Chapter 15: Non-Head and Neck Solid Tumors in Patients with Fanconi Anemia

Introduction

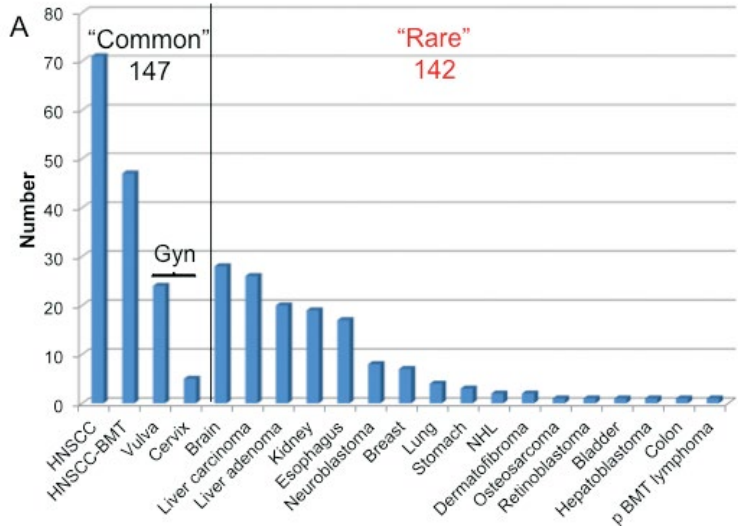
Cancer is a major concern in FA patients. This chapter will describe the most common types of non-head and neck solid tumors in patients with FA, the incidence and risk of developing these tumors, and the influences of age and genetic predisposition on cancer diagnosis. Specifically, cancer types and risks have been determined from case reports and case series in the literature from 1927 through 2012 (Figure 1A), and from follow-up of four cohorts in the US, Germany, and Israel, published from 2003 through 2010 (Figure 1B) [1-5]. This chapter will focus on solid tumors, and compare the numbers, ages, and observed/expected risk ratios [adjusted for age, sex, and birth cohort, compared with data from SEER [6]] of the more "common" solid tumors with those solid tumors that are considered to be "rare," in order to provide perspective.

Types of Solid Tumors

According to case series and case reports, the most common types of solid tumors that occur in patients with FA include head and neck squamous cell carcinomas, as well as gynecologic cancers (primarily vulvar and cervical cancers). These are discussed in *Chapter 14* and *Chapter 6,* respectively. The following types of solid tumors occur less frequently than head and neck cancers and gynecologic cancers in patients with FA:

- *Liver carcinomas (sometimes called "hepatocellular")*
- *Liver adenomas (these tumors are considered to be benign, but are not always clearly diagnosed until a biopsy has been performed)*
- *Brain tumors*
- *Kidney tumors (frequently of a type known as Wilms' tumor)*
- *Esophageal tumors*
- *Neuroblastomas (tumors that develop from nerve tissue)*
- *Breast tumors*

Figure 1. Number of solid tumors in patients with FA. A) 289 solid tumors reported in 2,250 literature case reports and series, from 1927 to 2012. 147 were "common" and 142 were "rare". Adapted from Shimamura and Alter [1]. B) 67 solid tumors reported in 459 patients in 4 cohort studies conducted by the National Cancer Institute (NCI), the Israeli Fanconi Anemia Registry (ISFAR), the German Fanconi Anemia Registry (GEFA), and the North American Survey (NAS) [2-5].



