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Inherited mutations in cancer susceptibility genes are common among breast cancer survivors who develop therapy-related leukemia

Jane Churpek, MD[1,2,5,*], **Rafael Marquez, BA**[2], **Barbara Neistadt, MHS**[2], **Kimberly Claussen, BA**[2], **Ming Lee, PhD**[3], **Matthew Churpek, MD, MPH, PhD**[2,4], **Dezheng Huo, PhD**[4], **Howard Weiner**[2], **Mekhala Bannerjee, MS**[2], **Lucy Godley, MD, PhD**[1,2,5], **Michelle Le Beau, PhD**[2,5], **Colin Pritchard, MD, PhD**[6], **Tom Walsh, PhD**[3], **Mary-Claire King, PhD**[3], **Olufunmilayo Olopade, MD**[1,2,5], and **Richard Larson, MD**[2,5]

[1]Center for Clinical Cancer Genetics, The University of Chicago, Chicago, IL

[2]Department of Medicine, The University of Chicago, Chicago, IL

[3]Division of Medical Genetics, Department of Medicine, University of Washington School of Medicine, Seattle, WA

[4]Department of Health Studies, The University of Chicago, Chicago, IL

[5]Comprehensive Cancer Center, The University of Chicago, Chicago, IL

[6]Department of Laboratory Medicine, University of Washington, Seattle, WA

Abstract

Background—Risk factors for therapy-related leukemia (TRL) development, an often lethal late complication of cytotoxic therapy, remain poorly understood and may differ for survivors of different malignancies. Breast cancer (BC) survivors now account for the majority of TRL cases, making study of TRL risk factors in this population a priority.

Methods—Patients with TRL following cytotoxic therapy for a primary BC were identified from The University of Chicago TRL registry. Those with an available germline DNA sample were screened with a comprehensive gene panel covering known inherited BC susceptibility genes. Clinical and TRL characteristics of all subjects and those with identified germline mutations are described.

Results—Nineteen (22%) of 88 BC survivors with TRL had an additional primary cancer and 40 (57%) of the 70 with available family history had a close relative with breast, ovarian, or pancreatic cancer. Of the 47 subjects with available DNA, 10 (21%) were found to carry a

[*]Corresponding author: Jane E. Churpek, M.D. The University of Chicago, 5841 S. Maryland Ave MC2115, Chicago, IL 60635, Phone: 773-834-1076, Fax: 773-702-9268, jchurpek@bsd.uchicago.edu.

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AUTHORSHIP

JEC, CCP, TW, M-CK, RAL, and OO designed research; JEC, RM, KC, BN, MKL, HW, MB, CCP, TW, and M-CK performed research; JEC, RM, KC, MKL, MMC, DH, LAG, MML, CCP, TW, M-CK, and RAL analyzed data; JEC, MML, RAL, and OO wrote the paper. All authors edited and approved the final manuscript.

deleterious inherited mutation in: *BRCA1* (n=3, 6%), *BRCA2* (n=2, 4%), *TP53* (n=3, 6%), *CHEK2* (n=1, 2%), and *PALB2* (n=1, 2%).

Conclusions—BC survivors with TRL have personal and family histories suggestive of inherited cancer susceptibility and frequently carry germline mutations in BC susceptibility genes. These data support the role of these genes in TRL risk and suggest that long term follow-up studies of women with germline mutations treated for BC and functional studies of the effects of heterozygous mutations in these genes on bone marrow function following cytotoxic exposures are warranted.

Keywords

therapy-related; leukemia; breast cancer; inherited

INTRODUCTION

Therapy-related leukemias (TRL), including therapy-related myeloid neoplasms (t-MN) and therapy-related acute lymphoblastic leukemia (t-ALL), are an often lethal, late complication of prior cytotoxic therapy for survivors of a first cancer.[1–4] With increases in cancer survivorship,[5] the number of cases of TRL is expected to rise. Thus, efforts to understand and prevent this complication are essential.

