

Cancer in Fanconi Anemia, 1927–2001

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BACKGROUND. Fanconi anemia (FA) is an autosomal recessive disease associated with an abnormal response to DNA damage. Although FA is well known for the association of aplastic anemia and characteristic birth defects, leukemia and solid tumors also occur at a high rate in this group of patients. A review of all reported cases is informative with regard to the specific types of cancer, the ages at which they occur, and the cumulative probability of their development.

METHODS. Medline and bibliographies of publications were searched for articles containing “Fanconi’s anemia” or “aplastic anemia” and all cases of FA from 1927 through 2001 were included in the database. Cancer cases were identified within these reports. Descriptive statistical analyses were performed using Stata7 software.

RESULTS. One thousand three hundred cases of FA were identified. Nine percent had leukemia (primarily acute myeloid leukemia), 7% had myelodysplastic syndrome, 5% had solid tumors, and 3% had liver tumors. Patients with cancer were older than the cancer-free patients at the time of diagnosis of FA. The median age for cancer (including leukemia) was 16, compared with 68 in the general population. The most frequent solid tumors were aerodigestive and gynecological carcinomas. In approximately 25% of patients with cancer, the malignancy preceded the diagnosis of FA.

CONCLUSIONS. If the competing risks of aplastic anemia and leukemia could be removed, the estimated cumulative probability of development of a solid tumor in FA patients is 76% by the age of 45 years. Carcinogenic pathways and cancer prevention, surveillance, and treatment can be studied to advantage in this genetic model of human cancer. *Cancer* 2003;97:425–40.

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Fanconi anemia (FA) is a rare autosomal recessive disease (Online Mendelian Inheritance in Man [OMIM] number 227650) that is a member of at least two classes of cancer predisposition syndromes. The first consists of autosomal recessive disorders of DNA repair and includes ataxia telangiectasia, xeroderma pigmentosum, Bloom syndrome, Werner syndrome, Rothmund Thomson syndrome, and Nijmegen breakage syndrome (OMIM numbers 20890, 278730, 210900, 277700, 268400, 251260, respectively). The second class comprises the inherited bone marrow failure syndromes, such as dyskeratosis congenita (DC), Diamond-Blackfan anemia (DBA), Shwachman-Diamond syndrome (SDS), severe congenital neutropenia (SCN), and amegakaryocytic thrombocytopenia (Amega; OMIM numbers 305000, 127550, 205900, 260400, 202700, 604498; reviewed by Alter¹). The disorders in the second group have diverse genetic mechanisms,

including autosomal recessive (DC, SDS, SCN), autosomal dominant (DC, DBA, SCN), and X-linked (DC) inheritance patterns.

Studies of cancer in patients with rare cancer predisposition syndromes have been important for the elucidation of pathways of malignancies in the general population. The roles of tumor suppressor genes such as p53 and retinoblastoma were clarified by examining families with Li-Fraumeni syndrome² and familial bilateral retinoblastoma.³ This list now includes additional autosomal dominant disorders, such as hereditary breast carcinoma, adenomatous polyposis coli, and many others.^{4,5} Germline mutations coupled with acquired somatic mutations in the same genes confer cellular homozygosity, loss of tumor suppressor activity, and malignant transformation.

The pathogenesis of the malignancies that occur in persons affected with the bone marrow failure syndromes remains unknown. However, progress is advancing rapidly with regard to the genes responsible for these syndromes. For example, at least eight genes are involved in the development of FA, six of which have been cloned.⁶ It has been proposed that several of the FA gene products form a complex that interacts with one or more other FA proteins, which ultimately may be involved in DNA damage response foci.⁷ One of the three or more DBA genes was identified as ribosomal protein subunit 19.⁸ The genes responsible for X-linked and autosomal dominant DC are dyskerin and the RNA subunit of telomerase, TR, respectively.^{9,10} Severe congenital neutropenia is inherited as an autosomal dominant disease, with heterozygous mutations in neutrophil elastase 2.¹¹ Amegakaryocytic thrombocytopenia is an autosomal recessive disorder, with mutations in both *c-mpl* genes.¹² In patients with SDS, which is also an autosomal recessive condition, the gene has been mapped to the centromere of chromosome 7 but has not been cloned.¹³ However, identification of the specific genes that underlie this heterogeneous group of diseases has not improved our understanding of how the cancers develop in these conditions.

Two important components of the investigation of cancer pathogenesis in this context are documentation of the types of cancer that occur excessively in each syndrome and definition of the epidemiologic characteristics of these cancers. This task has begun with FA because it is the most frequently reported rare inherited bone marrow failure syndrome and it has the highest risk of cancer among the disorders in this group. Although birth defects and aplastic anemia are the most frequently observed early manifestations, it is becoming increasingly clear that leukemia and solid tumors are the major complications in older FA patients. Review of FA cases reported in the medical

literature indicates that the hallmark neoplastic events are myeloid leukemias, liver tumors, head and neck carcinomas, and gynecologic malignancies.^{1,14} The ages at which these cancers occur are substantially younger than the ages at which these same cancers occur in the general population.

