# Cancer risks in Fanconi anemia: findings from the German Fanconi Anemia Registry

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## ABSTRACT

### Background

Fanconi anemia is an inherited genomic instability syndrome associated with progressive bone marrow failure leading to death or the requirement for hematopoietic stem cell transplantation, acute myeloid leukemia, and solid tumors. Prior epidemiological studies have quantified the risks of bone marrow failure, acute myeloid leukemia and solid tumors, but these estimates have not been replicated.

### Design and Methods

We assembled a cohort of 181 patients with Fanconi anemia mostly from Germany. We calculated the ratio of observed to expected cancers, and the risks of bone marrow failure, acute myeloid leukemia, and solid tumors by age.

### Results

The first adverse event was bone marrow failure in 66 patients, acute meyloid leukemia in 14 patients and solid tumors in 10 patients. The ratio of observed to expected cancers was 44 for all cancers, 26 for all solid tumors, and 868 for acute myeloid leukemia; these increased risks were statistically significant. Significantly elevated ratios of observed to expected cancers were observed for esophageal (6281), vulvar (2411), head and neck (240), breast (34) and brain (23) tumors. Absent or abnormal radii, and a five-item congenital abnormality score, were significant risk factors for bone marrow failure. The cumulative incidence of bone marrow failure by the age of 10 years varied from 12.6% in the lowest bone marrow failure risk group to 84% in the highest. The relative hazard of bone marrow failure was significantly higher in complementation group G versus A (relative hazard=2.2) and in C versus A (relative hazard=5.4).

### Conclusions

Findings from the German Fanconi Anemia Registry cohort validate prior risk estimates, and strongly support the concept that Fanconi anemia is a highly penetrant cancer susceptibility syndrome with early onset of acute myeloid leukemia and slightly later onset of specific solid tumors.

Key words: acute myeloid leukemia, neoplasms, bone marrow failure, Fanconi anemia, bone marrow transplantation, epidemiology.

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## Introduction

Fanconi anemia is an inherited bone marrow failure syndrome associated with congenital abnormalities, hypersensitivity to DNA cross-linking agents, progressive bone marrow failure leading to death or the need for hematopoietic stem cell transplantation, and a predisposition to acute myeloid leukemia and specific solid tumors.[1-3] It is a rare disorder resulting from autosomal or rarely X-linked recessive inheritance of mutations in at least 13 genes.[4] The Fanconi anemia gene products participate in a complex DNA damage response pathway that includes the BRCA1 and BRCA2 proteins.[4,5]

Previously, we used data from the North American Survey (NAS), a retrospective cohort of patients with Fanconi anemia from the United States and Canada, to develop estimates of cancer risks in Fanconi anemia, and to identify specific types of solid tumors occurring in excess.[6] These estimates are strikingly high, similar in magnitude to those for the classical cancer susceptibility syndrome of Li-Fraumeni.[7] We also developed a statistical model to predict the cumulative incidence of each adverse event type by age depending on the presence or absence of specific congenital abnormalities.[8]

Given the recent emphasis on cancer studies by the Fanconi anemia research community, and the needs of patients who require reliable risk estimates to inform medical decision-making, it is highly desirable to replicate these findings. Until now, it has not been possible to do so. Fanconi anemia is a rare disease, and for this reason, comparatively few epidemiological studies have been feasible. In this study, we use data from an independent cohort of patients with Fanconi anemia, the German Fanconi Anemia (GEFA) Registry, to assess the replication validity of our previous risk estimates.

## Design and Methods

### The GEFA Registry

We studied 181 patients with Fanconi anemia primarily from Germany identified by one of the authors (*WE*) through referrals and professional contacts from 1984 through 2006. Data for all identified patients have been regularly updated by the same author. Information on individual cases was entered into a Microsoft Excel spreadsheet, and anonymized data were subsequently transferred into MATLAB,[9] which was used for all statistical analyses. The database includes demographic information, Fanconi anemia complementation group (when known), detailed data describing any stem cell transplants, including conditioning regimens and outcomes, data on the presence or absence of ten specific congenital abnormalities that are readily apparent and diagnosed early in life (the same abnormalities studied in the NAS),[8] and data on each diagnosed malignancy. Congenital malformations were ascertained by personal examination by one of the authors or by detailed reports from the treating physicians. Inconclusive data were excluded from the analysis. Precise dates of each event were recorded in the database. To the extent possible in a single developed country with universal health care and national research associations for hematology/oncology, the database is likely to include most cases of Fanconi anemia who came to medical attention in Germany since 1984.