At present, TRL are thought to be direct consequences of mutational events induced by prior cytotoxic exposures, but exact mechanisms and risk factors remain unclear. Associations between specific exposures and the phenotype of the TRL that develops support a key role for the exposures in the genesis of TRL. For example, exposure to topoisomerase II inhibitors is associated with TRL characterized by clonal cytogenetic abnormalities involving *KMT2A*/*MLL* on chromosome band 11q23 with a short latency of 2–3 years post exposure. In contrast, exposure to alkylating agents or radiation is associated with TRL with abnormalities of chromosomes 5 and/or 7 which more often occur with a 5–7 year latency.[6] Further, the incidence of TRL is increased in breast cancer (BC) adjuvant trials using higher chemotherapy dose intensity, concomitant use of radiation, and/or the use of hematopoietic growth factors.[7, 8]

However, the observation of acute myeloid leukemia (AML) and ALL cases occurring in patients after undergoing surgery only for a primary malignancy[1–3, 9] raises the possibility that some TRL may be independent second primary cancers unrelated to prior cytotoxic exposures. Individuals with inherited cancer syndromes, like Li Fraumeni syndrome or dyskeratosis congenita, which predispose affected individuals to both leukemias and solid tumors, could explain some of these cases and present clinically like TRL. Another possibility is that individuals who carry an inherited mutation in a cancer susceptibility gene could be at higher risk for TRL after DNA damaging exposures than other patients.

Because breast cancer (BC) survivors now account for the largest number of TRL cases,[2, 10] and the genes responsible for inherited susceptibility to BC are well characterized, patients who develop TRL after BC represent an ideal population in which to examine the role of inherited cancer susceptibility in the etiology of TRL. However, a comprehensive

assessment of all currently known moderate to high penetrance BC susceptibility genes in patients with TRL after BC has not been performed. Here we present the clinical and TRL characteristics of 88 well-annotated BC survivors with TRL and the results of a comprehensive screen for inherited mutations in known BC susceptibility genes.

METHODS

Study population

Cases were drawn from The University of Chicago TRL registry, which contains data on all consented patients with a history of cytotoxic exposures for a prior malignant or nonmalignant condition who subsequently developed myelodysplastic syndrome (MDS) or an acute leukemia evaluated at The University of Chicago between 1972 and 2012. Additional clinical data were abstracted by individual chart review. Family histories consisted of physician documentation at initial consultation. Formal pedigrees were available for eight subjects who had prior cancer risk evaluation. This study was approved by The University of Chicago Institutional Review Board in accordance with the Declaration of Helsinki.

Definitions

Latency was defined as time from first cytotoxic exposure to the first bone marrow examination diagnostic of a TRL. Mechanism of action of chemotherapeutic agents was categorized, as previously defined.[4] Cytogenetic abnormalities were detailed according to the International System for Human Cytogenetic Nomenclature.[11]

Tissue sources

Constitutional DNA sources included EBV-transformed lymphoblastoid cell lines (LBLs) generated at the time of complete remission (CR), buccal swabs, peripheral blood (PB) or bone marrow (BM) at the time of CR, and cultured skin fibroblasts. A leukemia sample was used if it was the only sample available with sufficient DNA.

BC susceptibility gene sequencing

BROCA targeted genomic capture and next generation sequencing (NGS) was performed as previously described (Supplementary Table 1).[12] Single nucleotide variants (SNVs), small insertions and deletions (indels), and large genomic rearrangements (LGR) were identified as previously described.[12, 13] Deleterious mutations, defined as nonsense and frameshift mutations, LGR, and missense mutations with experimental evidence supporting their deleterious nature, were validated by independent PCR amplification and Sanger sequencing or by real-time PCR using TaqMan probes (Life Technologies). Variants were only considered germline if they were confirmed in a constitutional DNA source.

Acquired mutation sequencing

Oncoplex targeted genomic capture and NGS was performed as previously described (Supplementary Table 2).[14] All variants with data supporting a role in leukemia were

validated by independent PCR amplification and Sanger sequencing. Constitutional DNAs were used to confirm the somatic nature of identified variants when available.

