

Cancer in dyskeratosis congenita

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Dyskeratosis congenita (DC) is a rare inherited bone marrow failure syndrome. The spectrum of cancer susceptibility in this disorder of telomere biology has not been described. There were more than 500 cases of DC reported in the literature from 1910 to 2008; the National Cancer Institute (NCI) prospective DC cohort enrolled 50 cases from 2002 to 2007. Sixty cancers were reported in 52 literature cases, while 7 occurred among patients in the NCI DC cohort. The 2 cohorts were

comparable in their median overall survival (42 years) and cumulative incidence of cancer (40%-50% by age 50 years). The most frequent solid tumors were head and neck squamous cell carcinomas (40% of patients in either cohort), followed by skin and anorectal cancer. The ratio of observed to expected cancers (O/E ratio) in the NCI cohort was 11-fold compared with the general population ($P < .05$). Significantly elevated O/E ratios were 1154 for tongue cancer and 195 for acute myeloid

leukemia. Survival after bone marrow transplantation for aplastic anemia or leukemia was poor in both cohorts. The frequency and types of cancer in DC are surpassed only by those in Fanconi anemia (FA), indicating that FA and DC have similarly high risks of adverse hematologic and neoplastic events, and patients with these diseases should be counseled and monitored similarly. (Blood. 2009; 113:6549-6557)

Introduction

Dyskeratosis congenita (DC; MIM 305000, 127550, 224230) is one of the inherited bone marrow failure syndromes (IBMFs). The other syndromes in this family of disorders include Fanconi anemia (FA; MIM 227650), Diamond-Blackfan anemia (DBA; MIM 106550), Shwachman-Diamond syndrome (SDS; MIM 260400), severe congenital neutropenia (SCN; MIM 202700), amegakaryocytic thrombocytopenia (Amega; MIM 604498), and thrombocytopenia absent radii (TAR; MIM 274000). All of these syndromes have an increased risk of acute myeloid leukemia (AML), and FA, DC, and DBA appear to have increased risks of solid tumors. A brief review of the clinical appearances, genetics, and adverse outcomes in these syndromes was presented recently.¹ DC is thought to be a cancer-prone disorder because of anecdotal reports of cancer and the underlying pathology of abnormal telomere maintenance.²

For FA, detailed analyses of literature reports and retrospective/prospective cohorts indicated that the most frequent neoplasm was AML. In addition, head and neck and gynecologic squamous cell carcinomas (SCCs) were common adverse events.³⁻⁵ The quantitative risk of any cancer was approximately 50-fold that of the general population, and the risks of specific malignancies were extraordinarily high, in the thousands-fold for SCCs and hundreds-fold for AML. With the exception of FA and SCN, data on cancer risks in the other IBMFs are less well quantified, and are limited to case reports or crude rates from case series. These include increased frequencies of AML in all of the IBMFs, as well as SCCs in DC, and osteogenic sarcoma in DBA.¹

The link between DC and cancer is particularly intriguing, because DC is associated with defects in telomere biology. Patients with DC have very short telomeres and mutations have been

identified in telomere biology genes. However, to date there has been no comprehensive quantitative analysis of cancer risk in DC, or direct comparison with FA. Data from the United Kingdom Dyskeratosis Congenita Registry (DCR) indicated that the crude rate of malignancy among approximately 300 patients was 10%.⁶ In the only reported series, Dokal listed 4 cases of myelodysplastic syndrome (MDS), 1 Hodgkin lymphoma, and 8 carcinomas (2 of the tongue and 1 each of the bronchus, colon, larynx, esophagus, pancreas, and skin).⁷

This report includes an extensive examination of all cases of DC published between 1910 and 2008, and focuses on determination of the types and frequencies of malignancies that occur in DC. Despite many limitations, literature review can provide initial information about the categories of neoplasms that occur in excess and the probability that a patient will develop cancer. Some of the limitations include evolving changes in the recognition and diagnosis of DC (most of the early cases were in the dermatologic literature, while most recent cases have involved aplastic anemia, MDS, or AML), overpublication of reports of patients with adverse outcomes such as cancer, and underpublication of reports of patients without adverse events. In addition, survival has improved over time, as well as recognition of complications such as pulmonary fibrosis, particularly after hematopoietic stem cell transplantation.

To provide more reliable information about cancer incidence in DC than is available from the literature, we report here the first quantitative analysis of cancer risks in consistently characterized patients with DC enrolled in the National Cancer Institute's Inherited Bone Marrow Failure Syndrome (NCI IBMFS) cohort between 2002 and 2007 and followed up through 2008. We were

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Table 1. Cancer in DC literature cases, 1910-2008

Characteristics	All cases	No cancer	All cancers*	P†
Number of cases (%)	552	500	52 with 61 cancers (9.4%)	
Male:female (ratio)	418:133§ (3.1:1)	376:123§ (3.1:1)	42:10 (4.2:1)	.5
Median age at cancer, y (range)	NA	NA	29 (1.5-68)	NA
Number deceased (%)	144/521§ (28%)	114/469§ (24%)	30/52 (58%)	.004
Median age at death, y (range)	21 (2-70)	17 (2-68)	29 (19-70)	<.001
Median survival, y, by Kaplan-Meier method (95% CI)‡	42 (37-49)	46 (39-55)	39 (35-44)	.3

NA indicates not applicable.