Signed informed consent was obtained from patients, parents or legal guardians, according to the Helsinki convention. This study was conducted in accordance with the ethical standards of the Federal Ministry of Education and Research of Germany. All analyses were conducted under the auspices of the Institutional Review Board of the Inherited Bone Marrow Failure Syndrome Program of the National Cancer Institute.

Some earlier patients were also reported to the International Fanconi Anemia Registry (IFAR) and the European Concerted Action on Fanconi Anemia Research (EUFAR). Eighteen patients were from outside of Germany.

### Statistical methods

We used a competing risks approach to estimate cause-specific hazard functions and cumulative incidence curves for bone marrow failure, acute myeloid leukemia and solid tumors, as previously described for the NAS.[6] For each specific type of cancer, we compared the observed number of cancers occurring prior to transplant to the expected number (O/E ratio) based on the experience of the Connecticut Tumor Registry.[10] We studied the association between the risk of bone marrow failure and two previously identified predictors of bone marrow failure.[8]

The first predictor was the presence of radial ray abnormalities (patients with absent or abnormal radii were scored as 1, and patients with normal radii were scored as 0). The second predictor was a five-item congenital abnormality score with possible values from 0 through 5, inclusive. The value of the congenital abnormality score equals the number of abnormalities in the set: developmental delay, cardiopulmonary abnormality, abnormal kidney, abnormal hearing or deafness, and abnormal head size. We obtained *individualized* estimates of the relative hazard of bone marrow failure for each combination of radial ray abnormalities and congenital abnormality score, and incorporated these estimates in an absolute risk model.[8] We also modeled the joint effects of complementation group, radial ray abnormalities, and congenital abnormality score. For patients who received transplants, we evaluated the mortality rate during the high-risk period from 0 to 6 months following the transplant, and the subsequent rate of squamous cell cancers of the head and neck.[11] All statistical tests were two-sided. $p$-values less than or equal to 0.05 were considered statistically significant.

## Results

As of 15 June 2006, data from 181 patients were entered into the GEFA registry. The patients were born between 1951 and 2005, with one-half born in 1990 or later. Forty-eight patients had received transplants between 1984 and 2006 before any history of malignancy. Prior to receiving any transplants, the 181 patients contributed a total of 2556 person-years of follow-up to the first adverse event (Table 1). The first adverse event was bone marrow failure in 66 (including 48 who received a transplant prior to any malignancy), acute myeloid leukemia in 14, and solid tumors in 10; 91 patients remained free from these complications.

Cause-specific hazards and cumulative incidence curves for each adverse event are shown in Figure 1 (panels A and C, respectively). Previously derived estimates for the NAS[11] are also presented for comparison (Figure 1, panels B and D). In GEFA, the hazard of bone marrow failure peaked at 4.2%/year at the age of 10 (Figure 1A). The hazard of acute myeloid leukemia increased to 1.4%/year at the age of 20. The hazard of solid tumors increased from 0.7%/year at the age of 20, to 5.3%/year at the age of 40, and to ~10%/year at the age of 49. In GEFA, the cumulative incidence by age 49 was 50% for bone marrow failure and 28% for solid tumors (Figure 1C). The cumulative incidence of acute myeloid leukemia was 8% by the age of 20, increasing to 22% by the age of 36 on the basis of three events that occurred at ages 32.5, 35.0, and 35.7 years. Cause-specific hazards in GEFA are not significantly different from prior estimates obtained from the NAS (Figure 1B); consequently, the cumulative incidence curves for each adverse event are also very similar (Figure 1D).

GEFA patients were at extraordinary risk of specific malignancies (Table 2). In GEFA, the ratio of observed to expected cancers (O/E ratio) was 44 for all cancers, 26 for all solid tumors, and 868 for acute myeloid leukemia; significantly elevated O/E ratios were observed for esophageal (6281), vulvar (2411), and head and neck (240) cancers. These O/E ratios were qualitatively similar to previously reported O/E ratios in NAS (shown in Table 2 for comparison). In GEFA, O/E ratios were also significantly elevated for breast (34) and brain (23) cancers; in NAS, O/E ratios were also significant for cervical cancer (174), liver cancer (363), and osteosarcoma (79).