This review of FA case reports and case series comprises an updated and more complete analysis than the previous report.¹⁴ In addition, it provides more detailed information that will contribute to a more thorough investigation of cancer in FA patients by retrospective and prospective studies of identified cases. Modern assessment of carcinogenesis in FA will require correlation of specific genotypes, phenotypes, and types of cancer. That type of analysis is not possible from a body of literature that extends over 75 years and consists primarily of case reports that do not contain much of the needed information. However, evaluation of the literature does provide direction for future studies.

MATERIALS AND METHODS

The medical literature was searched for all cases of FA using Medline, supplemented after reviewing the bibliographies of each publication. The search terms were "Fanconi's anemia" or "aplastic anemia." All languages were included and articles were read in the original languages or after translation. Cases were accepted as having FA if their lymphocytes had increased chromosome breakage after challenge with a DNA crosslinking agent, if they antedated the era of chromosome breakage performed but were diagnosed as FA by the original authors, or appeared to this reader to be FA. Rare cases that may have been misclassified (e.g., DC) were excluded. Cases of leukemia, solid tumors, and myelodysplastic syndrome (MDS) were identified by careful scrutiny of all of the articles.

This study involves a review of the literature that has been performed continuously by the author since 1970 and includes cases reported from 1927 through 2001. Duplicate publications were combined into single case reports. Because there is no risk to human subjects, the study has not been approved explicitly by an Institutional Review Board. However, this study has formed the background for the author's clinical investigations of patients with inherited bone marrow failure syndromes and been approved implicitly by the Institutional Review Boards at several institutions, the most recent of which is the National Cancer Institute (NCI).

Information for individual cases was entered into a Lotus 123 spreadsheet and subsequently transferred into Stata7, which was used for all statistical analyses.¹⁵ The cumulative probability of development of

TABLE 1
Complications in the FA Literature Cases, 1927–2001

Characteristics	All	Leukemia	MDS ^a	Solid tumor	Liver tumor
No. of cases	1301	116	89	68	37
Percent of total	100	8.9	6.8	5.3	2.8
Male:female	711:578	70:46	46:42	23:45 (23:34) ^b ^c	22:15
Ratio	1.2	1.5	1.1	0.5 (0.59) ^b ^c	1.5
Age at diagnosis of FA (yrs)					
Mean	8.3	10.1 ^c	11.3 ^c	12.7 ^c	9.2
Median	7	8.6	9.3	9	7
Range	0–48	0.13–28	0.2–43	0–44	3–48
Age at complication (yrs)					
Mean	—	14.5	15.7	22.6 ^c	15.7
Median	—	14	14	25.5	13
Range	—	0.13–29	1.8–43	0.2–45	6–48
No. reported deceased	488	84	44	41	30
Percent reported deceased	38	72	51	61	81
Estimated median survival age (yrs)	20	16	21	31 ^c	16

FA: Fanconi anemia; MDS: myelodysplastic syndrome.

^a Includes 13 patients who subsequently developed leukemia.

^b Excluding women with only gynecologic cancer.

^c $P < 0.01$ compared with patients without that complication.

each complication was calculated as the complement of the Kaplan–Meier product limit estimate (the “1-KM” estimator).¹⁶ The outcomes of interest were leukemia, MDS, liver tumors, and solid tumors. Myelodysplastic syndrome that did not progress to leukemia was tabulated separately. This is because it is not clear whether MDS in FA patients is in fact a premalignant condition.¹⁷ Cases were censored if the patients died or were alive before the development of the event identified as the outcome for that analysis. For example, a case would be censored (i.e., analytically not at risk) with regard to the occurrence of a solid tumor if the patient had died, had a bone marrow transplant, or developed another complication such as leukemia before the diagnosis of a solid tumor.

Continuous distributions were compared using the Wilcoxon rank sum test, binomial probabilities evaluated by an exact binomial probability test, and gender ratios compared by the Fisher exact test. Descriptive statistics were analyzed using Stata7 software.¹⁵

RESULTS

Sufficient data were available for analysis of 1301 case reports of FA. Of these cases, 220 patients (crude rate 17%) had one or more cancer (Table 1). The male-to-female ratio was 1.2:1, which is significantly higher than the ratio of 1.0 expected in autosomal recessive diseases ($P < 0.001$). Males were younger than females at diagnosis of FA, with a median of 6.5 years in males and 7.5 years in females ($P < 0.01$) and a range for

both genders of 0–48 years. The crude death rate overall was 38%, with a cumulative median survival age of 20 years. Leukemia was reported in 8.9%, MDS in 6.8%, solid tumors in 5.3%, and liver tumors in 2.8% of patients. The slight excess of males was consistent in all event categories, except among FA patients with solid tumors, among whom there was an excess of females, even after exclusion of patients with gynecologic malignancies. The patients who developed leukemia, MDS, or solid tumors, but not liver tumors, were significantly older at the time of diagnosis of FA than patients without these complications. This finding suggests that the patients with those events had a milder phenotype and therefore were not diagnosed until they sought medical attention for an adverse event (Fig. 1A). Patients who developed solid tumors were older than those who developed leukemia, MDS, or solid tumors (Fig. 1B). Crude death rates were higher in patients with cancer than in patients without cancer (Table 1; 52% vs. 35%, $P < 0.01$ by chi-square test).