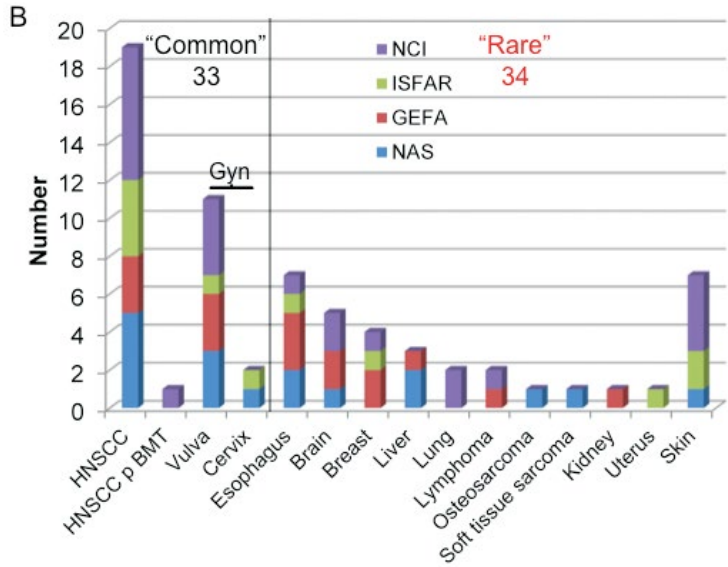
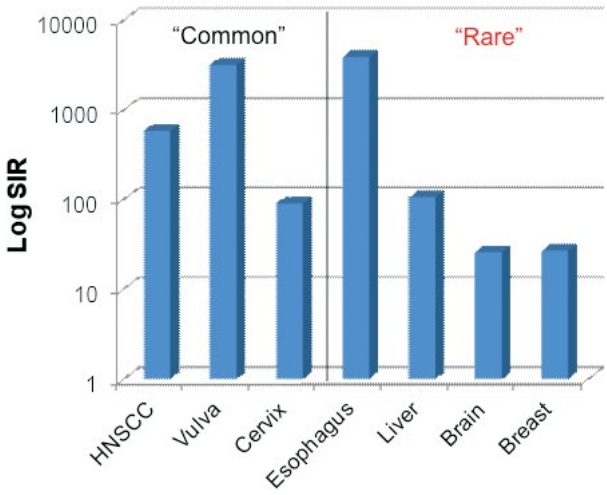


Figure 2. Ratio of observed to expected cancers in FA cohorts. The standardized incidence ratio (SIR) compares the observed numbers of cases to those expected from the US national cancer statistics (called SEER, for Surveillance, Epidemiology, and End Results), after adjustment for age, sex, and birth cohort. The SIR data are plotted on a logarithmic scale, because the values range from 10 to more than 1000.



A few additional types of solid tumors have been reported in only 2 to 4 patients with FA:

- *Lung tumors*
- *Stomach tumors*
- *Lymphomas (tumors that originate from the lymph nodes)*
- *Dermatofibromas (benign tumors that form on the skin)*
- *Osteosarcomas (tumors that form in the bones)*
- *Retinoblastomas (tumors that form in the retina of the eye)*
- *Bladder cancer*
- *Hepatoblastomas (tumors that form in the liver)*
- *Colon cancer*

Some patients with FA develop multiple cancers. Of the 2,250 patients described in case series and case reports, 31 patients had 2 or 3 different types of solid tumors, and 22 patients had 1 or more solid tumors in addition to acute myelogenous leukemia (AML) [1].

Incidence and Risk of Solid Tumors

Approximately 1 out of every 10 patients with FA in case reports, case series, and cohort studies had a solid tumor. However, this statistic does not take age into account. Combined data from the four cohort studies of patients with FA indicate that a solid tumor of any type is a major adverse outcome in FA: One estimate suggests that approximately 1 out of every 4 patients with FA will develop a solid tumor by the age of 45 [2-5], and the theoretical risk in patients with normal bone marrow increases to nearly 3 out every 4 patients, since these patients will live long enough to develop a cancer [2]. Therefore, solid tumors may be increasingly diagnosed in patients with FA as more patients survive hematopoietic stem cell transplantation (HSCT) and as mild cases of FA, such as patients with hematologic mosaicism (i.e., patients in whom a bone marrow stem cell has undergone a genetic event leading to correction of one of the mutated genes), are recognized more often [5,9].