*AML was included and MDS was not included in cancers.

†Comparing those with cancer with those without cancer.

‡The median survival values for patients with and without cancer describe subgroups defined by time-dependent rather than baseline characteristics; therefore, these values should be interpreted as descriptive characteristics of the population rather than predictive probabilities for individual patients.

§Some missing data.

able to calculate the relative risk of each type of cancer in the DC cohort compared with the general population, and the actuarial risk of cancer in DC as a function of age. We also examined the risk of MDS, and outcomes after bone marrow transplantation (BMT). Our analyses provide support of the view that the spectrum and magnitude of adverse outcomes in DC are similar to those in FA, and that surveillance and management might also be similar.

Methods

Literature review

The medical literature was searched for articles describing cases of DC, using Medline and Web of Science, using the search term “dyskeratosis congenita,” and supplemented after review of the bibliographies of each publication. Cases were also identified in articles from the same sources related to other inherited bone marrow failure syndromes or to aplastic anemia. All languages were included, either read in the original languages by one of the authors or after translation. These cumulative searches have been ongoing by one of the authors (B.P.A.) for more than 30 years. Cases were accepted if the reports provided sufficient phenotypic features for DC to be a likely diagnosis, and/or the cases had mutations in any of the genes that have been associated with DC.^{2,8} The subset of Hoyeraal-Hreidarsson syndrome was restricted to those with DC who had cerebellar hypoplasia, and the subset of Revesz syndrome to those with DC and exudative retinopathy. Cases of cancer as defined by the original authors were accepted without verification. Cases of MDS were not included as “cancer” but analyzed separately. Duplicate case reports were identified as much as possible by matching of descriptions in the publications or by prior citations. Where appropriate, all publications of a case are cited, unless the most recent clearly refers to earlier publications of that case. Data for cancer or MDS incidence in the general population came from the United States Cancer Registry Surveillance, Epidemiology and End Results (SEER) database.⁹ Because there was no risk to human subjects, this literature review was not explicitly approved by an institutional review board.

NCI IBMFS DC cohort

The NCI IBMFS cohort was established in 2002. This analysis includes all patients with DC enrolled through 2007 and followed up through 2008. The NCI DC cohort currently consists of 50 patients in 31 families. Diagnoses of DC were made in living participants by examination of medical records, clinical evaluation, documentation of very short telomeres,¹⁰ and/or identification of pathogenic mutations in DC genes where available.² Clinical features which we required to diagnose DC were modified from those of Vulliamy et al⁸ and included any of the diagnostic triad (dysplastic nails, lacy reticular pigmentation, and oral leukoplakia) and/or other characteristic physical findings, with or without hematologic manifestations. Mutations in genes in the telomere biology pathway were documented in 75% of the patients in the NCI DC cohort and included *DKC1*, *TERC*, *TERT*, and *TINF2*.^{11,12} Deceased family members had DC diagnosed based on review

of medical records, photographs, and pedigrees. Diagnoses of cancer or MDS were verified through the review of medical records. Follow-up time was from birth, and the analysis was both prospective and retrospective. This part of the study was approved by the Institutional Review Board of the NCI.

Statistics

Information for individual literature cases was initially entered into Lotus 1-2-3 Release 5 (IBM, Armonk, NY) spreadsheets, and then transferred and updated in Microsoft Excel 11.0 (Microsoft, Redmond, WA) spreadsheets. Data included demographics, physical manifestations of DC, age at onset of cancer or MDS, type of cancer, age at death, age at bone marrow transplant, and last age alive. Overall actuarial survival probabilities were calculated using the Kaplan-Meier product limit estimator.¹³ This approach provides estimates of hypothetical probabilities and incidences as if there were no competing risks. Median values and 95% confidence intervals for survivals were estimated using a spline-smoothed estimator of the actuarial curve and bootstrap resampling.¹⁴ The cumulative incidence of development of cancer in the literature cases was calculated as the complement of the Kaplan-Meier product limit estimator (the “1-KM” estimator).¹³ Cases were censored if the patients died or follow-up ended before the development of cancer. The outcomes of interest were solid tumors, AML, MDS, and severe bone marrow failure resulting in BMT or death.

Records for subjects in the NCI DC cohort were accumulated and maintained by Westat (Rockville, MD). In preparation for analysis, the data were cleaned and merged from several source files, and delivered to the NCI in an Excel spreadsheet. The information in the database was similar to that outlined above for the literature cases, with the addition of more details with regard to phenotype, mutated gene, where available, and telomere length. The observed number of cancers was compared with the expected number in the general population (O/E ratio) based on SEER, after adjustment for age, sex, race, and birth cohort.⁹

All statistical tests were 2-sided. *P* values less than or equal to .05 were considered statistically significant. Sex ratios were compared using the Fisher exact test. Statistics were analyzed using Microsoft Excel, Stata10 (StataCorp, College Station, TX),¹⁵ or MATLAB 20086 software (The MathWorks, Natick, MA).¹⁶

Results

Literature review

A search of Medline in October 2008, using the terms “dyskeratosis + congenita” and restricted to human studies, resulted in 433 citations; addition of “cancer” narrowed it to 161 citations. However, many of those articles were reviews or general discussions and did not include specific cases. In contrast, cumulative records of literature reports maintained by one author (B.P.A.) over 30 years led to the synthesis of 278 reports of 552 cases contributing

