, Oral Medicine, Oral Pathology, Oral Radiology and Endodontrics. *82:* 57-68, 1996.

19. Steinberg, B. M. and Auborn, K. J. Papillomaviruses in head and neck disease: pathophysiology and possible regulation, Journal of Cellular Biochemistry. *17F:* 155-164, 1993.

20. Brown, D. R. and Fife, K. H. Human papillomavirus infections of the genital tract, The Medical Clinics of North America. *74:* 1455-1485, 1990.

21. Campion, M. J. Clinical manifestations and natural history of genital human papillomavirus infection, Dermatologic Clinics. *9:* 235-249, 1991.

22. Doorbar, J. and Gallimore, P. H. Identification of proteins encoded by the L1 and L2 open reading frames of human papillomavirus 1a, J Virol. *61:* 2793-9, 1987.

23. Chow, L. T. and Broker, T. R. Papillomavirus DNA replication, Intervirology. *37:* 150-158, 1994.

24. Mansur, C. P. and Androphy, E. J. Cellular transformation by papillomavirus o ncoproteins, Biochimica et Biophysica Acta. *1155:* 323-345, 1993.

25. Banks, L. and Matlashewski, G. Cell transformation and the HPV E5 gene, Papillomavirus Report. *4:* 1-4, 1993.

26. Hudson, J. B., Bedell, M. A., McCance, D. J., and Laimins, L. A. Immortalization and altered differentiation of human keratinocytes in vitro by the E6 and E7 open reading frames of human papillomavirus type 18, Journal of Virology. *64:* 519-526, 1990.

27. Doorbar, J., Ely, S., Sterling, J., McLean, C., and Crawford, L. Specific interaction between HPV-16 E1-E4 and cytokeratins results in collapse of the epithelial cell intermediate filament network, Nature. *352:* 824-827, 1991.

28. Turek, L. P. The structure, function, and regulation of papillomaviral genes in infection and cervical cancer, Adv Virus Res. *44:* 305-56, 1994.

29. Bernard, H.-U. and Apt, D. Transcriptional control and cell type specificity of HPV gene expression, Archives of Dermatology. *130:* 210-215, 1994.

30. Desaintes, C. and Demeret, C. Control of papillomavirus replication and transcription, Seminars in Cancer Biology. *7:* 339-347, 1997.

31. Hoppe-Seyler, F. and Butz, K. Cellular control of human papillomavirus oncogene ranscription, Molecular Carcinogenesis. *10:* 134-141, 1994.

32. Stubenrauch, F., Malejczyk, J., Fuchs, P. G., and Pfister, H. Late promoter of human papillomavirus type 8 and its regulation, Journal of Virology. *66:* 3485-3493, 1992.

33. Higgins, G. D., Uzelin, D. M., Phillips, G. E., McEvoy, P., Marin, R., and Burrell, C. J. Transcription patterns of human papillomavirus type 16 in genital intraepithelial neoplasia:evidence for promoter usage within the E7 open reading frame during epithelial differentiation, Journal of General Virology. *73:* 2047-2057, 1992.

34. McBride, A. A., Romanczuk, H., and Howley, P. M. The papillomavirus E2 regulatory proteins, J Biol Chem. *266:* 18411-4, 1991.

35. Choo, K. B., Pan, C. C., and Han, S. H. Integration of human papillomavirus type 16 into cellular DNA of cervical carcinoma: preferential deletion of the E2 gene and invariable retention of the long control region and the E6/E7 open reading frames, Virology. *161:* 259-61, 1987.

36. Shirasawa, H., Tomita, Y., Sekiya, S., Takamizawa, H., and Simizu, B. Integration and transcription of human papillomavirus type 16 and 18 sequences in cell lines derived from cervical carcinomas, J Gen Virol. *68:* 583-91, 1987.

37. Cooper, K. and McGee, J. O. Human papillomavirus, integration and cervical carcinogenesis: a clinicopathological perspective, Molecular Pathology. *50:* 1-3, 1997.

38. Mohr, I. J., Clark, R., Sun, S., Androphy, E. J., MacPherson, P., and Botchan, M. R. Targeting the E1 replication protein to the papillomavirus origin of replication by complex formation with the E2 transactivator, Science. *250:* 1694-9, 1990.