The most frequent solid tumors in patients with FA appear to be squamous cell carcinomas of the head and neck, and gynecologic cancers. However, the *relative risk* of developing several types of rare cancers is very high. Therefore, patients with FA should be monitored closely for the development of any solid tumor.

Standardized incidence ratios (SIRs) based on the incidences of cancer observed in cohort studies of patients with FA and those expected for the general population [6] (after accounting for age and sex) reveal that the "rare" cancers of the esophagus and liver occur with high risks in the FA population. These tumors, as well as brain and breast, are extremely infrequent in the non-FA population, and thus have high ratios of observed to expected, or SIR (Figure 2).

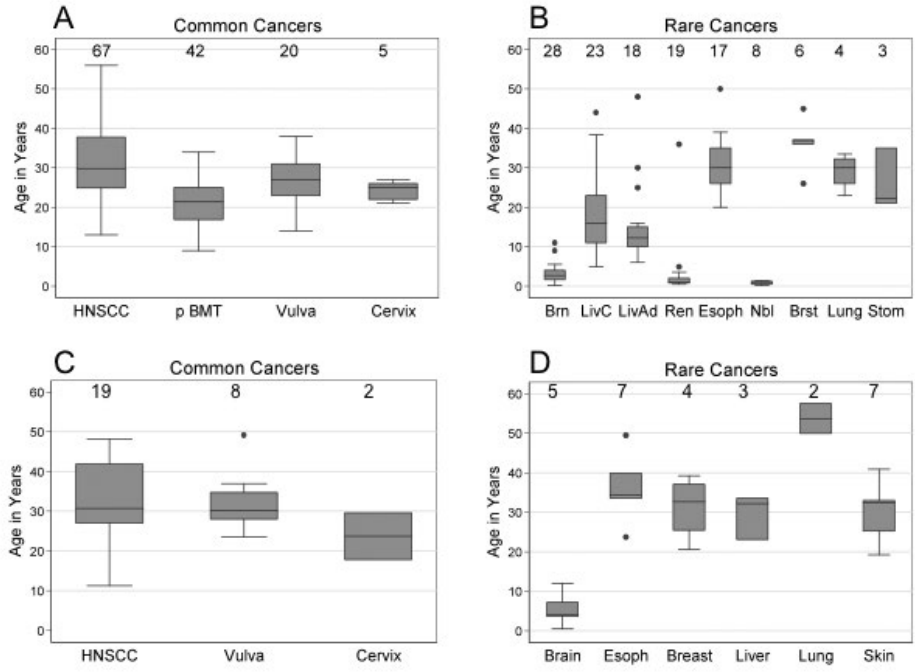
Age at Cancer Diagnosis

Most of the solid tumors in patients with FA that have been reported occurred when the patient was age 20 or older, although liver tumors were reported in teenage patients with FA and are perhaps related to the use of androgens for bone marrow failure. In addition, neuroblastomas and tumors of the brain and kidney were reported in children below age 10, and were found primarily in patients carrying mutations in both copies of the *FANCD1/BRCA2* gene [7]. Cancers of the esophagus, breast, lung, and stomach were reported in patients with FA starting at age 20 (Figure 3A and B). Case series and case reports

suggest that patients with FA who have undergone HSCT tend to develop head and neck squamous cell carcinoma starting in teenage years, whereas patients who have not received a transplant tend to develop head and neck squamous cell carcinoma starting at around age 20. In approximately 35% of the cancer cases reported in patients with FA, the diagnosis of solid tumors or AML preceded the diagnosis of FA; therefore, physicians may sometimes fail to recognize patients with undiagnosed FA who have cancer as their first manifestation [8, 9].