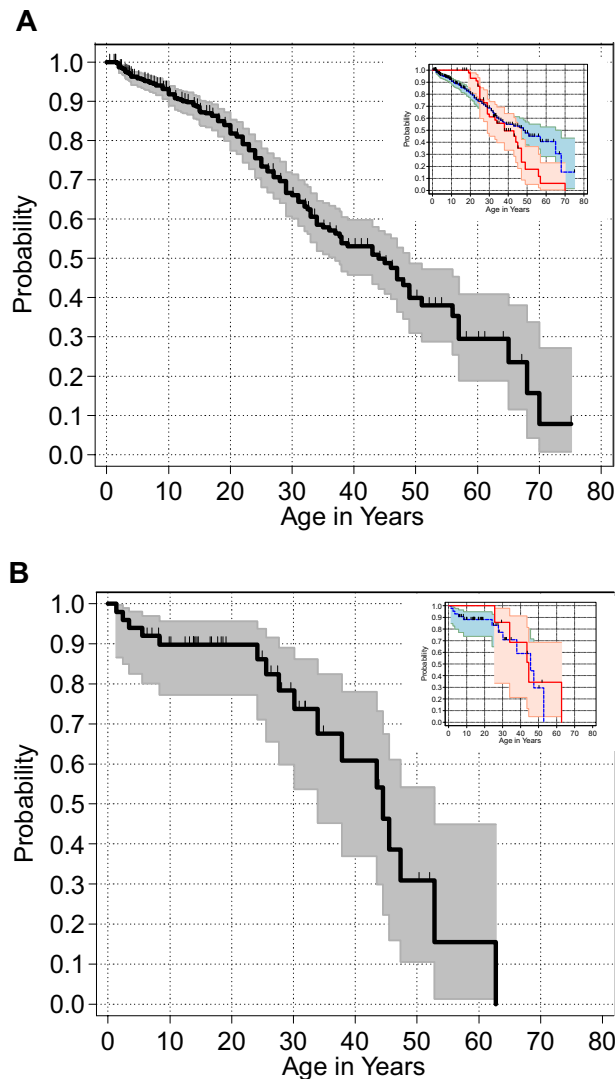


Figure 1. Cumulative survival in cases with dyskeratosis congenita, calculated using the method of Kaplan and Meier. (A) Cases reported in the literature through 2008, N = 552. (B) Cases enrolled in the NCI IBMFS DC cohort through 2007, N = 50. Data are the cumulative number of patients surviving, censored for age last known while alive. Insets show the survival curves for those with (solid red) and without (dashed blue) cancer.

10 806 person-years with sufficient information for this analysis (Table 1). Of the 552 patients, 52 had 61 cancers, for a crude rate of 9.4% of reported cases, similar to the crude rate reported by the group in the United Kingdom.⁶

The male:female ratio of all reported cases was 3.1:1; it was 4.2:1 for the cases with cancer ($P = .5$). The male excess may be biased by the original impression that DC was primarily an X-linked recessive disease, until the genetic proof of autosomal dominant inheritance in 2001.¹⁷ Cases reported through 2000 had a male:female ratio of 3.9:1, while the ratio from 2001 to 2008 was less, at 2.4:1 ($P = .001$). There was no difference in the male:female ratio of those with cancer compared with those without cancer.

The median age at which cancer was diagnosed was 29 years. The crude death rate in the literature cases was 58% for those who had cancer. The median age at death was higher in the cases with cancer versus those without cancer (29 compared with 17 years), suggesting either biased reporting of such outcomes, or escape from development of earlier fatal complications such as aplastic anemia. The median survival of the entire group, by Kaplan-Meier analysis (which takes into account the survivors as well as the deceased), was 42 years overall (Figure 1A); it was 39 years in those with and 46 in those without cancer (Figure 1A inset), but these ages are not significantly different because of the wide confidence intervals.

Sixty solid tumors were reported in 51 cases; in addition, one patient had AML (Tables 2-4). There were 24 head and neck SCCs (HNSCCs) in 22 patients. The next most frequent cancers were 8 patients with skin SCCs, followed by 6 with anorectal cancer, 4 each with stomach (2 gastric adenocarcinoma and 2 not specified) and lung cancer (2 bronchial, one lung adenocarcinoma, and one not specified), and 3 each with esophageal SCC and Hodgkin disease. Two reports were of colon cancer (one adenocarcinoma, one not specified), 2 pancreatic adenomas, and one each liver adenomas (no mention regarding androgen treatment), retinoblastoma, cervical SCC, and non-Hodgkin lymphoma. The ages of the patients at the time of diagnosis of all of the cancers except the lung and retinoblastoma were substantially younger than the ages expected for sporadic cancers, whether it was the first, second, or third cancer in the patients with DC.