Radial ray abnormalities and congenital abnormality

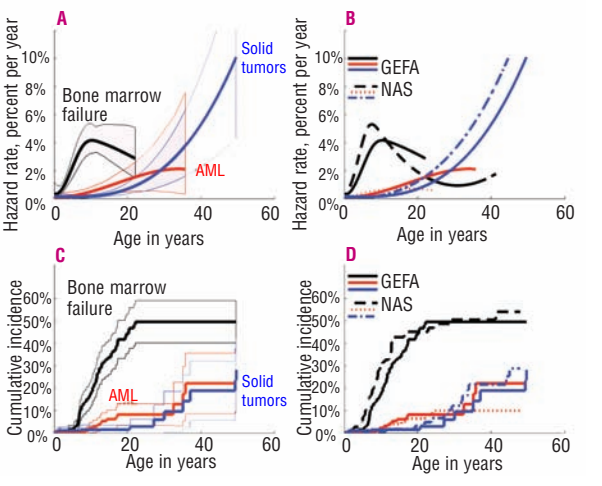


**Figure 1.** Annual hazard rates and cumulative incidence by age in GEFA and NAS. (A) For GEFA, annual hazard rates (incidence rate per year among subjects who are still at risk) of bone marrow failure (BMF), acute myeloid leukemia (AML), and solid tumors (ST), and 95% point-wise confidence envelopes (shaded regions). (B) Annual hazard rates of BMF (black), AML (red), and ST (blue) by age in GEFA (solid curves), compared to NAS (corresponding dashed, dotted, and dot-dashed curves). (C) For GEFA, cumulative incidence of BMF, AML, and ST by age (cumulative percent experiencing each endpoint as initial adverse event type), and 95% point-wise confidence envelopes (shaded regions). (D) Cumulative incidence of BMF (black), AML (red), and ST (blue) by age in GEFA (solid curves) compared to NAS (corresponding dashed, dotted, and dot-dashed curves).

**Table 1.** Demographic data and outcomes for patients in the German Fanconi Anemia Registry.

| | *All* | *A* | *B* | *C* | *D1/BRCA2+N*[b] | *D2* | *G* | *E* | *N.A.*[a] |
|---|---|---|---|---|---|---|---|---|---|
| N. of cases (%)[c] | 181 | 76 (68%) | 2 (1%) | 8 (7%) | 4 (4%) | 2 (2%) | 17 (15%) | 3 (3%) | 69 |
| Male to female ratio | 103:78 | 43:33 | 2:0 | 7:1 | 3:1 | 1:1 | 9:8 | 1:2 | 37:32 |
| RAD, (%)[d] | 13/127 (10%) | 4/61 (7%) | 0/2 (0%) | 1/6 (17%) | 1/2 (50%) | 0/2 (0%) | 0/17 (0%) | 1/1 (100%) | 6/36 (17%) |
| CABS, median | 1 | 1 | 1 | 1 | 1.5 | 2.5 | 1 | 3 | 1 |
| Person-y of follow-up | 2556.0 | 1182.6 | 14.7 | 83.2 | 8.6 | 52.0 | 205.0 | 43.6 | 966.2 |
| N. with BMF[e] | 66 | 28 | 0 | 6 | 0 | 0 | 10 | 1 | 21 |
| N. with AML[e] | 14 | 8 | 1 | 0 | 1 | 0 | 2 | 0 | 2 |
| N. with ST[e] | 10 | 4 | 0 | 0 | 3 | 0 | 0 | 0 | 3 |

*[a]N.A.: not available; BMF: bone marrow failure; AML: acute myeloid leukemia; ST: solid tumor; RAD: missing or abnormal radii; CABS: 5-item congenital abnormality score. [b]One patient was in complementation group N and three patients were in complementation group D1/BRCA2. [c]Percentages shown in this row are for 112 subjects with known complementation group. [d]Data shown in this row are number with missing or abnormal radii, out of total number for whom RAD and CABS were known, and the corresponding percentage. [e]Events here are counted in the competing-risks sense: BMF prior to AML, or ST; AML prior to BMF or ST; ST prior to BMF or AML.*

