A New Link Between Fanconi Anemia and Human Papillomavirus–Associated Malignancies

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In this issue of the Journal, Kutler et al. (1) provide evidence that Fanconi anemia patients have an inherited susceptibility to human papillomavirus (HPV)-associated malignancies. Fanconi anemia is a group of rare autosomal recessive conditions characterized by congenital abnormalities, progressive bone marrow failure, and a predisposition to both acute myelogenous leukemia and certain solid tumors. Systematic reviews of the Fanconi anemia literature, surveys of Fanconi anemia patients, and data from the International Fanconi Anemia Registry (IFAR) have identified an unusual preponderance of head and neck squamous cell carcinomas and anogenital tract malignancies among Fanconi anemia patients (2–5). For example, among 754 patients enrolled in the IFAR, 28% developed solid tumors by the age of 40 years (5). The risk of head and neck squamous cell carcinomas among Fanconi anemia patients enrolled in the IFAR is approximately 500-fold higher than it is among the general population (6). The majority of those Fanconi anemia patients did not have a history of alcohol or tobacco use, which are the strongest risk factors for head and neck squamous cell carcinoma in the general population (6). However, among the general population, a subset of head and neck squamous cell carcinomas and anogenital tumors share a common etiology: HPV [reviewed in (7,8)].

On the basis of these observations, Kutler et al. (1) hypothesized that HPV may also play a role in the pathogenesis of head and neck squamous cell carcinomas and anogenital tumors in Fanconi anemia patients. They detected HPV DNA, predominantly high-risk HPV type 16 DNA, in 15 of 18 head and neck squamous cell carcinomas and in all six vulvar squamous cell carcinomas analyzed from Fanconi anemia patients enrolled in the IFAR. The prevalence of HPV DNA in the 24 tumors from the Fanconi anemia patients was greater than it was in squamous cell carcinomas at the same anatomic sites from matched non–Fanconi anemia patients. All of the vulvar squamous cell carcinomas from the Fanconi anemia patients had warty or basaloid histopathology, the subset of carcinomas previously associated with the presence of DNA from high-risk types of HPV [reviewed in (7)]. The majority of the head and neck tumors in the Fanconi anemia patients arose from the anterior tongue, whereas most HPV-associated head and neck squamous cell carcinomas in the general population are tonsillar. In the general population, HPV-associated head and neck squamous cell carcinomas and vulvar tumors often have somatic mutations of the p53 tumor suppressor gene, whereas HPV-associated tumors at these sites usually have wild-type p53 alleles (7,9). The presence of wild-type p53 in the HPV-associated tumors is attributed to the ability of the HPV E6 protein to inactivate the wild-type p53 protein by inducing its degradation [reviewed in (10)]. Consistent with this E6-dependent mechanism, all 24 of the Fanconi anemia tumors analyzed by Kutler et al. (1) carried wild-type p53 alleles.

The only previously known syndrome associated with an inherited susceptibility to HPV-associated cancers is epidermodysplasia verruciformis, an autosomal recessive cancer-prone disorder characterized by a specific susceptibility to widespread, persistent cutaneous HPV infection, especially with the so-called epidermodysplasia verruciformis HPV types [reviewed in (11)]. Approximately one-half of epidermodysplasia verruciformis patients, particularly those infected with HPV type 5 or HPV type 8, eventually develop cutaneous squamous cell carcinomas on sun-exposed areas. Therefore, HPV-associated malignancies in epidermodysplasia verruciformis patients differ from the majority of those in Fanconi anemia patients. Epidermodysplasia verruciformis was recently linked to mutations in EVER1 and EVER2 (also known as TMC6 and TMC8, respectively), two highly conserved genes of unknown function that are members of the transmembrane channel-like gene family (12).

The molecular defect in Fanconi anemia results from biallelic inactivation of any of at least seven Fanconi anemia genes named FANCA, FANCB, FANCC, FANCD, FANCE, FANCF, and FANCG [reviewed in (13,14)]. Each of these genes has been placed in a cell cycle checkpoint and DNA repair pathway that includes the breast cancer (BRCA) tumor suppressor genes (i.e., the Fanconi anemia/BRCA pathway). The Fanconi anemia gene defects are associated with cellular hypersensitivity to DNA cross-linking agents and oxidative stress, increased double-strand DNA breaks and chromosomal instability, loss of telomere integrity, and cell cycle prolongation.

In the general population, HPV-associated cancers develop as a consequence of persistent HPV infection plus a series of genetic and epigenetic changes in an infected cell that often occur in association with viral DNA integration [reviewed in (15,16)]. Although increased risks of persistent HPV infection and HPV-associated tumors are seen in patients with immune dysfunctions resulting from HIV infection or allograft recipients [reviewed in (17)], no comparable information for HPV infection is available for Fanconi anemia patients. Although the immune impairment associated with the cytopenia of Fanconi anemia could play a role in HPV persistence, most Fanconi anemia patients do not have difficulties handling infections, and the IFAR patients who have undergone bone marrow transplantation do not appear to have a higher incidence of head and neck squamous cell carcinomas or vulvar cancer than Fanconi anemia patients not treated by bone marrow transplantation (5).