39. Ham, J., Dostatni, N., Gauthier, J.-M., and Yaniv, M. The papillomavirus E2 protein: a factor with many talents, Trends in Biochemical Sciences. *16:* 440-444, 1991.

40. Demeter, L. M., Stoler, M. H., Broker, T. R., and Chow, L. T. Induction of proliferating cell nuclear antigen in differentiated keratinocytes of human papillomavirus-infected lesions, Human Pathology. *25:* 343-348, 1994.

41. Jones, K. T. and Sharpe, G. R. Proliferating cell nuclear antigen decreases in normal human keratinocytes with differentiation stimuli but not in an HPV immortalised cell line, Acta Dermatologico-Venereology. *74:* 241-244, 1994.

42. Cheng, S., Schmidt-Grimminger, D.-C., Murant, T., Broker, T. R., and Chow, L. T. Differentiation-dependent up-regulation of the human papillomavirus E7 gene reactivates cellular DNA replication in suprabasal differentiated keratinocytes, Genes & Development. *9:* 2335-2349, 1995.

43. 'Laimins, L. A. Regulation of transcription and replication by human papillomaviruses. *In:* D. J. McCance (ed.) Human Tumor Viruses, pp. 201-223. Washington, D.C.: American Society for Microbiology, 1998.

44. Ustav, E., Ustav, M., Szymanski, P., and Stenlund, A. The bovine papillomavirus origin of replication requires a binding site for the E2 transcriptional activator, Proc Natl Acad Sci U S A. *90:* 898-902, 1993.

45. Enzenauer, C., Mengus, G., Lavigne, A., Davidson, I., Pfister, H., and May, M. Interaction of human papillomavirus 8 regulatory proteins E2, E6 and E7 with components of the TFIID complex, Intervirology. *41:* 80-90, 1998.

46. Goodwin, E. C., Naeger, L. K., Breiding, D. E., Androphy, E. J., and DiMaio, D. Transactivation-competent bovine papillomavirus E2 protein is specifically required for efficient repression of human papillomavirus oncogene expression and for acute growth inhibition of cervical carcinoma cell lines, J Virol. *72:* 3925-34, 1998.

47. Favre, M., Ramoz, N., and Orth, G. Human papillomaviruses: general features, Clin Dermatol. *15:* 181-98, 1997.

48. Syrjanen, K. J. Spontaneous evolution of intraepithelial lesions according to the grade and type of the implicated human papillomavirus (HPV), Eur J Obstet Gynecol Reprod Biol. *65:* 45-53, 1996.

49. Crum, C. P. and McLachlin, C. M. Cervical intraepithelial neoplasia, Journal of Cellular Biochemistry, Supplement. *23:* 71-79, 1995.

50. Southern, S. A. and Herrington, C. S. Molecular events in uterine cervical cancer, Sexually Transmitted Infections. *74:* 101-109, 1998.

51. Shrirasawa, H., Tomita, Y., Kubota, K., Kasai, T., Sekiya, S., Takamizawa, H., and Simizu, B. Transcriptional differences of the human papillomaviruss type 16 genome between precancerous lesions and invasive carcinomas, Journal of Virology. *62:* 1022-1027, 1988.

52. Johnsson, M. A., Blomfield, P. I., Bevan, I. S., Woodman, C. B. J., and Young, L. S. Analysis of human papillomavirus type E6-E7 transcription in cervical carcinomas and normal cervical epithelium using the polymerase chain reaction, Journal of General Virology. *71:* 1473-1479, 1990.

53. Syrjanen, K. Anogenital human papilloma virus and the problem of persistence, Eur J Dermatol. *8:* 5-7; discussion 20-2, 1998.

54. Bosch, F. X., Manos, M. M., Munoz, N., Sherman, M., Jansen, A. M., Peto, J., Schiffman, M. H., Moreno, V., Kurman, R., and Shah, K. V. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group [see comments], J Natl Cancer Inst. *87:* 796-802, 1995.

55. Riou, G., Favre, M., Jeannel, D., Bourhis, J., Le Doussal, V., and Orth, G. Association between poor prognosis in early-stage invasive cervical carcinomas and non-detection of HPV DNA, Lancet. *335:* 1171-4, 1990.