**Table 2. Observed cancers, and ratio of observed to expected cancers, among patients in the German Fanconi Anemia Registry (GEFA) and the North American Survey (NAS).**

| *Cancer type* | *GEFA, N. of observed cancers*[a] | *GEFA, O/E ratio*[c] | *NAS, N. of observed cancers* | *NAS, O/E Ratio* |
|---|---|---|---|---|
| Total cancers | 30 | 44[d] | 27 | 52 |
| Total solid tumors (non-hematologic malignancies)[b] | 12 | 26 | 18 | 51 |
| Leukemia (AML) | 17 | 868 | 9 | 649 |
| Non-Hodgkin's lymphoma | 1 | 27 (n.s.) | 0 | N.A. |
| Head and neck | 2 | 240 | 6 | 666 |
| Esophageal | 2 | 6281 | 2 | 2294 |
| Liver | 0 | N.A. | 2 | 363 |
| Vulvar | 3 | 2411 | 3 | 4199 |
| Cervical | 0 | N.A. | 2 | 174 |
| Breast | 2 | 34 | 0 | N.A. |
| Brain | 2 | 23 | 1 | 17 (n.s.) |
| Kidney | 1 | 37 (n.s.) | 0 | N.A. |
| Osteosarcoma | 0 | N.A. | 1 | 79 |
| Soft tissue sarcoma | 0 | N.A. | 1 | 48 (n.s.) |

*[a]In GEFA, a total of 30 cancers were observed in 23 patients prior to the patients receiving any stem cell transplant. One patient in complementation group D1/BRCA2 had three tumors (medulloblastoma, B-cell non-Hodgkin's lymphoma, and AML), one patient in complementation group N had two tumors (nephroblastoma and AML), and three patients in complementation group A each had two tumors (vulva and esophagus, vulva and tongue, and breast and AML). [b]Non-Hodgkin's lymphoma is considered to be a lymphatic malignancy, and is not counted as a hematological malignancy. [c]Expected cancer incidence rates calculated from the Connecticut Tumor Registry using the SEERSTAT software. NAS results differ slightly from previously published O/E values because control rate data have been updated. [d]All O/E values shown are statistically significant except where noted as not significant ("n.s.") where there were single cases. Rates are unstable (not available: N.A.) when no tumors were observed.*

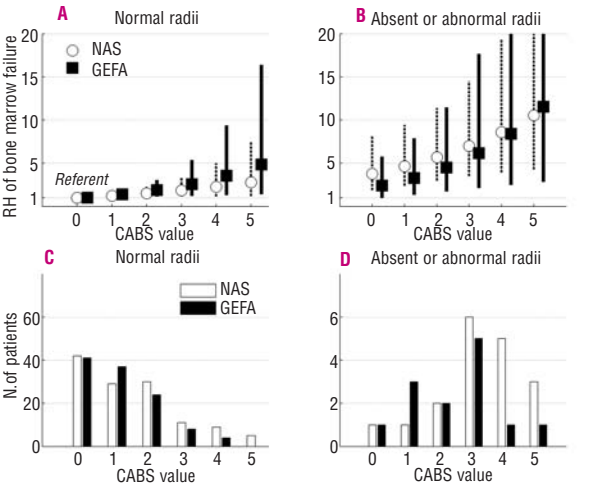


**Figure 2. Relative hazard of bone marrow failure (BMF) in GEFA and NAS according to Fanconi anemia phenotype. In each cohort, an absolute risk model was fitted for the rate of BMF by age. Models were fitted to 127 GEFA patients (see Table 1) and 144 NAS patients. BMF predictors were absent or abnormal radii versus normal radii (RAD), and a five-item congenital abnormality score (CABS). The referent group for each cohort comprises patients with normal radii and a CABS value of 0. (A) Relative hazards in GEFA (solid squares) and NAS (open circles) for each CABS value from 0 through 5, for patients with normal radii, with 95% point-wise confidence intervals (solid and dashed error-bars, respectively). (B) Relative hazards in GEFA (solid squares) and NAS (open circles) for each CABS value from 0 through 5, for patients with absent or abnormal radii, relative to patients with normal radii and a CABS value of 0. (C) Frequency of CABS values in GEFA (solid bars) and NAS (open bars), in patients with normal radii. (D) Frequency of CABS values in GEFA (solid bars) and NAS (open bars), in patients with absent or abnormal radii.**