Statistical methods

Kaplan-Meier curves were used to calculate overall survival (OS). Stata version 12.1 was used for all analyses (StataCorp; College Station, TX).

RESULTS

Clinical characteristics of BC survivors who developed TRL

In total, 88 female BC survivors were identified (Table 1). The median age at primary BC diagnosis was 52 years (range, 23–83). Nineteen women (22%) had an additional primary cancer diagnosis. A family cancer history was available for 70 subjects (80%), among whom 40 (57%) reported at least one first- or second-degree relative with breast, ovarian, or pancreatic cancer. Among those for whom prior cytotoxic exposure data were available (n=86; 98%), chemotherapy was a component of the exposures for 67 patients (78%). All but one received a multiagent regimen. Regimens incorporating both doxorubicin and cyclophosphamide were most common (n=37; 56%). Radiation exposure was reported for 68 patients (79%). Four patients (5%) had undergone a prior autologous stem cell transplant and 11 patients (13%) had received myeloid growth factors.

TRL characteristics in BC survivors

Most BC patients developed t-MN (n=81; 92%), but 7 cases (8%) of t-ALL were also observed (Table 1). The median latency from first cytotoxic exposure to TRL diagnosis among the 86 patients for whom latency was available was 58 months (interquartile range (IQR), 28–105 months). Clonal cytogenetic abnormalities were observed in 77 of the 84 subjects (92%) with an available karyotype. Among these, abnormalities of chromosomes 5 and/or 7 and recurring balanced translocations were both common, occurring in 51% (n=43) and 35% (n=29) of patients, respectively. Rearrangements involving *KMT2A/MLL* on chromosome band 11q23 were the most common (n=11 of 84; 13%), followed by t(15;17) (n=6; 7%), and those involving 21q22 (n=5; 6%) (Supplementary Table 3). Over one quarter of the observed recurring balanced translocations were t(9;11)(p22;q23) (n=8 of 29; 28%). OS after TRL diagnosis was poor (median 13 months; IQR, 5–22).

Inherited mutation detection and distribution

BROCA targeted capture and NGS of the 47 subjects with DNAs available resulted in >500-fold median coverage with 97% and 99.5% of bases covered at least 50- and 10-fold, respectively. The clinical characteristics of sequenced subjects did not differ from the 41 without available DNAs (Supplementary Table 4). Overall, 10 BC survivors (21%) who developed TRL carried a deleterious inherited mutation, distributed among *BRCA1* (n=3, 6%), *TP53* (n=3, 6%), *BRCA2* (n=2, 4%), *CHEK2* (n=1, 2%), and *PALB2* (n=1, 2%) (Figure 1). By TRL subtype, 8 of 43 patients (19%) with t-MN had an inherited mutation, distributed among all 5 of these genes. Of t-ALL cases, 2 of 4 (50%) had a mutation, both in *TP53*.

Observed patterns among those with specific inherited mutations included (Table 2): 1) those with germline *TP53* mutations were the only patients with an inherited mutation to develop t-ALL (2 of 3 (67%) vs 0 of 7 (0%) patients with inherited mutations in other genes), and all 3 developed TRL with complex karyotypes; and 2) those with a *BRCA1* or *BRCA2* mutation had an especially long latency to TRL development (median 133 vs 53 months in those without an inherited mutation), and most developed TRL featuring a normal karyotype (n=2 of 5, 40%) or a single karyotypic abnormality (n=2 of 5, 40%). Six of the 10 patients (60%) with an inherited mutation had a family history of cancer, 2 (20%) did not, and for the remaining 2 (20%), the family history was unknown (Table 3).

Additional informative cases

We identified three additional patients who did not fit our original study population who had previously identified germline *BRCA1* mutations. We include them here for descriptive purposes (Supplementary Table V): 1) one patient who developed chronic myeloid leukemia (CML) following BC treated with surgery only; 2) one patient who developed CML 33 months prior to a diagnosis of BC; and 3) one ovarian cancer survivor who developed a t-MN with a t(9;11) after cytotoxic chemotherapy.