As shown in Figure 1B, the types of cancers reported in cohort studies of patients with FA are very similar to those reported in the literature in case series and case reports: Head and neck squamous cell carcinomas and gynecologic cancers are the most common, followed by cancers of the esophagus, brain, breast, and liver. In addition, cohort studies revealed that brain tumors occurred primarily in patients with mutations in the *FANCD1/BRCA2* gene. Of the 459 patients participating in the cohort studies, 15 had multiple cancers. Of these 15 patients, 12 had 2 or 3 solid tumors, and 3 patients had a solid tumor and AML. The ages at diagnosis of cancer were also similar in the case series and case reports and cohort studies: Most of the common and rare solid tumors occurred between the ages of 20 to 40, brain tumors developed at age 10 or younger, and lung cancer occurred after age 40 (Figure 3C and D).

Figure 3. Age at cancer diagnosis in patients with FA. A and B, literature case series and case reports. C and D, cohort studies. X-axis abbreviations: HNSCC, head and neck squamous cell carcinoma; p BMT, after bone marrow transplant; Brn, brain; LivC, liver carcinoma; LivAd, liver adenoma; Ren, renal; Esoph, esophagus; Nbl, neuroblastoma; Brst, breast; Stom, stomach. The numbers above the boxes indicate how many cases are in each box. The line in the box is the median, the ends of the lines are the minimum and maximum values, the bottom and top of the boxes mark the first and third quartiles, and the dots above the lines are statistical outliers. Figure shown on next page.



Genes and Cancer

Recent studies suggest that patients with FA who have mutations in both copies of the *FANCD1*/*BRCA2* gene have highly predictable patterns of tumor development [7,10]. Among 27 patients with mutations in this gene, 2 had no cancer, 19 had 1 cancer, 3 had 2, and 3 had 3 cancers. There were a total of 34 cancers: 12 brain tumors, 10 AML, 7 Wilms' tumors, 4 acute lymphoblastic leukemia (ALL), and 1 neuroblastoma (Table 1). Five out of 6 patients with at least one copy of a mutation known as the IVS7 variant (either +2T>G or +1G>A) developed AML, whereas only 5 out of 21 patients with other mutations developed AML. Brain tumors were found in 3 out of 3 patients with the 6174delT mutation, 4 out of 4 patients with the 886delGT mutation, as well as 1 patient with both mutations. Two of 19 patients with other mutations also developed brain tumors. A specific mutation was not clearly identified for the 7 patients with Wilms' tumors.

Table 1. Number of cancers in patients with mutations in both FANCD1/BRCA2 genes.*

	Brain	AML	ALL	Wilms	Neuroblastoma
Total	12	10	4	7	1
As 1st Cancer	8	8	3	6	0
As 2nd Cancer	3	2	0	0	1
As 3rd Cancer	1	0	1	1	0
Median age in years at cancer diagnosis (range)	3.3 (1.3-9)	2 (0.9-6.3)	5.1 (4.9-10)	1 (0.5-6.6)	1.1

**Adapted from Alter et al. (7)*
Abbreviations: Acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL)

Future Challenges

Although the prognosis for people with FA is better than ever, many challenges remain. Future research should strive to improve strategies for cancer screening and prevention, particularly for cancers to which patients with FA are vulnerable. Avoiding tobacco and alcohol, combined with good oral hygiene, can help mitigate some environmental carcinogens, but these strategies alone are clearly not sufficient to prevent cancers in patients with FA. The vaccines against the human papillomavirus (HPV) that are currently available are prophylactic rather than therapeutic, and while they may help to prevent new cases of gynecologic squamous cell carcinomas, these vaccines may not reduce the incidence of head and neck squamous cell carcinoma, particularly of the oral cavity [(11)]. Screening methods and case management strategies that address the DNA repair defect in patients with FA may help to improve the treatment and prevention of cancer in these patients, but remain open research questions. As the number of patients with defined genotypes and mutations increases, the prognostic value of gene-cancer associations will improve, which may ultimately lead to earlier targeted screening and directed interventions.

Editor's note: Screening guidelines for organ-site specific cancers are discussed in previous chapters, including *Chapter 14* (head and neck squamous cell carcinoma) and *Chapter 6* (gynecologic cancers). In addition, *Chapter 20* provides a comprehensive list of all screening recommendations for individuals with FA.

Chapter Committee

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