Chapter 9

Solid Tumors

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Introduction

Cancer has been reported in people with dyskeratosis congenita (DC) and the related telomere biology disorders (TBDs) since DC was first described in the early 20th century. Three of the first reported cases developed oral or skin squamous cell carcinoma (SCC) [1-4]. Long term, prospective studies have aided in quantifying the types of cancer and age at onset in DC/TBDs. There is also a growing understanding of the role of telomeres in cancer biology. This chapter focuses on solid cancers in DC/TBDs. See Chapter 12, Myelodysplastic Syndromes and Acute Myeloid Leukemia in Telomere Biology Disorders for information on blood cancers in DC/TBDs.

Telomeres and Cancer

Telomeres play a significant role in chromosomal stability and telomere dysfunction is implicated in cancer biology [5, 6] (Figure 1). Telomeres consist of long tandem $(TTAGGG)_n$ DNA repeats and a protein structure at chromosome ends that protect genetic information by maintaining chromosomal stability during cellular division. Each time a cell divides, small amounts of telomeric DNA are lost due to DNA polymerase's inability to fully replicate 3' DNA ends. Consequently, telomeres shorten with each cell division and can be a marker of cellular aging. Telomere attrition over time results in a critically short telomere lengths, which triggers cell senescence and/or cell death. Cancer cells can bypass this process through upregulation of certain genes, including *TERT*, *TP53*, and/or *RB6*. This allows cancer cells to overcome short telomere-induced senescence and continue to divide.

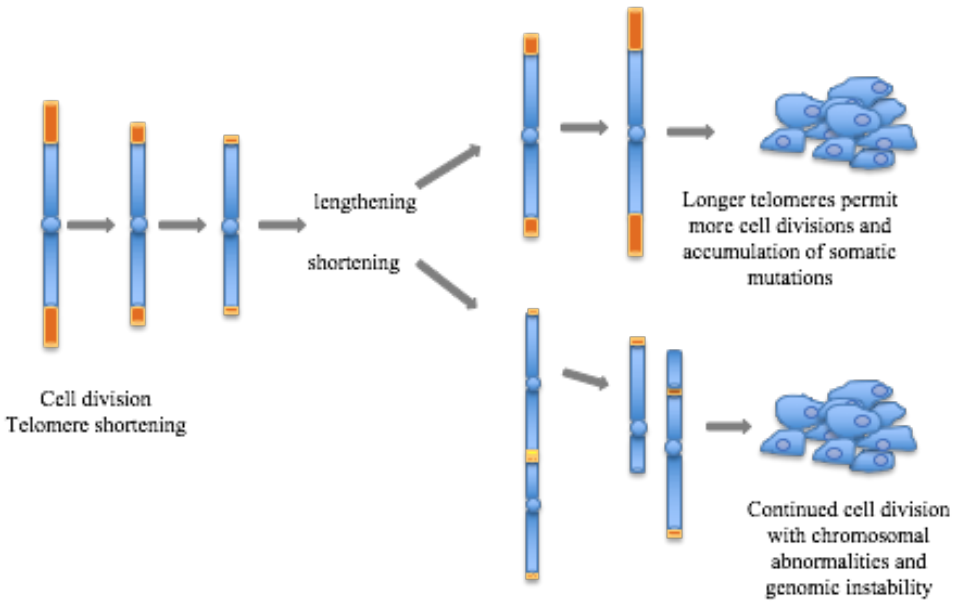

Figure 1. Schematic representation of the dual roles telomere length can play in cancer development. Telomeres, in orange, are long DNA repeats and a protein complex at chromosome ends. They shorten with each cell division due to the inability of DNA polymerase to replicate the 3' end of DNA. When telomeres get critically short, they may lengthen if the expression of certain genes, such as telomerase (*TERT*), TP53, or RB, is increased. This can allow cells to compensate by lengthening their telomeres or by alternative mechanisms.

Frequency and Types of Cancer in DC and the Related TBDs

In 2006, the crude rate (number of patients with DC and cancer divided by the total number of DC patients evaluated) of cancer in DC was estimated at around 10% [7]. A subsequent review of the scientific literature published between 1910 and 2008 found reports of cancer in 52 of 552 patients, a similar crude rate of 9.4% [8]. The types of cancer in that report included twenty-five patients with head and neck squamous cell carcinoma (HNSCC, 27 occurrences), eight with stomach, seven with anorectal, and seven with skin cancers [8].