Somatic mutations in TRL after BC

In order to identify somatic mutations that contribute to TRL post BC, we sequenced leukemia samples available from 9 subjects using Oncoplex. Somatic mutations were identified in 8 of the 9 subjects (Table 4). These mutations were distributed among 17 genes (Supplementary Table VI). The median number of somatic mutations per sample was 2 (range, 0 to 9). *FLT3* and*TET2* were the genes most commonly mutated, with each mutated in 3 of 9 (33%) subjects. Mutations in *ASXL1*, *NRAS*, and *WT1* were observed in 2 of 9 (22%) subjects. Combinations seen in *de novo* AML including a *KIT* exon 17 mutation in a t(8;21) t-MN and a *FLT3* mutation in a t(15;17) t-MN were identified. The leukemia sample from UPIN12, who developed a t-MN with a complex karyotype in the setting of a germline *BRCA1* mutation, had somatic mutations in *TET2*, *NRAS*, and *TP53*.

DISCUSSION

Through a comprehensive screen of inherited BC susceptibility genes, we found that one in five of the BC survivors with TRL in our series carry a deleterious inherited mutation. These mutations are distributed among five genes, all with key roles in DNA repair and/or DNA damage sensing pathways. In addition, many of the well-annotated BC survivors with TRL in our series have a personal history of additional malignancies and/or a family history of cancer in close relatives, suggesting a cancer-prone population. Our data support a role for inherited cancer susceptibility in TRL post-BC.

TRLs have typically been considered a direct and stochastic consequence of cytotoxic therapies. However, investigations have provided evidence in support of the role of underlying cancer susceptibility, particularly among BC survivors. Using SEER data, Martin *et al* demonstrated that young women with BC had the highest risk of t-MN development (RR 4.14) and that the age-dependent risk of TRL among these young women mirrored the

risk of developing a second BC or an ovarian cancer, suggesting a shared underlying genetic risk factor.[15] Two other small series also add support. In the first, sequencing of *BRCA1*, *BRCA2*, *TP53*, and *CHEK2* 1100delC identified deleterious germline mutations in 3 of 14 unselected BC patients with TRL (21%).[16] In the second, sequencing of *BRCA1* and *BRCA2* in 13 women with TRL after early onset BC identified germline *BRCA2* mutations among two (15%).[17] Our data add to the spectrum of genes involved and confirm the high yield of genetic testing in this population. Our findings support a recommendation for genetic testing for all women with TRL post-BC to allow primary prevention in at risk close relatives and those who survive their TRL.

All of the BC susceptibility genes with mutations identified in this series function to sense or repair DNA damage and most are closely tied to leukemia risk. *PALB2* and *BRCA2*, key components of the Fanconi anemia (FA) DNA repair pathway, cause FA, an inherited bone marrow failure syndrome featuring an 800-fold increased risk of MDS/AML, when mutations in both alleles are inherited.[18, 19] Reduced expression of *BRCA1*, a gene also involved in the FA pathway, has been demonstrated in t-MN cases,[20] and an increased risk of leukemia has been reported in an epidemiologic study in relatives of *BRCA1* mutation carriers.[21] Inherited mutations in *TP53* cause Li Fraumeni syndrome in which 3–5% of the tumors that develop are leukemias.[22, 23] *TP53* is also somatically mutated in 2% of *de novo* AML[24] and 11–38% of t-MN.[25, 26] Data for *CHEK2* involvement in leukemia are limited, but leukemias have been reported in kindreds with inherited *CHEK2* mutations.[27]

Observations from our study provide additional evidence that some cases of TRL are more likely independent secondary primary cancers, whereas others are more clearly linked to the cytotoxic exposures. UPIN 49, for example, carries an inherited *BRCA2* mutation and developed a t-MN with a t(3;21) 18 years after treatment for BC. This timeframe is well beyond the expected 2–3 years for t-MN with translocations involving 21q22,[6] suggesting a possible independent event. Our previous report of two cases of acute promyelocytic leukemia in women with BC treated with surgery only with *BRCA2* mutations[28] and the two cases of CML occurring either prior to BC or after BC treated with surgery alone in *BRCA1* mutation carriers reported here also support this idea and suggest that inherited heterozygous mutations in *BRCA1* and *BRCA2* may contribute to leukemia risk.