A single cancer was reported after BMT: rectal adenocarcinoma 14 months after transplantation for aplastic anemia, when the patient was 34 years old. Like patients with FA, most of the patients with DC who had multiple tumors had at least one HNSCC.³ Five

Table 2. Types and ages of solid tumors in DC literature cases

Type of cancer	No. of cancers	Male	Female	Median age, y (range)	Median age in general population, y	References
All solid tumors	60 in 51 pts	41	10	28 (1.5-68)	67	
HNSCC	24 in 22 pts	14	8	32 (17-49)	62	7,18-36
Skin SCC	8	7	1	21 (4-43)	68	7,17,37-43
Anorectal	6	6	0	28 (17-52)	61	18,19,31,40,44,45
Stomach	4	4	0	23 (16-44)	71	31,46-49
Lung	4	4	0	56 (52-68)	71	18,50,51
Esophagus	3	3	0	25, 38, 41	69	7,24,52
Hodgkin disease	3	3	0	23, 25, 28	38	7,31,53
Colon	2	2	0	20, 25	71	7,54
Pancreas	2	2	0	29, 29	72	7,53
Liver	1	1	0	32	65	51,55
Retinoblastoma	1	1	0	1.5	2	56
Cervix	1	0	1	31	48	57
Lymphoma*	1	1	0	43	67	12

pts indicates patients.
*Non-Hodgkin lymphoma.

Table 3. Multiple primary solid tumors in DC literature cases

Cancers	Sex	Age at cancer diagnosis, y	References
Tongue SCC, nasopharynx SCC, rectal adenocarcinoma, lung	M	49, 52, 52, 52	18
Buccal SCC, anorectal adenocarcinoma	M	28, 33	19
Esophagus SCC, cheek SCC	M	41, 44	24
Nasal SCC, tongue SCC	F	42, 44	27
Skin SCC, rectal adenocarcinoma*	M	33, 34	40
Hodgkin disease, cheek SCC, stomach adenocarcinoma	M	28, 43, 44	31

M indicates male; and F, female.

*Rectal cancer 14 months after bone marrow transplantation.

of the 6 patients with multiple cancers were male, and all of their tumors occurred at 28 to 52 years of age, younger than expected from the general population. Only one case of AML was reported (at age 29 years), as well as 8 cases with various types of MDS (Table 4). These diagnoses were also primarily in adults who were younger than expected in the general population. The reports did not mention evolution to AML in these 8 cases of MDS.

The actuarial risk of cancer (absent any competing risks) was approximately 40% by age 50, and more than 60% by age 68 (Figure 2A); this is slightly lower than the actuarial risk (> 75%) of solid tumors in FA patients by age 45.³ The actuarial risk of MDS in the patients with DC reached a plateau of 3% at 29 years of age (Figure 3A).

Sixty-five patients were reported to have undergone BMT, with several apparent survival plateaus: 64% at 730 days, 35% at 2920 days, 24% at 4015 days; the last death was at 7300 days from pulmonary fibrosis (Figure 4A). These findings might be related to small numbers, heterogeneity of patients, and/or follow-up from periods with different transplantation protocols. Nine of the 30 deaths post-BMT were due to pulmonary fibrosis. Thirty-four patients with sibling donors had an apparent early plateau of 71% survival from day 183 to > 2000, but the last death at 7300 days was in this group. The 18 with alternative donors had a later plateau of 31% at 730 days, but the last patient died at 2920 days, also from pulmonary fibrosis (Figure 4A inset). Although the sibling donor group had a statistically significant longer survival than the alternative donor group ($P = .04$), the long-term outcome in cases reported in the literature was poor, albeit these involved earlier and now abandoned BMT preparative regimens.⁶³

NCI IBMFS DC cohort

There were 50 patients in 31 families enrolled in the NCI IBMFS DC cohort, contributing 1179 person-years (Tables 5,6), approximately one-tenth the cases and person-years provided by the cases in the literature. At the close of the analytic period, the ages for the NCI cohort ranged from 6 to 52 years (median 18 years) for those alive, and 1 to 63 years (median 29 years) for those who had died before or during the study. The male:female ratio for the total group was 2.8:1, similar to the ratio in the literature cases ($P = .7$). Cancers were reported in 7 patients (14%), similar to the crude rate of 9%-10% in the literature ($P = .3$). The median age for cancer was 37 years (range 25-44 years), slightly older than the median of 29 years in the literature cases, but this difference was not

statistically significant because of the small numbers of patients ($P = .3$).

Eleven patients underwent BMT, 10 for severe aplastic anemia and one for AML that developed 5 years after MDS. Two of those who received transplants for aplastic anemia did not have the diagnosis of DC at the time of the transplantation. None of the 4 who survived transplantation has developed cancer to date, but the follow-up intervals have been short, 11 months to 9 years. The patient who survived 9 years developed significant pulmonary fibrosis 8 years after BMT. Seven patients died from severe bone marrow failure and did not undergo BMT. Five patients had MDS: one with only MDS; one who developed AML and died after BMT; one whose MDS ensued 13 years after cervical cancer; one whose MDS was followed 10 years later by tongue SCC; and one with a face basal cell carcinoma 10 years after MDS but within 1 year of BMT. Twenty-six patients (52%) had no hematologic or malignant complication. The Kaplan-Meier median survival age was 42 years (Figure 1B), the same as in the literature reports (Figure 1A). The median survival was also the same for those with or without cancer (Figure 1B inset).