The relatively young age of Fanconi anemia patients with head and neck squamous cell carcinoma or vulvar cancer sug-

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suggests that the period between HPV infection and development of cancer may be considerably shorter in this patient population than in the general population. This situation could arise if the combination of HPV infection and a defect in the Fanconi anemia pathway resulted in a decrease in the number of additional cellular changes required for progression to cancer and/or an increase in the rate at which these changes occurred. Many hypothetical interactions are possible. For example, because Fanconi anemia is associated with a high rate of apoptosis, which inhibits tumorigenesis, the ability of HPV E6 to inhibit apoptosis through both p53-dependent and p53-independent mechanisms [reviewed in (16)] may represent one mechanism by which HPV could cooperate with the Fanconi anemia defect to shorten the time to cancer development. Freie et al. (18) reported that the loss of p53 function in FANCC-negative mice was associated with an increased rate and incidence of tumor formation, a finding that is consistent with a putative E6–Fanconi anemia interaction. In addition, Fanconi anemia patients enrolled in the IFAR who developed squamous cell carcinoma were more likely to be homozygous for the p53 polymorphism encoding arginine at codon 72 (Arg72) when compared with ethnically matched Fanconi anemia patients without tumors (1), suggesting that this polymorphism, in the presence of Fanconi anemia and HPV, may tip the balance toward cancer development. The greater susceptibility of p53 protein containing the Arg72 polymorphism to degradation by the HPV E6 oncoprotein (19) has not been consistently linked to an increased risk for HPV-associated cancer in the general population [reviewed in (10,20)].

The recognition that HPV plays a role in the development of tumors in Fanconi anemia patients may stimulate some new research directions. For example, sexual transmission is the principal mode of genital and oral HPV infection in the general population (21), but it is not known whether this is also true for Fanconi anemia patients. The risks and timing of HPV exposure in Fanconi anemia, as well as a possible immune impairment in Fanconi anemia that may favor persistence over clearance of HPV infection, could be addressed experimentally by prospectively screening Fanconi anemia patients for incident oral and genital HPV infections. If exposure to HPV type 16 (and/or HPV type 18) occurs primarily during adolescence or later, the prophylactic HPV virus-like particle vaccine, which targets HPV type 16 (and HPV type 18) and is currently in clinical trials, might be able to prevent most Fanconi anemia cancers attributable to HPV (22,23).

One unexpected result reported by Kutler et al. (1) was that oral dysplastic lesions from Fanconi anemia patients with HPV DNA–positive tumors were negative for HPV DNA. If this finding was confirmed, it would suggest that oral dysplasia precedes HPV infection in Fanconi anemia. By contrast, in the general population, HPV infection is known to precede cervical dysplasia. Confirming the finding of Kutler et al. (1) would not only explain the heterogeneity of results among studies that have investigated the relationship between HPV and oral dysplasia (24), but would also have important implications for oral cancer screening.

It may be useful to explore possible functional interactions between Fanconi anemia gene defects and HPV in detail. In addition to the effects on apoptosis noted above, other possible interactions include HPV E6 induction of telomerase, which would overcome the telomere shortening associated with Fanconi anemia; HPV E7 stimulation of the cell cycle, which would antagonize the cell cycle prolongation that is characteristic of Fanconi anemia; and HPV E6 and E7 induction of genomic instability and double-strand DNA breaks (16,25), which would enhance similar defects in Fanconi anemia. Mouse models of HPV and Fanconi anemia can help address these interactions as well as other possible interactions (14,18,26).

Additional molecular analyses of HPV DNA and HPV gene expression in head and neck squamous cell carcinomas and anogenital tumors in Fanconi anemia patients are needed to determine the degree to which the viral parameters resemble HPV in tumors from the general population. For example, it will be interesting to determine whether the defects in double-strand DNA repair that characterize Fanconi anemia potenti ate HPV integration, and whether the defects in chromatin remodeling and transcription associated with Fanconi anemia facilitate dysregulated expression of HPV genes.

It would also be worthwhile to look for HPV in other solid tumors arising in Fanconi anemia patients, such as skin and esophageal carcinomas (3,5), because the role of HPV infection in the development of those tumors in the general population remains unclear. Conversely, the postulated functional interaction between the Fanconi anemia/BRCA pathway and HPV suggests that some cases of HPV-associated cancer in the general population might be associated with somatic disruption of that pathway. The estimated carrier rate for Fanconi anemia mutations is approximately 1 : 200 to 1 : 300 in the general population, and as high as 1 : 90 among Ashkenazi Jews. There might also be germline polymorphisms of the Fanconi anemia genes with more subtle effects in the general population that could predispose their carriers to the oncogenic effects of HPV. One might also consider whether HPV or other oncogenic infectious agents might have greater oncogenic activity in the context of cancer-prone syndromes other than epidermodysplasia verruciformis and Fanconi anemia.

Should the new findings reported by Kutler et al. (1) affect clinical practice? Certainly Fanconi anemia patients should be screened for cervical, vulvar, and oral cancers, and such screening should be initiated at a younger age than in the general population, perhaps at onset of sexual activity. However, we need to know more about the natural history and predictive value of oral HPV infection before HPV DNA detection can be incorporated into oral cancer screening. Clinicians should also consider the possibility of Fanconi anemia in young head and neck squamous cell carcinoma patients who do not smoke or drink alcohol, particularly in those patients with unusually severe toxicity from chemotherapy or radiation therapy.

A new frontier in the molecular epidemiology of HPV infection lies in the identification of host- and virus-specific factors that, in a minority of infected individuals, tip the balance toward disease progression rather than toward clearance of infection (27). HPV-associated cancer susceptibility syndromes can provide surprising new directions to guide this research.

REFERENCES