There were 116 reports of leukemia. Seven were acute lymphocytic leukemia and the remainder were acute myeloid leukemia (AML). In childhood sporadic AML, the proportion of each FAB type was approximately 25% M1, 27% M2, 5% M3, 26% M4, 16% M5, 2% M6, and 6% M7¹⁸ (see Table 2 for distribution of AML types). Among the 48 cases of FA in which the subtypes of AML were provided, there was an excess of M4 and M6 and a paucity of M1 and M2 ($P < 0.01$ for the observed compared with the expected distribu-

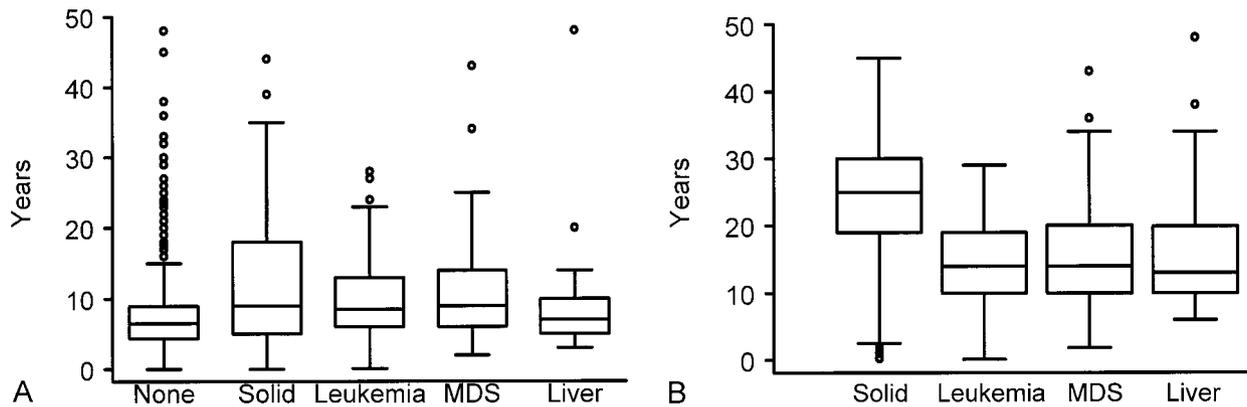


FIGURE 1. Age at diagnosis of Fanconi anemia (FA) and of complications in literature cases. Data are shown in box plots. The center line is the median, the bottom and top lines of the boxes are the 25th and 75th quartiles, respectively, and dots indicate outliers. (A) Age at diagnosis of FA patients. The FA patients with leukemia, myelodysplastic syndrome (MDS), and solid tumors were significantly older than the entire group of reported cases at the time at which FA was diagnosed. (B) Age at diagnosis of complications. The FA patients who developed solid tumors were older than those who developed leukemia, MDS, or liver tumors.

TABLE 2
Leukemia and MDS Cases in the Fanconi Anemia Literature, 1927–2001

Diagnosis	Male	Female	All patients	References
Leukemia				
ALL	4	3	7	19–24
AML, unspecified	26	18	44	14, 25–51
AML M1, acute myelocytic without maturation	2	1	3	52–54
AML M2, acute myelocytic with maturation	2	2	4	42, 55, 56
AML M3, APL	0	0	0	
AML M4, AMML	14	8	22	14, 57–74
AML M5, acute monocytic	6	4	10	47, 75–82
AML M6, erythroleukemia	6	2	8	26, 78, 83–87
AML M7, acute megakaryocytic	1	0	1	88
AML ANLL	1	5	6	82, 89–92
Other acute leukemia	8	3	11	29, 68, 80, 93–98
Total leukemia	70	46	116	
MDS				
MDS, no leukemia	39	37	76	14, 28, 29, 42, 47–49, 51, 86, 87, 90, 97, 99–123.
MDS, progressed to AML ^a	7	6	13	27, 31, 40, 42, 45, 47, 48, 54, 55, 75, 81, 82

MDS: myelodysplastic syndrome; ALL: acute lymphocytic leukemia; AML: acute myelocytic leukemia; APL: acute promyelocytic leukemia; AMML: acute myelomonocytic leukemia; ANLL: acute nonlymphocytic leukemia.

^a Included with leukemias.

tion). However, because the subtype was not indicated in more than one-half of the AML case reports, these disparities may not be real.

Eighty-nine patients had MDS, which progressed to leukemia in 13 of these patients. Because a primary review of pathologic material was not possible, the diagnoses of MDS and leukemia subtypes were tabulated according to the decision of the original authors. The term *MDS* was often used if cytogenetic marrow clones were observed, regardless of bone marrow morphology, and is not assumed in the context of FA that MDS represents an obligate precursor to leukemia.¹⁷ In fact, MDS and AML must be distinguished in

etiologic research to determine whether some forms of MDS are preleukemic in FA patients.