Seven cases of cancer (5 solid tumors and 2 AML, not including one basal cell carcinoma, which is not tracked by SEER) were observed, compared with 0.6 expected, for an O/E ratio of 11 (95% CI, 4-23; Table 6). All solid tumors were also significantly increased (O/E = 8; 95% CI, 2-20). Large and statistically significant increases were observed for tongue, the only type of HNSCC reported (O/E = 1 154; 95% CI, 232-3372) and AML (O/E = 195; 95% CI, 22-707). Single cases of cervical SCC and non-Hodgkin lymphoma were in excess, but were not statistically significant. The cumulative incidence of cancer was 53% by 44 years of age in the NCI DC cohort (Figure 2B), similar to 38% by 50 years of age and 65% by 68 years of age in the literature cases (Figure 2A).

SEER has been tracking MDS in the general population since 2001. The O/E ratio for this hematologic complication in the NCI DC cohort was 2663 (95% CI, 858-6 215). This extremely high risk, based on only 5 cases, reflects the young age at which MDS occurred in patients with DC: median 35 years (range, 19-61 years) compared with the median age of 70 years in sporadic cases. In fact, MDS was the most frequent complication and had the highest relative risk in our cohort. However, because MDS does not always develop into leukemia, we did not count MDS as a malignancy. One of our patients did have MDS at age 39, and AML at age 44; the AML was included in the cancer tabulation. The cumulative

Table 4. Leukemia and myelodysplastic syndrome in DC literature cases

	n	Male/female	Age, y	SEER	References
AML	1	1/0	29	67	58,59
2 RA, 2 RAEB, 2 mono7, 2 MDS	8	7/1	17.5 (8-29)	70	7,17,41,60-62

MDS were not subtyped.

RA indicates refractory anemia; RAEB, refractory anemia with excess blasts; and mono7, monosomy 7.

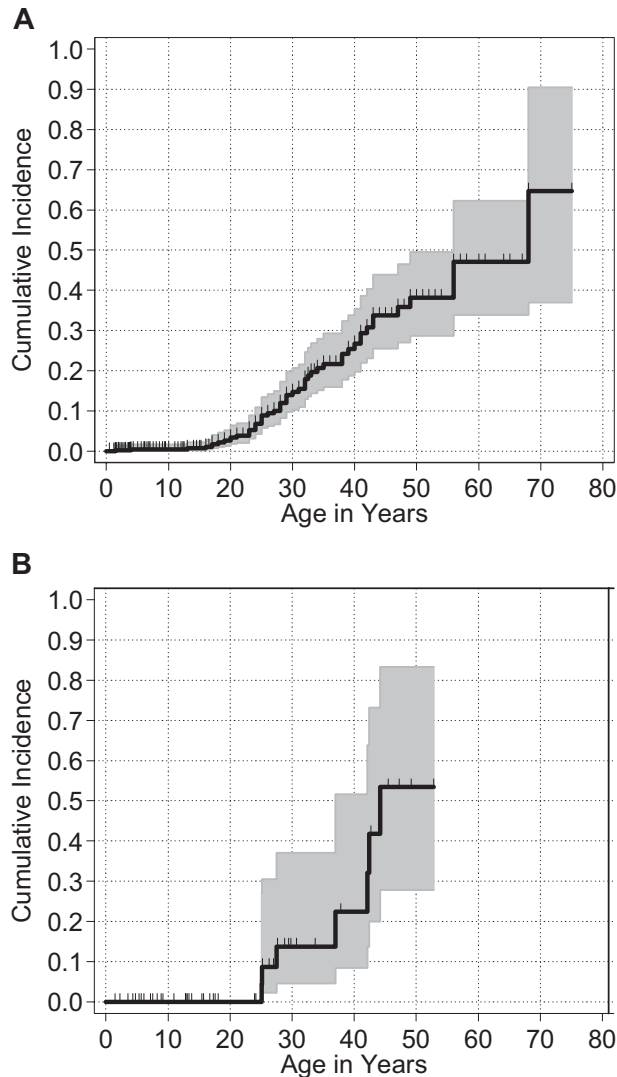


Figure 2. Cumulative incidence by age of development of cancer in cases with dyskeratosis congenita. (A) Cases reported in the literature through 2008, N = 52. (B) Cases enrolled in the NCI IBMFS DC cohort through 2007, N = 7. Data are the cumulative proportion experiencing each event as the cause of failure; shaded area is the 95% pointwise confidence envelope. Vertical lines indicate the age at which patients were censored with or without cancer.