In contrast, TRL with a t(9;11) seen in 10% of our patients and in three other series of BC patients suggest that BC survivors are uniquely predisposed to TRL with this abnormality. Chandra *et al* reported that 62% of the t-MN cases with t(9;11) at their institution were in the setting of a prior BC.[29] T(9;11) was identified among 11% (3 of 36) t-MN cases in a recent series of BC survivors[9] and was overrepresented among t-MN cases (11%, 20 of 182) vs *de novo* AML (1%, 35 of 2381) in a study in which BC survivors accounted for 37% of t-MN cases.[2] Further study of the non-homologous end joining repair mechanism implicated in the t(9;11) translocation in BC survivors with TRL is warranted.

Finally, we observed seven cases of t-ALL among our 88 BC survivors (8%) with TRL. We identified deleterious mutations, both occurring in *TP53*, among two of four cases (50%) studied. Both of these mutation carriers developed BC prior to age 30, a clinical phenotype that in and of itself warrants genetic testing. However, inherited mutations in *BRCA1* and

BRCA2 would be expected to account for the majority of mutations identified in early onset BC cases with *TP53* mutations expected in only about 4% of those with BC under age 30.[30] Our data suggest that when BC is followed by t-ALL, the likelihood of a *TP53* mutation is higher.

Our study has limitations. First, this is a small series, which limits our ability to assess for differences among different mutation carrier groups. Second, it is unknown how the proportion of mutation carriers identified in our study population compares to a similar population of BC patients who did not develop TRL. It took several decades to obtain the number of cases presented here, making it difficult to ascertain a control group of similarly treated BC patients with similar length of follow-up who did not develop TRL with which to compare our group. In addition, studies of *BRCA1* and *BRCA2* among unselected BC patients suggest that about 5% carry a deleterious mutation,[31, 32] but comprehensive panel-based genetic testing as used here has not yet been applied to a large, population-based group of BC patients. Thus, the true frequency of mutations in all of the genes studied here among a general population of BC patients is unknown and deserves further study.

In conclusion, we have demonstrated that one in five BC survivors who develop TRL carry an inherited mutation in a BC susceptibility gene. The mutations involve five genes, which all function to maintain DNA integrity, suggesting a role for these pathways in leukemia risk in the setting of cytotoxic exposures or for some, regardless of exposures. Our data suggest that a long-term prospective trial following similarly treated women with breast cancer for whom germline mutation status is known for the development of TRL and that functional testing of the role of these genes in bone marrow dysfunction following cytotoxic exposures are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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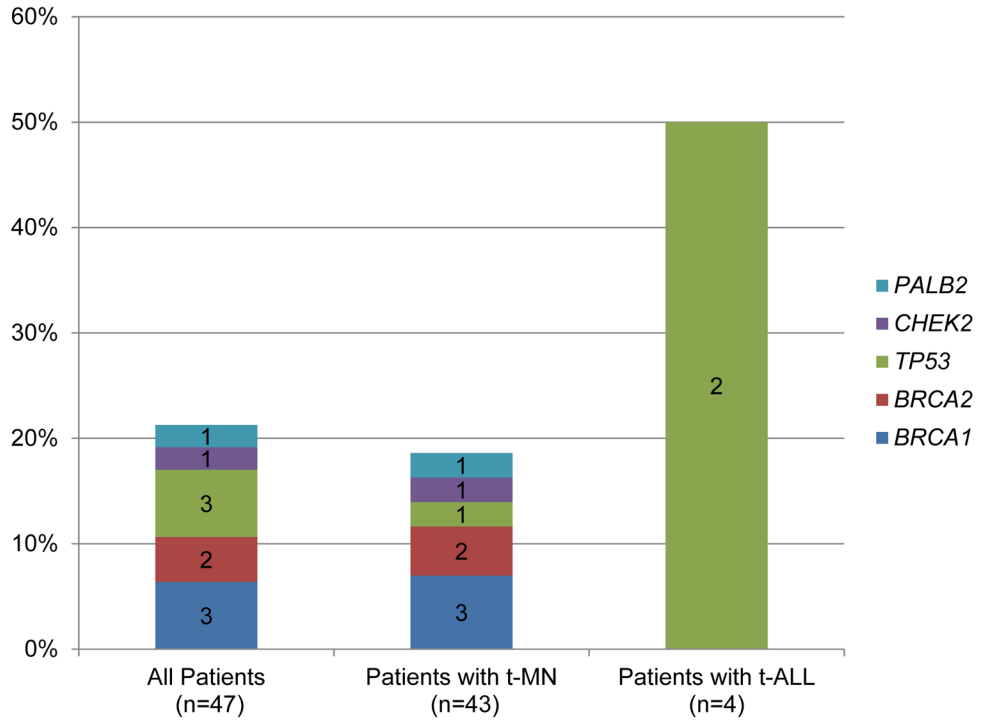