Eighty solid tumors were reported in 68 patients who had not received a bone marrow transplant. Six patients had two, and two patients had four, independent solid tumor primaries (Tables 3, 4). More than one-half of the tumors were head and neck, esophageal, and vulvar carcinomas. Other types of tumors that occurred in more than single cases include uterine cervix, brain (three medulloblastomas and three astrocytomas), nonmelanoma skin, breast, and lung carcinomas, lymphoma, and gastric and genitourinary carcinomas (mostly Wilms tumors). In addition, there

TABLE 3
Solid Tumor Cases in the Fanconi Anemia Literature, 1927–2001

Type	Male	Female	All patients	References
No bone marrow transplant				
Head, neck, and upper esophagus	13	13	26	30, 50, 59, 76, 87, 124–144
Esophagus	1	8	9	124, 145–153
Vulva and/or anus	—	10	10	66, 126, 130, 134, 154–159
Cervix	—	3	3	31, 155, 156
Brain	2	4	6	52, 160–163
Genitourinary	3	3	6	104, 134, 144, 160, 164–166
Skin (nonmelanoma)	1	5	6	42, 47, 134, 144, 159, 167
Breast	—	4	4	87, 134, 168–170
Lung	3	0	3	68, 87, 103
Lymphoma	1	1	2	171, 172
Gastric	2	0	2	173, 174
Colon	0	1	1	66
Osteogenic sarcoma	0	1	1	175
Retinoblastoma	0	1	1	55
Total cancers	26	54	80	
Total patients	23	46	68	
Six patients had two, and two patients had four solid tumor primaries.				
Following bone marrow transplant				
Head and neck	8	4 ^a	12	87, 176–187

^a One patient had tongue and vulvar carcinomas.

TABLE 4
Cases with Combinations of Malignancies in the Fanconi Anemia Literature, 1927–2001

Carcinomas	Gender	Reference
Colon, anus, vulva	Female	66
Cervix, vulva	Female	156
Gingiva, esophagus	Female	124
Vulva, tongue	Female	130
Wilms, medulloblastoma	Female	160
Hand, tongue, cervix, breast	Female	134
Perianal, eyelid	Female	159
Larynx, skin, bladder, nasopharynx	Male	144
Esophagus and liver hepatoma	Female	149
Tongue and liver hepatoma	Male	139
Liver hepatoma and CMML	Female	107
Liver hepatoma and AMML	Male	59
Liver tumor and AML	Male	43
Liver adenoma and leukemia	Male	95
Astrocytoma and AML M1	Female	52
Retinoblastoma and AML M2	Female	55
Cervix in situ and AML	Female	31

CMML: chronic myelomonocytic leukemia; AMML: acute myelomonocytic leukemia; AML: acute myelocytic leukemia.

were two FA patients with both head and neck carcinomas and a hepatoma. There were also seven patients who had leukemia in addition to another primary neoplasm, i.e., four patients had liver tumors and three patients had solid tumors. The combination

of cancers include oral, gynecologic, liver, and leukemia, but do not appear to present a specific informative pattern. There were insufficient detailed analyses in most cases to provide any insights into the pathophysiology of these instances of multiple primary cancers. Therefore, it is unclear to what extent the subsequent cancers may represent late neoplastic complications of the treatment employed to control the first cancer or whether both malignancies are an integral part of the natural history of FA.

In addition to the patients who developed cancer without having had a previous bone marrow transplant, 12 patients (8 males and 4 females) developed cancer after a bone marrow transplant (Tables 3, 5). All 12 patients had an oral carcinoma and one patient had an oval and a vulvar carcinoma. The total number of FA patients who have undergone a bone marrow transplantation is unknown. Without this denominator, the effect of transplant on the trajectory toward solid tumors in FA patients cannot be determined from these case reports. The interval between transplant and the diagnosis of cancer ranged from 3 to 15 years and survival subsequent to the development of cancer was poor.

Liver tumors were reported in 37 patients (Table 6). Twice as many had hepatomas²³ as had adenomas.¹³ The male excess among patients with liver tumors was similar to the male excess in the entire FA

TABLE 5
Tumors after BMT in the Fanconi Anemia Literature, 1927–2001

BMT (yr)	Gender	Cancer age (yr)	Cancer (type)	Interval (yrs)	Result (yr)	References
20	Female	25, 29	Cheek, tongue	5, 9	D, 30	176, 177
14	Female	24	Tongue	10	A, 32	176
9	Female	18	Buccal	9	D, 18	183
9	Female	23, 24	Vulva, tongue	14, 15	A, 25	184
6	Male	12	Tongue	6	D, 12	178, 179
8	Male	11	Tongue	3	D, 11	180, 181
8	Male	16	Tongue	8	A, 16	182
19	Male	33	Tongue	14	D, 33	188
N/A	Male	N/A	Tongue	5	A, N/A	186
8	Male	13	Tongue	5	D, 13	187
10	Male	25	Pharynx	15	D, 25	187
N/A	Male	19	Tongue	N/A	D, 19	87

BMT: bone marrow transplant; D: dead; A: alive; N/A: data not available.