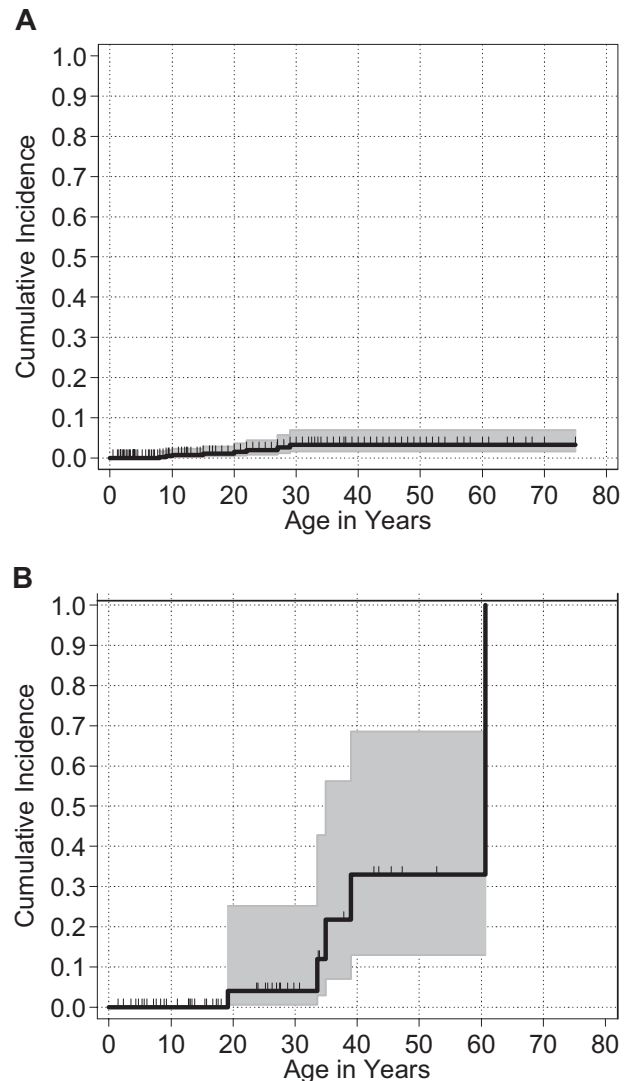


Figure 3. Cumulative incidence by age of development of MDS in cases with dyskeratosis congenita. (A) Cases reported in the literature through 2008, N = 8. (B) Cases enrolled in the NCI IBMFS DC cohort through 2007, N = 5. Data are the cumulative proportion experiencing each event as the cause of failure; shaded area is the 95% pointwise confidence envelope. Vertical lines indicate the age at which patients were censored with or without MDS.

incidence of MDS reached a plateau of 33% by 39 years of age, but the last case occurred at 60 years of age (Figure 3B). Although the plateau age was similar in the literature and the NCI DC cohorts, the cumulative incidence was much higher in the NCI cohort (33% vs 3%). This is the only parameter where the NCI cohort had a higher result than the literature cases, perhaps associated with a referral bias in the NCI cohort, or underreporting in the literature.

A preliminary examination of the correlation of genotype with outcome identified one *DKCI* patient with AML and one with MDS; 4 *TERC* patients with MDS, plus cervical SCC, tongue SCC, and progression to AML in each of 3; one *TINF2* patient with diffuse small cell noncleaved lymphoma, and 2 tongue SCCs in patients in whom the gene has not yet been identified. Thus 50% of the 8 patients with mutations in *TERC* had solid tumors, MDS, or AML, compared with 3 of the 39 with other or unknown mutated genes. Although this is highly statistically significant ($P = .009$), the numbers are too small to draw a strong conclusion.

Four of the 11 transplanted patients survived, with a 1-year survival probability plateau of 36% at 271 days, lower than the

survival in the literature cases at that time point (> 60%), but the numbers are small (Figure 4B). Similar to the cases in the literature, the 3 whose donors were siblings appear to have done better than the 8 with alternative donors, but the numbers are very small (Figure 4B inset), and the difference between sibling and alternative donors in the NCI cohort is not significant ($P = .3$).

Discussion

This report is the first to summarize the types and incidence of cancer in patients with DC, and to quantify the very high risk of cancer in this syndrome with abnormal telomere biology. The types of cancers identified in the literature reports and in the NCI DC cohort were similar and were primarily HNSCC (mostly tongue), skin SCC, anogenital, stomach, esophagus, and lymphomas, as well as AML. We determined the O/E ratios for cancer only in the NCI cohort, due to uncertainty regarding denominators and birth cohorts in the literature reports. In addition, the NCI cohort

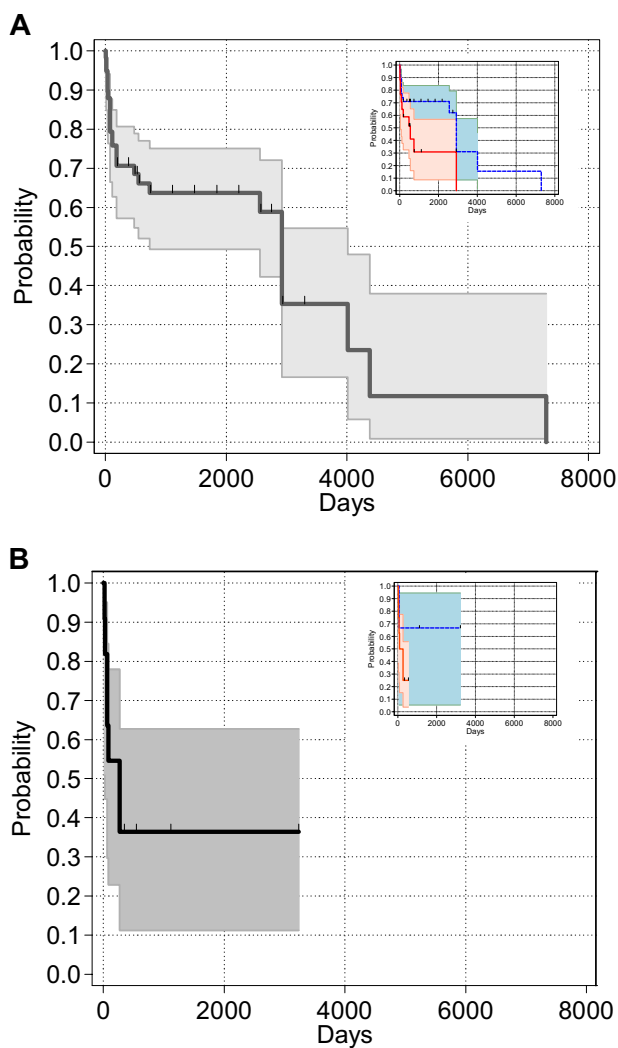


Figure 4. Cumulative survival in cases with dyskeratosis congenita after bone marrow transplantation, calculated using the method of Kaplan and Meier. (A) Cases reported in the literature through 2008, N = 65. (B) Cases enrolled in the NCI IBMFS DC cohort through 2007, N = 11. Data are the cumulative number of patients surviving, censored for last known age alive. Insets show the survival curves for those with sibling (dashed blue) and alternative (solid red) donors.