score were documented in 127 GEFA patients (70%). Using the absolute risk model, radial ray abnormalities and the congenital abnormality score were significantly associated with the hazard of bone marrow failure in univariate analysis ($p$=0.040 and 0.008, respectively). The two predictors were statistically significant together ($p$=0.006). Controlling for radial ray abnormalities, congenital abnormality score remained significant ($p$=0.014), but radial ray abnormalities was not nominally significant after controlling for congenital abnormality score ($p$=0.08). In GEFA, the congenital abnormality score appears to be a stronger predictor than radial ray abnormalities of bone marrow failure; for purposes of risk prediction, it is reasonable to include both variables in the model.

Together, radial ray abnormalities and congenital abnormality score separated GEFA patients into distinct bone marrow failure prognostic groups (Figure 2, Panels C and D). This model was compared to the same model previously developed in the NAS (Figure 2, Panels A and B). For each combination of radial ray abnormalities and congenital abnormality score values, the relative hazards (RH) of bone marrow failure were not significantly different from prior estimates obtained in NAS. In GEFA, after adjusting for radial ray abnormalities, the RH increased by a net of 1.38-fold for each unit increase in the congenital abnormality score value (95% confidence interval [CI]=1.07–1.75-fold, $p$=0.011). Hence, compared to people with a congenital abnormality score of 0, those with a score of 5 were at $1.38^5$=5.0-fold higher risk of bone marrow failure. In NAS, the corresponding RH value per unit increase in congenital abnormality score was 1.23-fold (95% CI=1.0–1.49-fold). In GEFA patients with absent or abnormal radii and a congenital abnormality score of 5, the RH was 11.5-fold higher (95% CI=2.9–46.4-fold higher) compared to GEFA patients with normal radii and a congenital abnormality score of 0. The corresponding and comparable RH value in NAS was 10.6 (95% CI=4.2–26.8).

In GEFA, the estimated cumulative incidence of bone marrow failure by the age of 10 years varied from 12.6% in the lowest bone marrow failure risk group with normal radii and a congenital abnormality score of 0 (Figure 3A), to 84.0% in the highest bone marrow failure risk group with absent or abnormal radii and a congenital abnormality score of 5 (Figure 3B). Because of competing risks, patients at lower risk

of bone marrow failure are more likely to live long enough to develop acute myeloid leukemia or solid tumors, and conversely. In the group at lowest predicted risk of bone marrow failure (Figure 3A), by the age of 49 years the cumulative incidence of solid tumors was 33.6%, and that of acute myeloid leukemia 23.7%, whereas only 1.4% of patients in the group at the highest predicted risk of bone marrow failure are expected to avoid bone marrow failure and develop either acute myeloid leukemia or a solid tumor as the first adverse event.

The complementation group was known for 112 GEFA patients (62%); data on radial ray abnormalities and congenital abnormality score were available for 91 of these patients. Because of the small numbers of patients with rare complementation groups, we further restricted the analysis to patients in complementation groups A, G, and C (84 of the 91 patients). For this subset, we fitted a multivariate model for the hazard rate of bone marrow failure that included the baseline hazard function (Figure 4A), congenital abnormality score (Figure 4B), radial ray abnormalities (Figure 4C), and complementation group (Figure 4D). After adjusting for radial ray abnormalities and congenital abnormality score, the RH was significantly higher in complementation group G versus A (RH=2.2, 95% CI=1.1–4.6, $p$=0.044) and in complementation group C versus A (RH=5.4, 95% CI=2.0–14.6, $p$=0.001). In the same model, radial ray abnormalities were associated with bone marrow failure after adjustment for complementation group and congenital abnormality score (RH=3.4, 95% CI=0.8–14.2), but not significantly so ($p$=0.09). In contrast, congenital abnormality score was significantly associated with bone marrow failure after adjustment for complementation group and radial ray abnormalities (RH increases by 1.39-fold for each unit increase in congenital abnormality score, 95% CI=1.03–1.86-fold, $p$=0.03).

The 48 patients who received a transplant prior to any malignancy contributed an additional 216 person-years of follow-up. Conditioning regimens varied over the study period. Subsequent to receiving a transplant, there were 20 deaths and three patients developed solid tumors. The three malignancies (tongue, liver, and esophagus) occurred at the ages of 13, 23, and 34, respectively, at 2, 16, and 17 years after mismatched, matched, and matched transplants.