Figure 1.

Inherited mutations in breast cancer susceptibility genes among 47 subjects with therapy-related leukemia

Table 1

Clinical characteristics, prior cytotoxic exposures, and therapy-related leukemia characteristics of 88 breast cancer survivors

	Number (%)
Age at diagnosis of breast cancer	
≤35	9 (10)
36–45	14 (16)
46–55	29 (33)
≥56	34 (39)
Unknown	2 (2)
Race/Ethnicity	
Caucasian (non-AJ)	65 (74)
Caucasian (AJ)	3 (3)
African American	5 (6)
Other/Unknown	15 (17)
Additional cancer diagnoses (n=19) *	
Second primary breast cancer	7 (8)
Ovarian cancer	3 (3)
Other	12 (14)
Family history of cancer in a first or second degree relative (n=70)	
Breast cancer	33 (47)
Breast, ovarian, or pancreatic cancer	40 (57)
Prior therapy	
Chemotherapy + Radiation	49 (56)#
Chemotherapy only	18 (20)#
Radiation only	19 (22)
Unknown	2 (2)
Chemotherapy class exposures	
Topoisomerase II inhibitor	40 (45)
Alkylating agent	58 (66)
Unknown	8 (9)
Type of therapy-related leukemia	
t-MN	81 (92)
t-ALL	7 (8)
Latency; median in months (IQR) **	58 (28–105)
Cytogenetics**	
Normal karyotype	**7 (8)**

	Number (%)
Abnormal karyotype	**77(88)**
Abnormalities of chromosome 5 and/or 7	43 (49)
Recurring balanced translocations	29 (33)
Other clonal abnormality	7 (8)
Unknown	**4 (5)**
Overall survival; median in months (IQR)	
From breast cancer diagnosis****	102 (60–173)
From therapy-related leukemia diagnosis	13 (5–22)

* Includes three women with multiple primary tumors; other cancers include: uterine (n=2), melanoma (n=2), lung (n=2), non-Hodgkin lymphoma (n=2), osteosarcoma (n=1), bladder (n=1), cervical (n=1), multiple myeloma (n=1)

Specific agents were unknown for n=4 in the chemotherapy + radiation group and n=2 in the chemotherapy only group

** Latency was unknown for 3 patients

*** 2 patients had abnormalities of both chromosomes 5 and/or 7 and a recurring balanced translocation (t(15;17) and t(9;22))

**** Overall survival was unknown for 3 patients

Abbreviations: AJ=Ashkenazi Jewish; t-MN=therapy-related myeloid neoplasm; t-ALL=therapy-related acute lymphoblastic leukemia; IQR=interquartile range

Table 2

Clinical and cytogenetic characteristics by germline mutation status among 47 sequenced subjects*