TABLE 6
Liver Tumor Cases in the Fanconi Anemia Literature, 1927–2001

Type	Male	Female	All patients	References
Adenoma	7 ^a	6	13	95, 176, 188–195
Hepatoma	15	8	23	30, 33, 43, 59, 87, 107, 138, 139, 149, 196–212
Not stated	0	1	1	176, 192
Total liver tumors	22	15	37	

^a One patient had adenomas before bone marrow transplant and died 15 years later with hepatocarcinoma after hepatitis C virus infection.¹⁸⁸ Several patients were mentioned in more than one reference.

group. All of the hepatoma patients and all but one of the patients with an adenoma had received oral androgen therapy for aplastic anemia.¹⁹⁹ One patient had adenomas before the bone marrow transplant and died 15 years later with hepatocarcinoma after having developed a hepatitis C virus infection.¹⁸⁸

The median age for all cancers in FA patients, including leukemia, was 16 years of age. This is substantially younger than the median age of 68 for the same types of cancer in the general population (Table 7).²¹³ The median age for leukemia was 14, for solid tumors 26, and for liver tumors 13 years of age. The most striking solid tumors, in terms of frequency and the young age at which they occurred, were carcinomas of the head and neck, esophagus, vulva, and uterine cervix. The median age of the 12 patients who developed oral carcinomas following a bone marrow transplant was 21 years. This is significantly younger than the age of 28 for patients with head and neck carcinoma who had not received a bone marrow transplant ($P = 0.02$), suggesting a possible adverse effect of transplant on the risk of developing an oral carcinoma.

The cumulative incidence curves (1-KM) for FA-

TABLE 7
Median Ages (Years) for Cancers in the FA Literature, 1927–2001

Cancer	General age ^a	FA age	FA range	FA no.
All sites	68	16	0.1–48	211
All solid tumors	—	26	0.2–45	68
Leukemia (AML)	68	14	0.1–29	116
Liver	68	13	6–48	37
Head and neck	64	28	13–41	26
Head and neck after BMT ^b	—	21 ^b	11–33	12
Esophagus	68	27	20–36	9
Vulva/anus	72	27	20–37	10
Cervix	47	25	22–32	3
Brain	56	3	0.5–11	6
Breast	63	37	26–45	4

FA: Fanconi anemia; AML: acute myelocytic leukemia; BMT: bone marrow transplant.

^a General population data from the Surveillance, Epidemiology, and End Results program.²¹³

^b Only these patients received a BMT. $P = 0.02$ for median age compared with FA patients with head and neck carcinoma who had not received a BMT.

related adverse events shown in Figure 2 indicate the probability of developing each major complication if the other, competing, risks were removed. The patterns of these curves are consistent with the appearance of these events at ages younger than