These first studies were informative but not entirely accurate estimates of cancer in people with DC. They did not consider that cases with cancer are more likely to be reported than those without cancer (i.e., reporting bias). Simply comparing percentages of patients with cancer results in a significant underestimate of risk because age, sex, birth cohort, competing risks of adverse events (i.e., pulmonary fibrosis, liver cirrhosis, or hepatopulmonary syndrome) are not considered. Importantly, they also did not provide risk comparisons with the general population. Long-term cohort studies of people with DC/TBDs enrolled regardless of their prior medical history have been helpful in fine-tuning cancer risk estimates, in guiding patient management, and identifying areas in need of further study. However, these studies remain limited because of the wide spectrum of disease manifestations and multiple modes of inheritance in DC/TBDs.

In 2018, investigators at the National Cancer Institute published an updated study on cancer in 197 individuals with DC from 108 families [9]. There were up to 15 years of follow-up from study participants, which equated to 5655 person-years of data. The median age for developing any solid tumor was 38 years (range 18-61). Twenty cancers occurred before hematopoietic cell transplantation (HCT) and three occurred after HCT. Nearly 20% of patients with DC developed at least one solid cancer by age 65 years

(cumulative incidence). Solid cancer was more frequent and occurred at younger ages in patients after HCT (Figure 2).

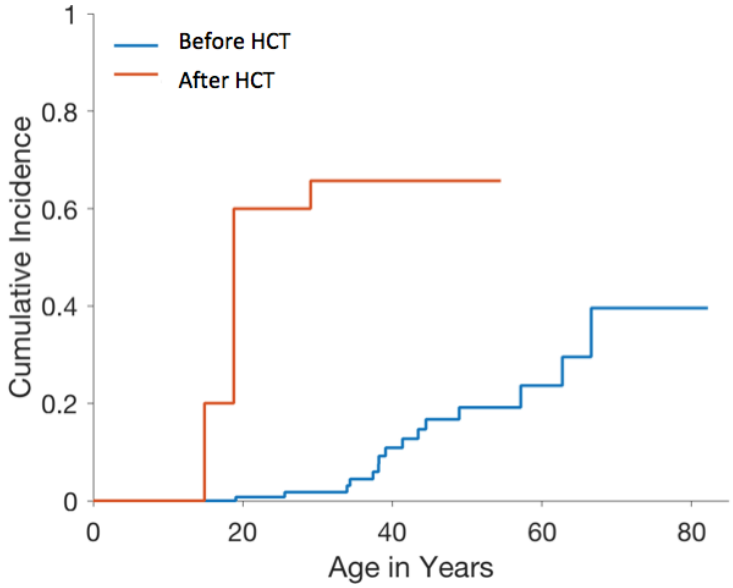

Figure 2. Cumulative incidence of solid tumors in people with DC by hematopoietic cell transplantation (HCT) status.

Figure adapted from Alter et al, *Haematologica* 2018.

After accounting for age, sex, race, and birth year, the number of observed (O) cancer cases in inidividuals with DC with the expected (E) number of cancer cases in the general population, the data show that those with DC had a 4.2-fold increased risk (O/E ratio) of any cancer (solid organ and blood cancers combined) compared with the general population (Table 1) [9]. Patients who had undergone HCT had an approximately 30-times higher risk of cancer than those in the general population. MDS and AML appeared at a 578- and 24-fold increased risk. The O/E ratio for any HNSCC was 74, the predominant subtype being tongue HNSCC with an O/E ratio of 216.