	No mutation (n=37)**	*BRCA1* or *BRCA2* (n=5)	*TP53* (n=3)	*PALB2* (n=1)	*CHEK2* (n=1)
Age at primary diagnosis (years; range)	53 (31–79)	50 (33–53)	23 (23–24)	51	42
Latency (median in months; range)	53 (11–792)	133 (30–408)	48 (30–81)	90	21
Therapy-related leukemia type					
t-MN	35 (95)	5 (100)	1 (33)	1 (100)	1 (100)
t-ALL	2 (5)	0	2 (67)	0	0
Cytogenetics (n; %)					
Normal karyotype	4 (11)	2 (40)	0	0	0
Clonal abnormality	30 (81)	3 (60)	3 (100)	1 (100)	1 (100)^
Balanced translocations#	14 (38)	1 (20)	1 (33)	0	1 (100)^
Chr 5 and/or 7 abn***#	15 (41)	2 (40)	1 (33)	1 (100)	0
Complex***	11 (30)	1 (20)	3 (100)	1 (100)	0
Unknown	3 (8)	0	0	0	0
Survival from TRL diagnosis (median in months; IQR)	13 (7–27)	14	29	14	52

* Tissue sources used for sequencing included: LBLs (n=24), buccal swabs (n=8), PB or BM in remission (n=6), skin fibroblasts (n=1), and PB or BM samples with leukemia (n= 8).

** 1 patient's age at diagnosis and latency were unknown.

^ Patient had FISH studies only.

2 subjects had both a balanced translocation (t(15;17) and t(9;22)) and an abnormality of chromosome 5 and/or 7.

*** Complex karyotype as defined in ref [33]. 11 of 15 subjects with chromosome 5 and/or 7 abnormalities with no inherited mutation had a complex karyotype as well as 1 of 2 subjects with *BRCA1*/*BRCA2*, 1 subject with a *TP53*, and the 1 subject with a *PALB2* mutation.

Abbreviations: IQR=interquartile range; abn=abnormalities; TRL=therapy-related leukemia; t-MN=therapy-related myeloid neoplasm; t-ALL=therapy-related acute lymphoblastic leukemia; chr=chromosome

Table 3

Detailed clinical characteristics of the 10 breast cancer survivors who carry inherited BC susceptibility gene mutations and developed therapy-related leukemia

Patient ID	Gene	Mutation	Age at Breast Cancer Dx	Chemo /XRT	Other tumors	Family cancer history	TRL type	TRL latency (mo)	TRL OS (mo)	Sample used for sequencing	Karyotype at TRL Diagnosis
UPIN12	*BRCA1*	dup ex13	33	Y/Y	Ovary; 2nd Breast	Breast; Prostate	t-MN	408	3	BM leukemia; confirmed in buccal DNA	45,XX,add(4)(q23),del(5)(q13.3q33),del(6)(p21.3p23),−7,+8, −16[20]
UPIN19	*BRCA1*	del ex13–15	53	Y/Y	2nd Breast; NHL	Breast; Ovary; Colon; Melanoma; Uterine	t-MN	133	59#	Skin fibroblasts	46,XX[30]
UPIN81	*BRCA1*	187delAG	50	Y/Y		Thyroid: Lymphoma; Head & Neck	t-MN	30	6#	PB in CR	46,XX[30]
UPIN49	*BRCA2*	5301insA	48	Y/N		Unknown	t-MN	216	14	LBL	46,XX,t(3;21)(q26.2;q22.3)[30]/46,XX[1]
UPIN52	*BRCA2*	8138del5	51	Y/Y		Unknown	t-MN	63	7	LBL	45,XX,−7[27]/46,XX[3]
UPIN04	*TP53*	E339X	24	Y/N		Leukemia; Brain; Lung	t-ALL	30	66	LBL; confirmed in BM in CR	96,XXXX,+X,+1,+2,−4,−5,+6,−9,+10,+12,+14,−15,−16,−17,+18,+21,+22[7]/ 97,idem,+mar[10]/46,XX[11]/Two related non-clonal abnormal cells
UPIN60	*TP53*	G245S	23	Y/Y	Sarcoma in XRT field	Sarcoma	t-MN	81	29	LBL	46,XX,der(15)del(15)(q23q24)t(15;17)(q2 4.1;q21.1),der(17)t(15;17)(q24.1;q21.1)[2 4]/48,XX,idem,+8,+8[12]/46,XX[4]
UPIN09	*TP53*	I232T	23	Y/Y		None	t-ALL	48	28	BM in CR	54,XX,+X,+4,+6,+14,+17,+18,+21,+21[3]/46,XX[23]
UPIN53	*PALB2*	Y1183X	51	N/Y		Breast	t-MN	90	14	LBL	45,XX,−2,der(3)t(2;?;3)(p11.2;?;p11.1), der(5)del(5)(q15q33.3)t(5;12)(q33.3;q22), del(7)(q11.2q36),+8,add(9)(q34),der(12)t (5;12)(q33.3;q22),der(12)t(3;12)(p11.2;p1 3),−18[15]/46,idem,+mar[3]/46,XX[2]
UPIN70	*CHEK2*	1100delC	42	Y/Y		None	t-MN	21	52	Buccal	FISH only: +9,inv(16),+21