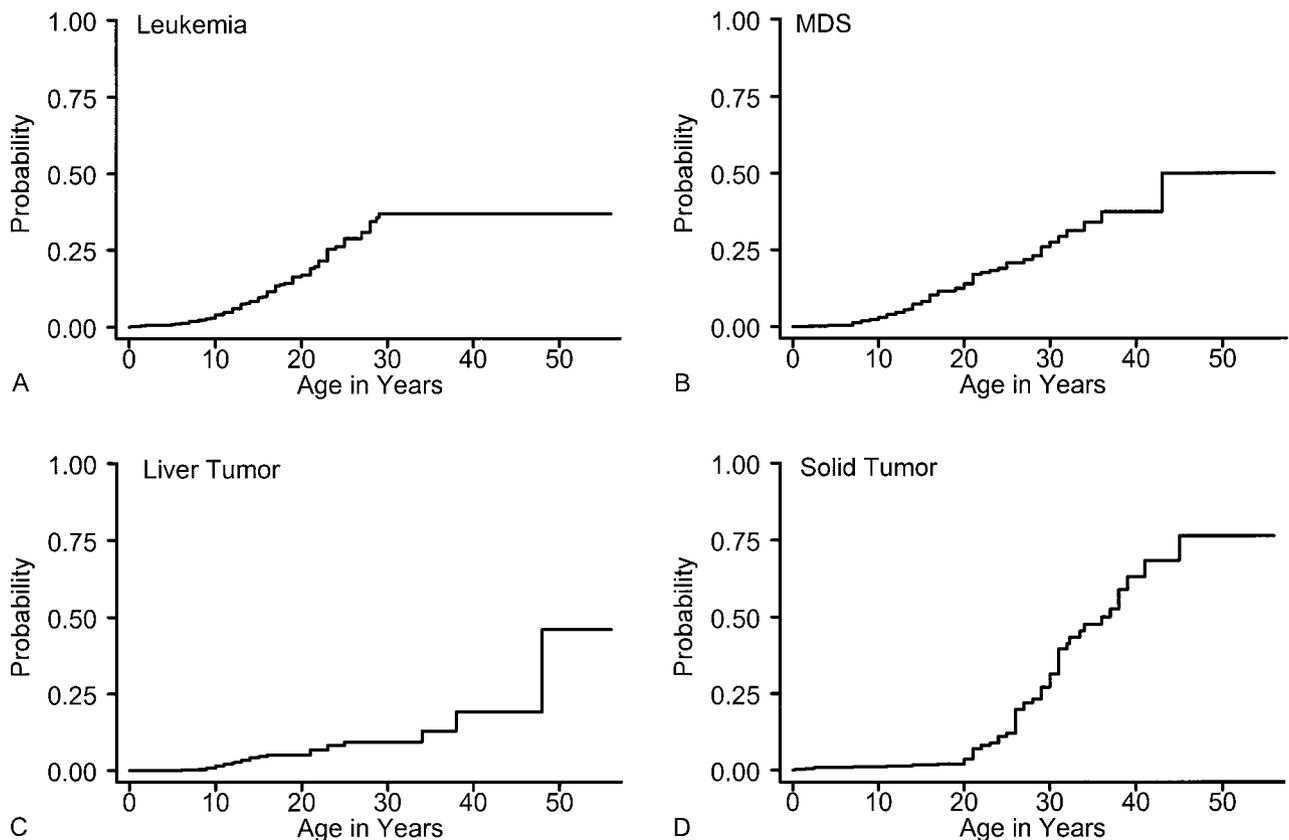


FIGURE 2. Cumulative probability of development of complications in Fanconi anemia patients. (A) 115 patients with leukemias, (B) 87 patients with myelodysplastic syndrome, (C) 36 patients with liver tumors, and (D) 66 patients with solid tumors.

expected and with remarkably high absolute risks. The cumulative incidence of leukemia is 37%, which reached a plateau by age 29. The cumulative incidence of MDS is 50%, with a possible plateau at age 43, supporting the suggestion that MDS frequently is not a prelude to AML in FA patients.¹⁷ Liver tumors reached a maximum of 46%, with no plateau. Solid tumors had the most dramatic cumulative incidence curve, which reached 76% by age 45. The contour of the 1-KM curve for solid tumors differs from that of the other complications: the risk of a solid tumor increases very slowly in childhood and then rises steeply and linearly after age 20, with no sign of a plateau.

The data in Table 1 show that patients with cancer and FA were older at the time of diagnosis of FA than were patients who had not developed cancer. The explanation for this age discrepancy is provided in Figure 3. Several patients with cancer were not diagnosed with FA before seeking medical attention for an adverse event. Diagnosis of FA was delayed in 22% of patients with solid tumors, 27% of patients with leukemia, 29% of patients with MDS, and 6% of patients

with liver tumors. In a few patients, the age at diagnosis of FA or of the complication was not reported. These figures may be overestimates, due to the limited amount of detail in some case reports. However, they highlight the clinical importance of considering the diagnosis of FA in patients with FA types of cancer, who otherwise lack the typical risk factors for those cancers, particularly those in whom the cancer diagnosis is made at an unusually young age. For example, the occurrence of a squamous cell carcinoma of the tongue in a 20-year-old woman who does not smoke should prompt consideration of FA as the underlying medical condition and should lead to performance of a screening chromosome breakage test. This information has therapeutic implications because FA patients may be sensitive to the cytotoxic effects of chemotherapy and ionizing radiation. As a result, the cancer treatment plan may require modification.²¹⁴

DISCUSSION

There are many limitations to using literature case reports as a source of epidemiologic data with regard to the risk of cancer in FA patients. There is almost

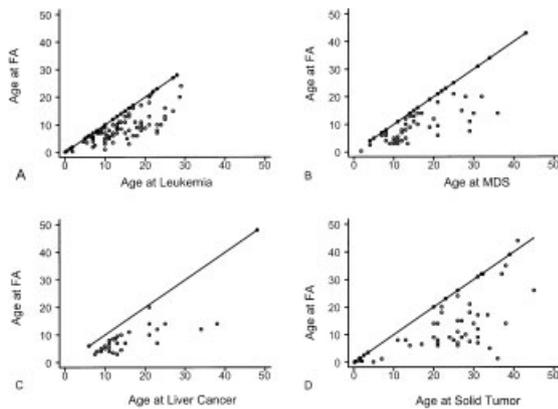


FIGURE 3. Age at diagnosis of Fanconi anemia (FA) occurred at or later than the diagnosis of complications in (A) 30 of 110 patients with leukemias, (B) 23 of 78 patients with myelodysplastic syndrome, (C) 2 of 31 patients with liver tumors, and (D) 13 of 60 patients with solid tumors. The straight line shows the coincidence of the diagnosis of FA with the diagnosis of the complication. The age at diagnosis of FA and/or cancer was missing in some cases.