Table 1. Types of cancer in people with DC and comparison with the general population. Table adapted from Alter et al, *Haematologica* 2018[6]. One hundred ninety-seven patients with DC from 108 families were evaluated.
*Tongue cancer is a subset of head and neck squamous cell carcinoma (HNSCC).
O/E: number of cancers observed in patients with DC divided by the number of cancers expected in someone of the same age in the general population using the NCI Surveillance and End Results database (https://seer.cancer.gov)
Abbreviations: CI, confidence interval; HNSCC, head and neck squamous cell carcinoma; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; NHL, non-Hodgkin lymphoma.

	no HCT 197 people with DC 5644 person-years evaluated				**After HCT** 60 people with DC 248 person-years evaluated			
	Age at cancer	**# cases**	**O/E**	**95% CI**	**Age at cancer**	**# cases**	**O/E**	**95% CI**
All cancers	38 (18-63)	27	4.2	2.8-6.1	19 (15-29)	3	30	6-8
All solid cancers	38 (18-61)	17	3.1	1.8-4.9	18.8	1	13	0.3-73
HNSCC	38 (18-61)	11	74	37-133	18.8	1	432	11-2404
Tongue*	33 (18-42)	8	216	94-427	18.8	1	1561	40-8699
Blood and lymph node cancers								
AML	40 (28-56)	5	73	23-169				
MDS	31 (4-73)	18	578	343-914				
NHL	57 (43-65)	3	11	2.2-30	29.1	1	141	4-786
Hodgkin lymphoma					14.9	1	164	4-914

Another study evaluated cancer in 180 patients with telomere biology disorders from 113 families, of whom 14 had classic DC (defined as having at least one of oral leukoplakia, nail dystrophy, and/or abnormal skin pigmentation) [10]. MDS and AML were the most common malignancies in this study, occurring in 18 patients (see Chapter 12, Myelodysplastic Syndromes and Acute Myeloid Leukemia in Telomere Biology Disorders for more information). There were five patients with six solid organ cancers (three HNSCC, two anal SCC, and one rectal adenocarcinoma) with a median age at cancer of 35 years (range 25-53). Four of these five patients met the investigators' criteria of classic DC and these four also had pathogenic variants in *DKC1*. This publication and a review from the same group implied that "cancer is relatively rare in short telomere syndromes" [10, 11]. It is true that cancer in DC/TBDs may occur at a lower rate than in other inherited cancer susceptibility syndromes. For example, approximately 90% of people with Li-Fraumeni syndrome due to germline *TP53* pathogenic variants will have at least one cancer prior to 70 years of age [12, 13]. However, cancer in people with DC/TBDs occurs at much higher frequency and much younger ages than in people in the general population [14]. This information is crucial in tailoring cancer screening and prevention recommendations.

Treatment of Cancer in DC/TBDs

Treatment of cancer in people with DC is especially challenging because patients may also have bone marrow failure, pulmonary fibrosis, liver cirrhosis, and/or many of the other clinical manifestations associated with DC/TBDs. Consequently, patients with DC and cancer may have more treatment-related complications than people without DC.

We reviewed the cancer treatment records of 38 patients with DC participating in the NCI IBMFS cohort study (ClinicalTrials.gov Identifier: NCT00027274, https://marrowfailure.cancer.gov) [9] (Vasta et al, unpublished data). Forty-five cancers (before and after HCT) occurred in these 33 patients (non-melanoma skin cancers were

excluded from this analysis). Affected genes were six *DKC1*, one *RTEL1*, nine *TERC*, six *TERT*, six *TINF2*, one *WRAP53*, and nine unknown.

Six patients with AML (median age at AML 36 years, range 25-56) passed away due to therapy-related complications. Two patients had chemotherapy-alone toxicities including infections and acute respiratory distress syndrome. Four patients underwent HCT but succumbed to transplant-related infections. There were four cases of post-transplant lymphoproliferative disease treated with Rituximab. Four patients developed non-Hodgkin lymphoma (NHL); two died within a year of diagnosis, one died of other causes 10 years after diagnosis, and the outcome was unknown for one. The outcome for a patient with Hodgkin lymphoma was not available.

HNSCC was notable for 21 occurrences in 11 patients. There were 14 localized cancers requiring resection in 4 patients, including one patient with 11 resections (Figure 3). Seven invasive cancers occurred in seven patients and were treated with different modalities, likely due to each patient's specific needs. Unfortunately, all patients with invasive HNSCC died due to the cancer or therapy-related complications.