56. Resnick, R. M., Cornelissen, M. T. E., Wright, D. K., Eichinger, G. H., Fox, H. S., Schegget ter, J., and Manos, M. M. Detection and typing of human papillomavirus in archival cervical cancer specimens by DNA amplification with consensus primers, Journal of National Cancer Institute. *82:* 1477-1484, 1990.

57. Arends, M. J., Buckley, C. H., and Wells, M. Aetiology, pathogenesis, and pathology of cervical neoplasia, Journal of Clinical Pathology. *51:* 96-103, 1998.

58. Schiffman, M. H. and Brinton, L. A. The epidemiology of cervical carcinogenesis, Cancer. *76:* 1888-901, 1995.

59. Barbosa, M. S. The oncogenic role of human papillomavirus proteins, Critical Reviews in Oncogenesis. *7:* 1-18, 1996.

60. Cannizzaro, L. A., Durst, M., Mendez, M. J., Hecht, B. K., and Hecht, F. Regional chromosome localization of human papillomavirus integration sites near fragile sites, oncogenes, and cancer chromosome breakpoints, Cancer Genet Cytogenet. *33:* 93-8, 1988.

61. Chu, T. Y., Shen, C. Y., Lee, H. S., and Liu, H. S. Monoclonality and surface lesion-specific microsatellite alterations in premalignant and malignant neoplasia of uterine cervix: a local field effect of genomic instability and clonal evolution, Genes Chromosomes Cancer. *24:* 127-34, 1999.

62. Park, J., Sun, D., Genest, D. R., Trivijitsilp, P., Suh, I., and Crum, C. P. Coexistence of low and high grade squamous intraepithelial lesions of the cervix: morphologic progression or multiple papillomaviruses?, Gynecol Oncol. *70:* 386-91, 1998.

63. Kalantari, M., Karlsen, F., Johansson, B., Sigurjonsson, T., Warleby, B., and Hagmar, B. Human papillomavirus findings in relation to cervical intraepithelial neoplasia grade: a study on 476 Stockholm women, using PCR for detection and typing of HPV, Hum Pathol. *28:* 899-904, 1997.

64. Stoppler, H., Stoppler, M. C., and Schlegel, R. Transforming proteins of the papillomaviruses, Intervirology. *37:* 168-179, 1994.

65. Gissmannn, L. Papillomaviruses and human oncogenesis, Current Opinion in Genetics and Development. *2:* 97-102, 1992.

66. Howley, P. M., Scheffner, M., Huigbretse, J., and Munger, K. Oncoproteins encoded by the cancer-associated human papillomaviruses target the products of the retinoblastoma

and p53 tumor suppressor genes, Cold Spring Harbor Symposia on Quantitative Biology. *LVI:* 149-155, 1991.

67. Donehower, L. A. and Bradley, A. The tumor suppressor p53, Biochimica et Biophysica Acta. *1155:* 181-205, 1993.

68. Munger, K. and Phelps, W. C. The human papillomavirus E7 protein as a transforming and transactivating factor, Biochimica et Biophysica Acta. *1155:* 111-123, 1993.

69. Jones, D. L. and Munger, K. Interactions of the human papillomavirus E7 protein with cell cycle regulators, Seminars in Cancer Biology. *7:* 327-337, 1997.

70. Hubbert, N. L., Sedman, S. A., and Schiller, J. T. Human papillomavirus type 16 E6 increases the degradation rate of p53 in human keratinocytes, Journal of Virology. *66:* 6237-6241, 1992.

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

72. Butz, K., Shahabeddin, L., Geisen, C., Spitkovsky, D., Ullmann, A., and Hoppe-Seyler, F. Functional p53 protein in human papillomavirus-positive cancer cells, Oncogene. *10:* 927-36, 1995.

73. Levine, A. J. The p53 tumor suppressorr gene and product, Biol.Chem.Hoppe-Seyler. *374:* 227-235, 1993.

74. Selter, H. and Montenarh, M. The emerging picture of p53, International Journal of Biochemistry. *26:* 145-154, 1994.

75. Gartel, A. L. and Tyner, A. L. Transcriptional regulation of the p21((WAF1/CIP1)) gene, Exp Cell Res. *246:* 280-9, 1999.