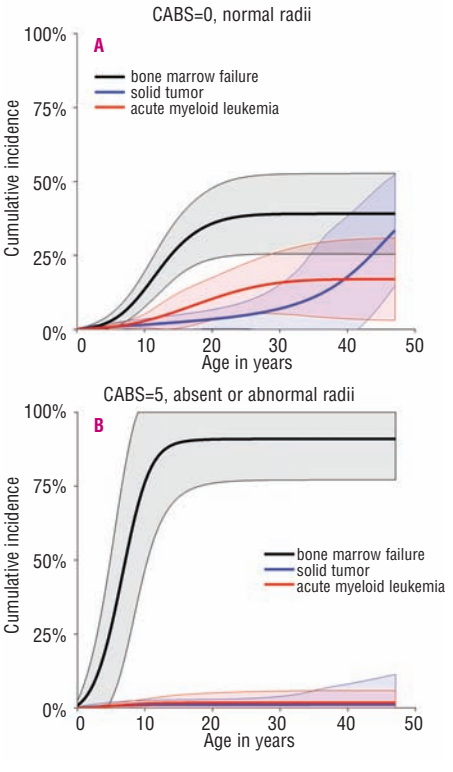


**Figure 3.** Cumulative incidence of bone marrow failure (BMF), acute myeloid leukemia (AML), and solid tumors (ST) by age, in GEFA. Shaded regions show 95% point-wise confidence limits. CABS values are the congenital abnormality score. (A) Patients with CABS=0 and normal radii are at relatively low risk of BMF compared to patients with more congenital abnormalities. (B) Patients with CABS=5 and absent or abnormal radii are at relatively high risk of BMF compared to patients with fewer congenital abnormalities. By competing risks, patients in (A) are more likely to experience AML or ST as the initial adverse event, while patients in (B) are less likely.

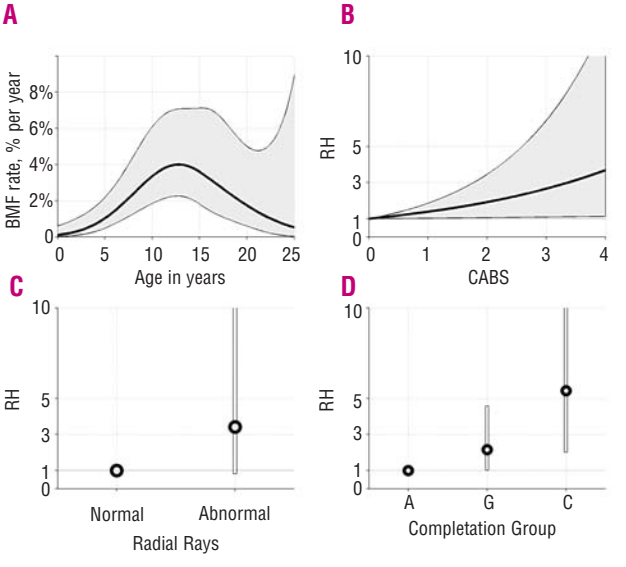


**Figure 4.** Proportional hazards model for the rate of bone marrow failure (BMF) in GEFA. Model fitted to data for 84 GEFA patients known to belong to Fanconi anemia complementation groups A (61 patients), G (17 patients), or C (6 patients). (A) Baseline hazard function describing BMF rate by age (solid curve), and 95% point-wise confidence limits (shaded regions). (B) Relative hazard of BMF for increasing CABS values (solid curve), and 95% point-wise confidence limits (shaded regions), compared to CABS=0. (C) RH for patients with absent or abnormal radii (5 patients), and 95% point-wise confidence interval (error bar), versus normal radii (79 patients). (D) Relative hazard values and 95% point-wise confidence limits for patients in complementation groups G or C versus A.

The age-specific hazard of solid tumors was 3.8-fold higher in transplanted patients than in untransplanted ones. This increased risk did not attain statistical significance ($p$= 0.11), but was similar in magnitude to the elevated risk (4.4-fold) observed in the Hôpital Saint Louis (SLH) transplant cohort.[11] During 2000-2004, none of five patients with matched donors and three of 18 patients with mismatched donors died in the period from 0–6 months after transplantation. In patients with matched donors, acute and chronic graft-versus-host diseases were statistically significant risk factors for death beyond 6 months, as was also the case in the SLH cohort.