includes only patients from North America, comparable with the geographic range of the SEER database, whereas the literature included cases from all parts of the world, for which we had no data on sporadic cancers. The O/E ratios were statistically significantly very high, 11-fold for all sites and 8-fold for solid tumors, as well as a remarkable more than 2500-fold risk for MDS. Even more striking are the O/E ratios of more than 1100-fold for tongue cancer, and close to 200-fold for AML. In addition, approximately 10% of the DC cases from either source had from one to 3 cancers, all at much younger ages than in the general population.

Use of the literature as the source of epidemiologic data to assess cancer risk in patients with DC has limitations. Publication bias will result in overestimation of risk, due to overreporting of cases with cancer and underreporting of cases without cancer. Recognition of DC in patients with or without cancer may be limited to the subsets with the diagnostic triad (dyskeratotic nails, lacy reticular pigmentation, and oral leukoplakia) or other clinical features (reviewed elsewhere),² and thus, may miss many cases. Many of the early reports were in the dermatologic literature, with emphases on clinical features and limited discussion of outcomes. Patients with severe phenotypic features may be recognized early with hematologic events, and may die of those hematologic complications before development of cancer, as we have observed in patients with FA.^{5,64} The diagnosis of DC was based solely on clinical phenotypes until the identification of mutated genes in the last decade and the clinical application of testing for short telomeres that was developed in the last 2 years.¹⁰ The early literature also consisted primarily of males, because DC was thought to be primarily an X-linked recessive disorder. Many of the reports did not include all the details required to confirm the diagnosis of DC, thus the authors' assignments were accepted unless they were clearly incorrect. The ages at diagnosis of DC were often not provided, although the ages at diagnosis of cancer were usually indicated. Several cases of Hoyeraal-Hreidarsson and Revesz syndromes were described before the recognition that they are subsets of DC with early onset, characteristically severe phenotypes, and short survival.⁷⁰ Another limitation of the literature is the possibility that duplicated reports were not identified as such. Finally, the adverse events could not be validated. Despite all these caveats, the literature does provide insight into the spectrum of cancers in patients with DC, and estimates of relative frequencies and ages. This resource has been very informative regarding the recognition that cancer is a major concern in DC.

Table 5. Cancer in the NCI IBMFS DC cohort

	Total no. of cases	No history of cancer	All cancers*	P†	BMT‡	BMF§	MDS	No event¶
Number of cases (%)	50	43	7 (14%)		11 (22%)	7 (14%)	5 (9%)	26 (52%)
Male:female	37:13	33:10	4:3	.4	6:5	5:2	1:4	22:4
Median age at outcome, y (range)	NA	NA	37 (25-44)		14 (2-47)	28 (1-53)	35 (19-61)	NA
Number deceased (%)	18/50 (36%)	14/44†† (30%)	4/6†† (67%)	.2	7/11 (64%)	7/7 (100%)	2/4 (50%)	0
Median age at death, y (range)	29 (1-63)	26†† (1-63)	39†† (26-44)	.3	24 (2-47)	28 (1-53)	46 (30-62)	NA
Median survival, y (95% CI), by Kaplan-Meier method**	42 (36-49)	42 (35-49)	46 (35-56)	.6	32 (14-42)	23 (5-40)	NA	NA

BMF indicates bone marrow failure; and NA, not available.

*Data on all cancers include 2 patients with AML (one of whom had MDS that evolved into AML, and then underwent a BMT).

†Comparing those with cancer with those without cancer.

‡Includes 1 patient who had MDS and then AML.

§Severe BMF leading to transplantation (scored in BMT) or death.

||Includes 1 patient with only MDS; 1 whose MDS evolved to AML; 2 with solid tumors (MDS 13 years after cervical cancer, and tongue SCC 10 years after MDS); and one with a facial basal cell carcinoma 10 years after MDS but within a year after BMT. Thus, 3 MDSs are already counted under All cancers.

¶No adverse event, that is, no solid tumor before BMT, AML, BMF, or MDS.

#The median survival values for patients with and without cancer describe subgroups defined by time-dependent rather than baseline characteristics; therefore, these values should be interpreted as descriptive characteristics of the population rather than predictive probabilities for individual patients.

††One patient who had cervical cancer and died later with MDS is included in the numbers and ages of death without cancer.