76. Waga, S., Hannon, G. J., Beach, D., and Stillman, B. The p21 inhibitor of cyclin-dependent kinases controls DNA replication by interaction with PCNA, Nature. *369:* 574-578, 1994.

77. Shackelford, R. E., Kaufmann, W. K., and Paules, R. S. Cell Cycle Control, Checkpoint Mechanisms, and Genotoxic Stress, Environ Health Perspect. *107:* 5-24, 1999.

78. Greenblatt, M. S., Bennett, W. P., Hollstein, M., and Harris, C. C. Mutations in the p53 tumor suppressor gene: clues to cancer etiology and molecular pathogenesis, Cancer Research. *54:* 4855-4878, 1994.

79. Paquette, R. L., Lee, Y. Y., Wilczynski, S. P., Karmakar, A., Kizaki, M., Miller, C. W., and Koeffler, H. P. Mutations of p53 and human papillomavirus infection in cervical carcinoma, Cancer. *72:* 1272-80, 1993.

80. Helland, A., Karlsen, F., Due, E. U., Holm, R., Kristensen, G., and Borresen-Dale, A.-L. Mutations in the TP53 gene and protein expression of p53, mdm2 and p21/WAF-1 in primary cervical carcinomas with no or low human papillomavirus load, British Journal of Cancer. *78:* 69-72, 1998.

81. Min, B.-M., Baek, J.-H., Shin, K.-H., Gujuluva, C. N., Cherrick, H. M., and Park, N.-H. Inactivation of the p53 gene by either mutation or HPV infection is extremely frequent in human oral squamous cell carcinoma cell lines, European Journal of Cancer. *30B:* 338-345, 1994.

82. Scheffner, M., Werness, B. A., Huigbretse, J. M., Levine, A. J., and Howley, P. M. The E6 oncoprotein encoded by human papillomavirus types 16 and 18 promotes the degradation of p53, Cell. *63:* 1129-1136, 1990.

83. Penhallow, J., Steingrimsdottir, H., Elamin, F., Warnakulasuriya, S., farzaneh, F., Johnson, N., and Tavassoli, M. p53 alterations and HPV infections are common in oral SCC: p53 gene mutations correlate with the absence of HPV16-E6 DNA, International Journal of Oncology. *12:* 59-68, 1998.

84. Scheffner, M., Munger, K., Byrne, J. C., and Howley, P. M. The state of the p53 and retinoblastoma genes in human cervical carcinoma cell lines, Proceedings of National Academy of Sciences, U.S.A. *88:* 5523-5527, 1991.

85. Desaintes, C., Hallez, S., Detremmerie, O., and Burny, A. Wild-type p53 down-regulates transcription from oncogenic human papillomavirus promoters through the epithelial specific enhancer, Oncogene. *10:* 2155-61, 1995.

86. Kurvinen, K., Syrjanen, K., and Syrjanen, S. p53 and bcl-2 proteins as prognostic markers in human papillomavirus-associated cervical lesions, Journal of Clinical Oncology. *14:* 2120-2130, 1996.

87. Pillai, M. R., Halabi, S., McKalip, A., Jayaprakash, P. G., Rajalekshmi, T. N., Nair, M. K., and Herman, B. The presence of human papillomavirus-16/18 E6, p53, and bcl-2 protein in cervicovaginal smears from patients with invasive cervical cancer, Cancer Epidemiology, Biomarkers & Prevention. *5:* 329-335, 1996.

88. Miwa, K., Miyamoto, S., Kato, H., Imamura, T., Nishida, M., Yoshikawa, Y., Nagata, Y., and Wake, N. The role of p53 inactivation in human cervical cell carcinoma development, British Journal of Cancer. *71:* 219-226, 1995.

89. Ngan, H. Y. S., Stanley, M., Liu, S. S., and Ma, H. K. HPV and p53 in cervical cancer, Genitourinary Medicine. *70:* 167-170, 1994.

90. Sheets, E. E. and Yeh, J. The role of apoptosis in gynaecological malignancies, Ann Med. *29:* 121-6, 1997.

91. Slebos, R. J. C., Lee, M. H., Plunkett, B. S., Kessis, T. D., Williams, B. O., Jacks, T., Hedrick, L., Kastan, M. B., and Cho, K. R. p53-dependent G1 arrest involves pRB-related proteins and is disrupted by the human papillomavirus 16 E7 oncoprotein, Proceedings of National Academy of Sciences, U.S.A. *91:* 5320-5324, 1994.