certainly publication bias, in which cases with cancer would be overreported and cases without cancer would be underreported. FA can have a relatively mild phenotype and internists and medical oncologists are generally unfamiliar with this typically pediatric disorder. Consequently, there are undoubtedly persons with FA in whom cancer developed without the diagnosis of FA being made. Therefore, determination of crude or actuarial cancer rates is compromised by the inaccuracy of both numerators and denominators. The diagnosis of FA itself is problematic because it was confirmed by tests of chromosome breakage in only 60% of the reports. Cases reported before the era of chromosome breakage tests were biased toward patients with overt physical anomalies, and thus may have included more patients with a higher risk of hematologic complications who may not have survived long enough to develop solid tumors. Many of the reports lacked some of the details that would have helped to confirm the diagnosis of FA, the specific type of cancer, or the exact age at diagnosis of FA or the adverse outcome. Nonetheless, a careful assessment of the literature can generate etiologic clues that may be pursued in more carefully designed epidemiologic studies and provide rough estimates of cancer risk in the setting of a rare disease that is not easy to study.

Analysis of the cumulative probability of development of a specific complication such as leukemia or a solid tumor was performed using 1-KM, which estimates the hypothetical cumulative incidence that would be observed if the competing risks could be removed. Within this constraint, the data reviewed suggest that

the cumulative probability of developing leukemia, liver tumors, and solid tumors in FA patients is close to 40% by age 30, about 50% by age 45, and an astounding 76% by age 45, respectively. The method used to analyze these data does not account for competing risks, but rather censors patients at the time of development of other FA-related complications. Therefore, the cumulative probability determinations assume that the adverse event being analyzed is the only adverse event to which the patients are susceptible. For example, solid tumors occur infrequently in childhood, increase rapidly in frequency in adults in their 20s, and then have a more than linear rise throughout the rest of the life span. In this analysis, if the competing risks of aplastic anemia, leukemia, or liver tumors were removed, patients with FA would have at least a 76% risk of development of a solid tumor by age 45. A bone marrow transplant or gene therapy would prevent or treat those competing risks so that the high estimate of the risk of solid tumor may indeed be the natural history of FA.

Despite these limitations in the quantitative analyses due to competing risks, the descriptions of the types of cancers and the ages at which they occurred are not likely to suffer from reporting biases. Leukemia, MDS, and liver tumors are the major adverse events that are not related to bone marrow failure in FA patients in teenage and young adulthood, with a median of 14 years of age. In contrast, solid tumors occur primarily in young adults, with a median of 26 years of age, which is significantly older than patients with other complications.

Reporting bias is also less likely to have influenced the types of complications that occur in FA patients. The FA-related leukemias differ from leukemia in the general population in several important ways.²¹³ In FA patients, 94% of the leukemias were myeloid and only 6% were lymphoid, compared with 84% of the leukemias being lymphoid in non-FA children. The age distribution of leukemia in FA patients was normally distributed around a mode of 14 years, in contrast to the general population in which the incidence of AML is higher in infants, declines around age 10, and then rises slightly in the late teens. There were relatively more M4 and M6 AMLs and fewer M1 and M2 in the FA group. However, these data are difficult to interpret because subtype information was missing in more than one-half of the AML cases.

Cases of FA with MDS were analyzed separately from AML. Only 13 of the 89 cases with MDS progressed to AML. MDS in FA patients may be different from primary MDS in non-FA adults.¹⁷ Patients with FA may have MDS for long periods of time, with clonal fluctuation and without leukemic transformation. The

age distribution of the literature cases with MDS resembled that of the leukemia group, with a normal distribution around a mode of 15 years. The Surveillance, Epidemiology, and End Results (SEER) program does not collect data on MDS so that general population information is not readily available. However, in a French registry, MDS did not have a pediatric peak and the incidence rose very slowly until past the age of 50 years.²¹⁵

The types of cancer reported in FA patients are less likely to suffer from publication bias than are the numbers. The most frequent cancers (more than 40%) occurred in the aerodigestive category, consisting of squamous cell carcinomas of the oral, oropharyngeal, pharyngeal, and esophageal regions. The next most common (16%) were gynecologic cancers, namely, carcinomas of the vulva and uterine cervix. In a few cases, the presence of human papilloma virus was mentioned, but most cases were not evaluated for this potential causative agent.^{216,217} The other types of cancers summarized in Table 3 were less common and do not present a specific cancer pattern that is discernible from information in the literature.

It is noteworthy that all of the patients with cancer following a bone marrow transplant had cancer in the head and neck region, primarily tongue carcinoma. The younger age for these cancers in the transplant group suggests that the preparation for transplant with irradiation, immunosuppression, myelosuppression, and/or posttransplant complications such as graft-versus-host disease and/or infections may further increase the risk of malignancy over and above that which would be observed as part of the natural history of FA. The French FA bone marrow transplant group suggested that the crude estimate of the risk of development of a solid tumor following transplant in FA patients was 42% by 12 years after transplant.²¹⁸

Liver tumors were also relatively common, with the majority occurring in teenagers, but with a right skew of patients in their 20s. All but one had received oral androgens for several years, which certainly contributed to the risk. Although two-thirds were called hepatoma, they generally were not malignant and rarely were the primary cause of death. Liver tumors were present in at least six patients who also had another solid tumor or leukemia. The latter cancers were more relevant to the patient's outcome.

