discussed earlier, these kinases participate in the cascade that promotes both cell survival and metabolic alterations that enhance cell growth. Tax also directly upregulates the expression of cyclin D2 and represses the expression of multiple CDK inhibitors, changes that promote cell cycle progression. Finally, Tax can activate the transcription factor NF-κB, which promotes the survival of many cell types, including lymphocytes.

- **Increased genomic instability.** Tax may also cause genomic instability by interfering with DNA-repair functions and inhibiting cell cycle checkpoints activated by DNA damage. In line with these defects, HTLV-1-associated leukemias tend to be highly aneuploid.

The precise steps that lead to the development of adult T-cell leukemia/lymphoma are still not known, but a plausible scenario is as follows. Infection by HTLV-1 causes the expansion of a nonmalignant polyclonal cell population through stimulatory effects of Tax on cell proliferation. The proliferating T cells are at increased risk of mutations and genomic instability due to the effects of Tax, and possibly other viral factors as well. This instability allows the accumulation of mutations and chromosomal abnormalities, and eventually a monoclonal neoplastic T-cell population emerges.

Oncogenic DNA Viruses

As with RNA viruses, several oncogenic DNA viruses that cause tumors in animals have been identified. Of the various human DNA viruses, five—HPV, Epstein-Barr virus (EBV), hepatitis B virus (HBV), Merkel cell polyoma virus, and Kaposi sarcoma herpesvirus, also called human herpesvirus 8—have been implicated in the causation of human cancer. Merkel cell polyomavirus has been identified in Merkel cell carcinomas and is described in Chapter 25. Kaposi sarcoma herpesvirus is discussed in Chapters 6 and 11. Although not a DNA virus, hepatitis C virus (HCV) is also associated with cancer and is discussed here briefly.

Human Papillomavirus. At least 70 genetically distinct types of HPV have been identified. Some types (e.g., 1, 2, 4, and 7) cause benign squamous papillomas (warts) in humans. In contrast, high-risk HPVs (e.g., types 16 and 18) have been implicated in the genesis of squamous cell carcinomas of the cervix, anogenital region, and head and neck (particularly tumors arising in the tonsillar mucosa). These cancers are sexually transmitted diseases, caused by transmission of HPV. In contrast to cervical cancers, genital warts have low malignant potential and are associated with low-risk HPVs, predominantly HPV-6 and HPV-11. Interestingly, in benign warts, the HPV genome is maintained in a nonintegrated episomal form, while in cancers the HPV genome is integrated into the host genome, suggesting that integration of viral DNA is important for malignant transformation. As with HTLV-1, the site of viral integration in host chromosomes is random, but the pattern of integration is clonal. Cells in which the viral genome has integrated show significantly more genomic instability. Because the integration site is random, there is no consistent association with a host proto-oncogene. Rather, integration interrupts the viral DNA within the E1/E2 open reading frame, leading to loss of the E2 viral repressor and overexpression of the oncoproteins E6 and

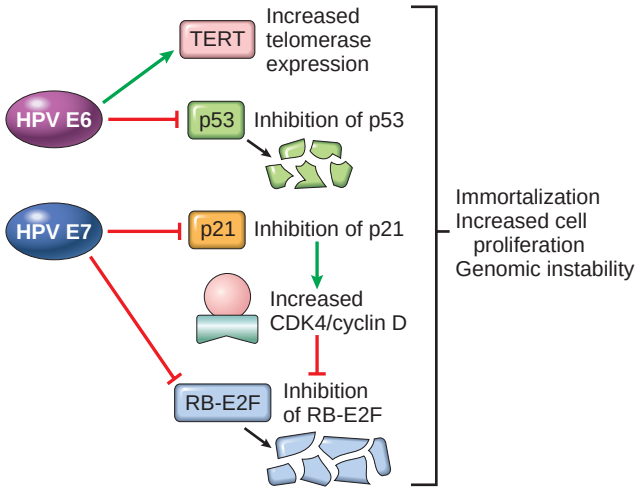

Figure 7-45 Transforming effects of HPV E6 and E7 proteins. The net effect of HPV E6 and E7 proteins is to immortalize cells and remove the restraints on cell proliferation (see Fig. 7-29). TERC, telomerase catalytic subunit. (Modified from Münger K, Howley PM: Human papillomavirus immortalization and transformation functions. Virus Res 2002;89:213-228.)

E7. Indeed, **the oncogenic potential of HPV can largely be explained by the activities of the two viral genes encoding E6 and E7** (Fig. 7-45).

- **Oncogenic activities of E6.** The E6 protein binds to and mediates the degradation of p53, and also stimulates the expression of TERT, the catalytic subunit of telomerase, which you will recall contributes to the immortalization of cells. E6 from high-risk HPV types has a higher affinity for p53 than E6 from low-risk HPV types. Interestingly the E6-p53 interaction may offer some clues regarding polymorphisms and risk factors for development of cervical cancer. Human *TP53* is polymorphic at codon 72, encoding either a proline or arginine residue at that position. The p53 Arg72 variant is much more susceptible to degradation by E6. Not surprisingly, infected individuals with the Arg72 polymorphism are more likely to develop cervical carcinomas.
- **Oncogenic activities of E7.** The E7 protein has effects that complement those of E6, all of which are centered on speeding cells through the G_1-S cell cycle checkpoint. It binds to the RB protein and displaces the E2F transcription factors that are normally sequestered by RB, promoting progression through the cell cycle. As with E6 proteins and p53, E7 proteins from high-risk HPV types have a higher affinity for RB than do E7 proteins from low-risk HPV types. E7 also inactivates the CDK inhibitors p21 and p27. Finally, E7 proteins from high-risk HPVs (types 16, 18, and 31) also bind and presumably activate cyclins E and A.

To summarize, **high-risk HPV types express oncogenic proteins that inactivate tumor suppressors, activate cyclins, inhibit apoptosis, and combat cellular senescence.** Thus, it is evident that HPV proteins promote many of the hallmarks of cancer. The primacy of HPV infection in the causation of cervical cancer is confirmed by the effectiveness of HPV vaccines in preventing cervical cancer. However, infection with HPV itself is not sufficient for