## Discussion

This is the first comprehensive analysis of the natural history of Fanconia anemia in patients from Germany. The GEFA (German) and NAS (North American) cohorts are similar in size, with 181 and 145 patients, respectively, and thus analyses of data from both cohorts have comparable statistical power. Both are retrospective cohorts that might be affected by referral or volunteer bias. Because of their respective interests, the GEFA cohort might over-represent patients with hematologic problems, and the NAS cohort might over-represent patients with a history of cancer. Neither cohort is well-suited to identifying patients who are diagnosed with Fanconi anemia subsequent to a diagnosis of cancer. Hence, the risk of cancer in adults with Fanconi anemia might be underestimated. With these caveats in mind, we found striking similarities in the two cohorts.

In the GEFA, the cause-specific hazards of bone marrow failure, acute myeloid leukemia, and solid tumors, and the corresponding cumulative incidence curves, were qualitatively and quantitatively similar to previously reported estimates from the NAS.[6] Furthermore, there was good agreement with regard to the specific types of solid tumors occurring in excess.

There was also good agreement between the ratios of observed to expected numbers of cancers, when GEFA and NAS patients were compared to demographically matched cohorts from the general North American population. We used referent rates from the Connecticut Tumor Registry, a widely-used North American registry that was established prior to the birth of the oldest GEFA patient,[10] because referent cancer rates from Germany that are contemporaneous with the GEFA cohort are not available.[12] In recent years, however, variation in cancer incidence between Germany (Saarland) and the United States (Connecticut) has been minor compared to the striking relative risks we observed. Hence, O/E ratios for GEFA would likely have been very similar had a suitable German registry been available. Thus, regarding the risk of solid tumors in Fanconi anemia, reports from the NAS, the IFAR,[13] a systematic synthesis of literature cases,[14] and this report from the GEFA, are consistent: patients with Fanconi anemia are at extraordinary risk of specific solid tumors, notably, squamous cell cancers of the head and neck (risk elevated by several hundred fold), squamous cell cancers of the esophagus (risk elevated by several thousand fold), and vulvar cancers in women (risk elevated by several thousand fold). In addition, the risk of breast and brain tumors was elevated in the GEFA cohort and that of cervical and liver cancers and osteosarcoma in the NAS.

We also replicated the previous finding from the NAS that abnormal radii, and a five-item congenital abnormality score, separate Fanconi anemia patients into distinct bone marrow failure risk groups. In GEFA, the estimated cumulative incidence of bone marrow failure by the age of 10 years varied from 12.6% in the lowest bone marrow failure risk group to 84% in the highest, very similar to the range of 18% to 83% previously estimated from the NAS.[8] These estimates can be useful for clinical decision making.[15] In this study, we also found that the congenital abnormality score and being in complementation group G or C were significant and independent risk factors for bone marrow failure. This finding is consistent with reports from the EUFAR[16] and the IFAR.[17]

Finally, we evaluated the outcome of 48 GEFA patients who received a transplant prior to any malignancy, under protocols similar to those in use at the SLH during the same period.[11] Mortality rates were similar, as was the elevated incidence of post-transplant malignancies.

Fanconi anemia was first recognized 80 years ago by the astute clinician Guido Fanconi.[18] Progress in understanding the molecular basis of Fanconi anemia has been remarkable over the last 15 years. At the clinical level, the GEFA experience validates previous epidemiological studies. It is now clear that Fanconi anemia is both a major bone marrow failure syndrome, and also a highly penetrant cancer susceptibility syndrome. For patients, quantitative estimates of risk derived from the NAS or GEFA cohorts appear to be valid, at least for patients of predominantly European ancestry. These findings, together with major advances in the treatment of bone marrow failure,[19,20] strongly suggest that solid tumors will become the predominant clinical problem of patients with Fanconi anemia.

## Authorship and Disclosures

PSR, BPA and WE designed the study; WE set up the database and was involved in the care of patients; PSR analyzed the data and wrote the paper; all authors participated in writing the paper. The authors reported no potential conflicts of interest.

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