92. Demers, G. W., Foster, S. A., Halbert, C. L., and Galloway, D. A. Growth arrest by induction of p53 in DNA damaged keratinocytes is bypassed by human papillomavirus 16 E7, Proceedings of National Academy of Sciences, U.S.A. *91:* 4382-4386, 1994.

93. Kessis, T. D., Slebos, R. J., Nelson, W. G., Kastan, M. B., Plunkett, B. S., Han, S. M., Lorincz, A. T., Hedrick, L., and Cho, K. R. Human papillomavirus 16 E6 expression disrupts the p53-mediated cellular response to DNA damage, Proceedings of National Academy of Sciences, U.S.A. *90:* 3988-3992, 1993.

94. Alfandari, J., Shnitman Magal, S., Jackman, A., Schlegel, R., Gonen, P., and Sherman, L. HPV16 E6 oncoprotein inhibits apoptosis induced during serum-calcium differentiation of foreskin human keratinocytes, Virology. *257:* 383-96, 1999.

95. Pillai, R. M., Nair, P., Nair, K. M., and Jayaprakash, P. G. Decreased programmed cell death in the uterine cervix associated with high risk human papillomavirus infection [In Process Citation], Pathol Oncol Res. *5:* 95-103, 1999.

96. Furuya, H., Yabushita, H., Noguchi, M., and Nakanishi, M. [Apoptosis and cell growth fraction in normal, dysplastic and neoplastic squamous epithelium of uterine cervix], Nippon Rinsho. *54:* 1916-21, 1996.

97. Mythily, D. V., Krishna, S., and Tergaonkar, V. Pleiotropic effects of human papillomavirus type 16 E6 oncogene expression in human epithelial cell lines, J Gen Virol. *80:* 1707-13, 1999.

98. Liu, Y., Tergaonkar, V., Krishna, S., and Androphy, E. J. Human Papillomavirus Type 16 E6-enhanced Susceptibility of L929 Cells to Tumor Necrosis Factor alpha Correlates with Increased Accumulation of Reactive Oxygen Species, J Biol Chem. *274:* 24819-24827, 1999.

99. Kilic, G., Cardillo, M., Ozdemirli, M., and Arun, B. Human papillomavirus 18 oncoproteins E6 and E7 enhance irradiation- and chemotherapeutic agent-induced apoptosis in p53 and Rb mutated cervical cancer cell lines, Eur J Gynaecol Oncol. *20:* 167-71, 1999.

100. Storey, A., Thomas, M., Kalita, A., Harwood, C., Gardiol, D., Mantovani, F., Breuer, J., Leigh, I. M., Matlashewski, G., and Banks, L. Role of a p53 polymorphism in the development of human papillomavirus-associated cancer, Nature. *393:* 229-234, 1998.

101. Rosenthal, A. N., Ryan, A., Al-Jehani, R. M., Storey, A., Harwood, C. A., and Jacobs, I. J. p53 codon 72 polymorphism and risk of cervical cancer in UK, Lancet. *352:* 871-872, 1998.

102. Helland, A., Langerod, A., Johnsen, H., Olsen, A. O., Skovlund, E., and Borresen-Dale, A.-L. p53 polymorphism and risk of cervical cancer, Nature. *396:* 530-531, 1998.

103. Storey, A., Thomas, M., Kalita, A., Harwood, C., Gardiol, D., Mantovani, F., Breuer, J., Leigh, I. M., Matlashewki, G., and Banks, L. p53 polymorphism and risk of cervical cancer, Nature. *396:* 531-532, 1998.

104. Josefsson, A. M., Magnusson, P. K. E., Ylitalo, N., Quarforth-Tubbin, P., Ponten, J., Adami, H. O., and Gyllensten, U. B. p53 polymorphism and risk of cervical cancer, Nature. *396:* 531, 1998.

105. DiPaolo, J. A., Popescu, N. C., Woodworth, C. D., and Zimonjic, D. B. Papillomaviruses and potential copathogens, Toxicology Letters. *88:* 1-7, 1996.