Table 6. Types of cancers and observed/expected ratio in the NCI IBMFS DC cohort

Cancer	Age, y	Observed	Expected	O/E	95% CI
All sites, median (range)	37 (25-44)	7*	0.6	11†	4-23
All solid tumors, median (range)	37 (25-42)	5*	0.5	8†	2-20
Tongue	25, 25, 42	3	0	1154†	232-3372
AML	28, 44	2	0.01	196†	22-707
Cervical SCC	37	1	0.02	43	0.6-236
Lymphoma, non-Hodgkin	42	1	0.03	34	0.5-191
Basal cell carcinoma, face	29	1*	NA	NA	NA
MDS, median (range)	35 (19-61)	5	0	2663†	858-6215

For all cancer types other than MDS, expected cancer incidences were calculated from SEER 9 Registry rates 1973-2005 for white/black/other. Time at risk before 1973 used 1973-1974 rates, and time at risk after 2005 used 2000-2005 rates. For MDS, expected rates were calculated from SEER 9 Registry rates for 2001-2005.⁹

NA indicates not available.

*Basal cell carcinoma case was not included in O/E because SEER does not track nonmelanoma skin cancer and not included in solid tumors because it followed BMT.

† $P < .05$ that the true O/E ratio equals 1.0 (exact 2-sided tests).

The NCI DC cohort may have similar biases, related to patterns of referral and volunteerism. There may be volunteerism bias by patients or families where cancer had already occurred, because it is a study at the NCI. There may be under-representation of patients with DC who have undergone BMT, or who have severe bone marrow failure and are not interested in participating in a cancer epidemiology study due to more immediate medical concerns. Healthy patients with DC (or undiagnosed silent carriers) may have no interest in enrolling in a study.

Despite these limitations, we found that the types, frequencies, and relative risks of cancers in DC closely resemble those which we reported previously in 3 independent analyses of FA, based on literature,³ the North American Survey (NAS),⁴ and the German Fanconi Anemia Registry (GEFA).⁵ The most frequent cancers in DC were HNSCCs, which are the second most common cancers in FA. The next most common cancers in DC were skin SCC, which were not tabulated in the FA studies. Frequent in both DC and FA were anogenital cancers, primarily anorectal in DC and gynecologic in FA; future studies may determine whether these have similar pathophysiologies (eg, related to human papilloma virus). Esophageal cancer was also reported in high frequencies in both DC and FA. Although liver tumors were common in FA,^{1,3} there was only one such case in DC. This may be related to less frequent use of androgens to treat bone marrow failure in DC, or to their use for shorter periods of time or in lower doses. Because androgens are used in DC, and serious complications such as splenic peliosis have been reported,⁶⁵ surveillance for hepatic complications should be provided for patients receiving androgens.

Only one case of cancer was reported after BMT in a DC patient, which was rectal carcinoma 14 months after BMT. This is in contrast to more than a dozen cases with tongue cancer in transplant recipients with FA.⁶⁶ However, the recent long-term survival after transplantation in FA is close to 90% for those with HLA-identical donors, and more than 50% for those with less perfect matches.⁶⁷ In DC, the long-term survival has been less than 25%, with many patients developing hepatic and/or pulmonary complications; there may not have been sufficient survival time to develop post-BMT malignancies.

The median actuarial survival ages were the same in the literature cases and in the NCI cohort (42 years). This is double the survival in FA,³ but much shorter than expected for the general population. The actuarial cumulative incidence of any cancer was 40% by 50 years of age, and more than 60% by 68 years of age in the literature cases, and around 50% by 45 years of age in the NCI cohort. These cumulative incidences are very high, albeit less than the more than 75% cumulative incidence of solid tumors in FA patients by 45 years of age.³

Although the O/E ratio for all sites in DC (11-fold) is less than the 25- to 50-fold reported in 2 independent FA cohorts,^{4,5} it is statistically significant, despite the small numbers of cases. The very high O/E ratios for tongue cancer (1154-fold) and AML (196-fold) are in the same order of magnitude as we reported in FA (66- and 240-fold for HNSCC, and 649- and 868-fold for AML). Thus, DC and FA both have very high risks of similar types of cancers.

The strengths of our studies are the comparable results from 2 independent sources of patients with DC (literature cases and the NCI cohort), with regard to overall survival, frequency of cancer, poor survival after BMT, and the categories of cancers that developed. The higher cumulative incidence of MDS in the NCI compared with the literature patients may reflect biased enrollment in the former and/or biased recognition or reporting in the latter.

The evidence suggests that DC is a cancer-prone IBMFS; the magnitude of the cancer risk is similar although slightly less than in FA; and the types of cancer are very similar in DC and FA. Among patients with IBMFSs, those with FA have the highest risk of cancer, and those with DC are second. The risk of AML in patients with SCN may be third (cumulative incidence ~20% after 10 years on treatment with granulocyte-colony stimulating factor), although the time scale is different.⁶⁸ Solid data with regard to cancer risk for the other IBMFSs will only emerge as prospective syndrome-specific cohorts are analyzed in the future. It is thus critical that patients with DC, whether symptomatic or silent carriers, receive counseling and surveillance with regard to their risks of severe BMF, MDS, AML, and solid tumors, similar to the recommendations for patients with FA.⁶⁹

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Authorship

Contribution: B.P.A. performed the literature review, wrote the protocol, diagnosed and enrolled the participants, examined the patients, and wrote the paper; N.G. diagnosed and examined the patients, reviewed the medical records, and wrote the paper; S.A.S. diagnosed and examined the patients, performed some of

the genotyping, and wrote the paper; and P.S.R. performed statistical analyses and wrote the paper.

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