What has happened in this field in the 6 years since this topic was last reviewed?¹⁴ The number of FA patients reported to have had malignant complications of their disease has increased by 50–100%, but the estimated proportion of known FA cases with these complications is similar (15% then, 17% now). These estimates are remarkably similar to the 16% of

patients found to have cancer in a North American retrospective cohort study of FA.²¹⁹ Although this proportion is high for a young patient population, it is less impressive when viewed as a crude rate. Use of cumulative incidence analyses, particularly after accounting for competing risks, indicates that FA has a remarkably high risk of specific malignancies, with penetrance comparable to other tumor predisposition syndromes.²¹⁹ The most serious early adverse event in patients with FA is severe aplastic anemia, which can often be managed with medical treatment (such as androgens and growth factors) or even cured with hematopoietic stem cell transplant using bone marrow, cord blood, or peripheral blood stem cells. In addition, the use of genetically corrected autologous stem cells may be available in the future.²²⁰ It must be emphasized that elimination of the early hazard of death from hematopoietic failure increases the competing risks related to malignancy. Even stem cell transplant or gene therapy may not totally eliminate the risk of leukemia because a few residual uncorrected host FA cells may persist, retaining the risk of undergoing malignant transformation.

Of much more compelling concern is the risk of solid tumors in the older FA patient. The literature review (this study) and a pilot survey²¹⁹ indicate that the cumulative incidence of one or more solid tumors in FA patients is greater than 75% by age 45, if competing risks are removed from the analysis. The optimism and satisfaction that derive from our increasingly effective ability to manage the aplastic anemia of FA must be tempered with the recognition that the control of morbidity and mortality from solid tumors now represents the greatest challenge faced by patients with FA and their health care providers. The possible exacerbation of that cancer predisposition by the current techniques used for bone marrow transplant represents a specific therapeutic conundrum that will prove difficult to solve. Epidemiologic studies heighten awareness of this enormous problem and identify areas in which additional research is required.

What can be done, now that it is clear that solid tumors are inevitable in the majority of FA patients as they get older? Researchers must evaluate whether additional risk factors are interacting with the genetic predisposition to malignancy that characterizes FA patients. Some of these risk factors may be environmental, such as smoking, viruses, oxidants, sun exposure, and other factors known to be carcinogenic in the general population. The role of other genes must be analyzed, particularly those that are involved in activating or inactivating carcinogens, as possible modifiers of FA-related cancer risk. Cancer surveillance must be initiated in young FA patients at much

earlier ages than is currently advised in the general population. Although evidence-based practice guidelines do not exist, good medical care must be provided. To this end, the Fanconi Anemia Research Fund, Inc., the United States-based family support group, has published results of a clinical consensus meeting.²²¹ The report summarized current expert opinion regarding suggested cancer surveillance guidelines in this population.

Experts agree that cancer surveillance in persons with FA must be targeted to the sites with the highest risk:

1. An annual bone marrow examination, with aspirate for cell types, biopsy for cellularity, and cytogenetics, may provide early evidence for MDS or leukemia and will help to clarify the relation between these conditions in FA patients.
2. Liver function tests and ultrasound examinations often identify patients with adenomas or hepatomas before they become symptomatic.
3. Screening for solid tumors is more complex, because of the multiplicity of cancer types.
 - a. Screening for aerodigestive cancers and precancerous lesions can be performed by oral surgeons, head and neck surgeons, and otorhinolaryngologists, using direct visualization of the oropharynx and fiberoptic endoscopy.
 - b. Gynecologic examinations for vulvar and cervical tumors are recommended to begin with menarche. Human papillomavirus surveillance in addition to pap smears should be considered, given the known etiologic role for this viral agent in the sporadic counterparts of these two cancers.
 - c. Patients and their health care providers should provide this disease-specific surveillance in the context of comprehensive general medical care, including screening recommendations which have been promulgated for the general population. The longer FA patients live, the greater their risk of developing the nonneoplastic illnesses faced by everyone as they age. It does not seem prudent, therefore, to neglect the general health care of FA patients while focusing on their known, disease-related risks.
 - d. Finally, because patients with FA have high cancer risks, they may provide a population in which the role of new screening modalities can be rapidly validated. These patients should be encouraged to participate in clinical trials designed to develop more effective cancer screening strategies.

Currently, there are no specific recommendations

for cancer prevention in FA patients that differ from those for the general population. Unfortunately, cancer management in FA patients is much more difficult than in the general population because of their increased sensitivity to chemotherapy with DNA crosslinkers and the variable but potential increased side effects from radiotherapy.²¹⁴ To develop better approaches to prevention, screening, and management, it is important to understand the types of cancer that develop in FA patients and identify additional factors that contribute to cancer risk. Researchers at the NCI have launched a comprehensive epidemiologic study of cancer in FA patients, which will address many of these pressing clinical and etiologic questions (www.marrowsfailure.cancer.gov).

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