106. Galloway, D. A. and McDougall, J. K. The disruption of cell cycle checkpoints by papillomavirus oncoproteins contributes to anogenital neoplasia, Seminars in Cancer Biology. *7:* 309-315, 1996.

107. Hashida, T. and Yasumoto, S. Induction of chromosome abnormalities in mouse and human epidermal keratinocytes by the human papillomavirus type 16 E7 oncogene, Journal of General Virology. *72:* 1569-1577, 1991.

108. Yin, X. Y., Grove, L., Datta, N. S., Long, M. W., and Prochownik, E. V. C-myc overexpression and p53 loss cooperate to promote genomic instability, Oncogene. *18:* 1177-84, 1999.

109. Heselmeyer, K., Macville, M., Schrock, E., Blegen, H., Hellstrom, A. C., Shah, K., Auer, G., and Ried, T. Advanced-stage cervical carcinomas are defined by a recurrent pattern of chromosomal aberrations revealing high genetic instability and a consistent gain of chromosome arm 3q, Genes Chromosomes Cancer. *19:* 233-40, 1997.

110. Davies, R., Hicks, R., Crook, T., Morris, J., and Vousden, K. Human papillomavirus type 16 E7 associates with a histone H1 kinase and with p107 through sequences necessary for transformation, J Virol. *67:* 2521-8, 1993.

111. Ludlow, J. W. and Skuse, G. R. Viral oncoprotein binding to pRB, p107, p130, and p300, Virus Research. *35:* 113-121, 1995.

112. LeCouter, J. E., Kablar, B., Whyte, P. F., Ying, C., and Rudnicki, M. A. Strain-dependent embryonic lethality in mice lacking the retinoblastoma- related p130 gene, Development. *125:* 4669-79, 1998.

113. Bowman, T., Symonds, H., Gu, L., Yin, C., Oren, M., and Van Dyke, T. Tissue-specific inactivation of p53 tumor suppression in the mouse, Genes Dev. *10:* 826-35, 1996.

114. Grana, X., Garriga, J., and Mayol, X. Role of the retinoblastoma protein family, pRB, p107 and p130 in the negative control of cell growth, Oncogene. *17:* 3365-3383, 1998.

115. Weinberg, R. A. The retinoblastoma protein and cell cycle control, Cell. *81:* 323-30, 1995.

116. Hartwell, L. H. and Kastan, M. B. Cell cycle control and cancer, Science. *266:* 1821-1828, 1994.

117. Farnham, P. J., Slansky, J. E., and Kollmar, R. The role of E2F in the mammalian cell cycle, Biochimica et Biophysica Acta. *1155:* 125-131, 1993.

118. Nevins, J. R. E2F: a link between the RB tumor suppressor protein and viral oncoproteins, Science. *258:* 424-429, 1992.

119. Helin, K. Regulation of cell proliferation by the E2F transcription factors, Current Opinion in Genetics and Development. *8:* 28-35, 1998.

120. Imai, Y., Matsushima, Y., Sugimura, T., and Terada, M. Purification and characterization of human papillomavirus type 16 E7 protein with preferential binding capacity to the underphosphorylated form of retinoblastoma gene product, J Virol. *65:* 4966-72, 1991.

121. McIntyre, M. C., Ruesch, M. N., and Laimins, L. A. Human papillomavirus E7 oncoproteins bind a single form of cyclin E in a complex with cdk2 and p107, Virology. *215:* 73-82, 1996.

122. Zerfass, K., Schulze, A., Spitkovsky, D., Frieman, V., Henglein, B., and Jansen-Durr, P. Sequential activation of cyclin E and cyclin A gene expression by human papillomavirus type 16 E7 through sequences necessary for transformation, Journal of Virology. *69:* 6389-6399, 1995.

123. Antinore, M. J., Birrer, M. J., Patel, D., Nader, L., and McCance, D. J. The human papillomavirus type 16 E7 gene product interacts with and *trans*-activates the AP1 family of transcription factors, The EMBO Journal. *18:* 1950-1960, 1996.

124. Steele, C., Cowsert, L. M., and Shillitoe, E. J. Effects of human papillomavirus type 18-specific antisense oligonucleotides on the transformed phenotype of human carcinoma cell lines, Cancer Research. *53:* 2330-2337, 1993.