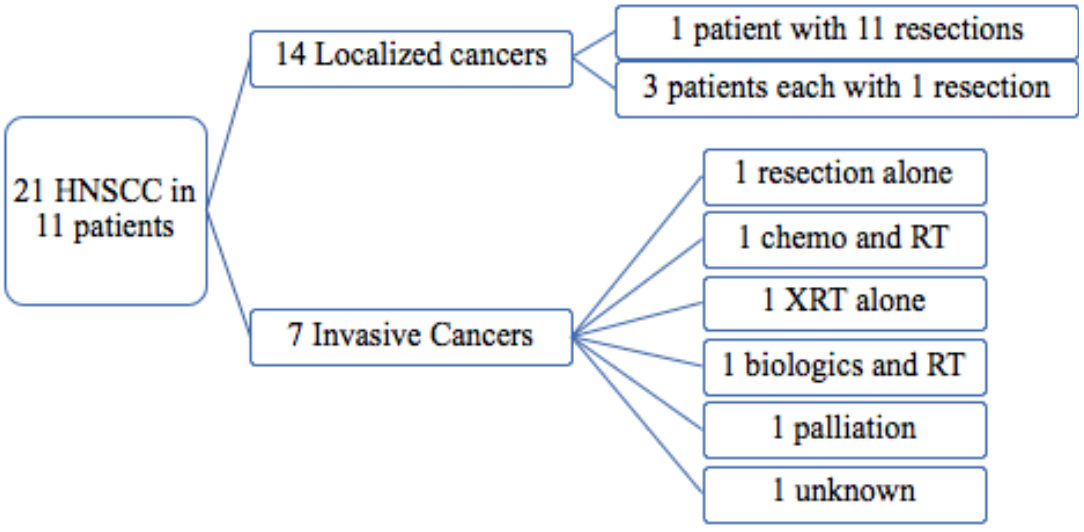

Figure 3. Head and neck squamous cell carcinoma (HNSCC) in patients with DC. Cancer treatment records were reviewed for 11 patients with 21 HNSCCs. Affected genes were 1 *DKC1*, 1 *RTEL1*, 3 *TERC*, 2 *TINF2*, 1 *WRAP53*, and 3 unknown. Abbreviations: RT, radiation therapy; chemo, chemotherapy

These descriptive data and other case reports suggest that people with DC/TBDs have unique sensitivities to chemotherapy and radiation therapy. Additional studies are needed to improve understanding of cancer therapy-related side effects.

Cancer Prevention and Surveillance

Prospective studies of cancer screening in patients with DC/TBDs have not yet been conducted and are urgently needed. In general, early cancer diagnosis is important to reduce cancer-related morbidity and mortality in patients with DC/TBDs. For example, screening can identify HNSCC when it is still amenable to surgical resection only. Table 2 lists the current recommendations.

Table 2: Cancer screening and prevention methods recommendations for people with DC/TBDs. These recommendations are based on expert opinion as no prospective clinical trials of cancer prevention have been conducted for DC/TBDs. Everyone should also follow the same cancer screening recommendations as the general population. More information on cancer screening in the general population is available at http://www.cancer.gov/cancertopics/screening.

Cancer	Approximate Start Age	Screening Method	Prevention
HNSCC	10 years	Annual oral exam, nasolaryngoscopy	No smoking or drinking alcohol. Good oral hygien See also Chapter 8
Gynecologic	16 years or after first period	Annual gynecologic exam, pap smear, HPV test	HPV vaccine See also Chapter 21
Rectal	18 years	Physical exam, check stool for blood annually	
Esophagus	20 years	Esophagoscopy, as needed	No smoking or drinking alcohol
Liver	Infancy	Liver ultrasound, liver function tests	No drinking alcohol; chelate iron if transfused See also Chapter 19
Skin	Infancy	Dermatology exam, annually	Sun protection See also Chapter 6
Leukemia	Infancy	Complete blood counts, bone marrow aspirate, biopsy	See also Chapter 12
Lung	40 years	Chest X-ray, lung function tests, as clinically indicated	No smoking See also Chapter 14

Summary

Patients with DC meet the criteria for “cancer-prone” with most of the cancers presenting at younger ages than expected and more commonly than expected when compared with the general population. The most common solid tumor is HNSCC, which is amenable to early detection with cancer screening. All patients and/or their families are encouraged to promptly report to health care professionals any changes in their health, and physicians should have a low index of suspicion for cancer in patients with DC/TBDs. Those diagnosed with cancer may need a modified cancer treatment plan that addresses potential therapeutic sensitivities and co-occurring illnesses.

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