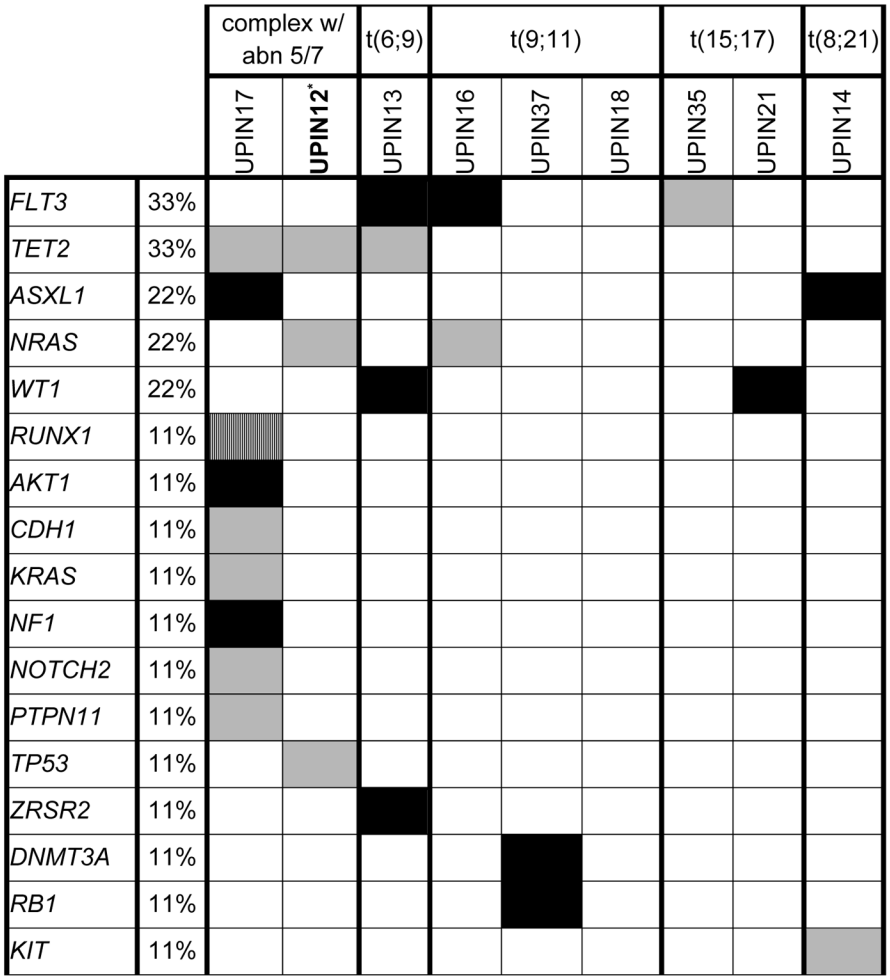
*Latency from primary cancer diagnosis for this subject;

#Still in follow-up.

Abbreviations: Dx=diagnosis; TRL=therapy-related leukemia; OS=overall survival; mo=months; NHL=non-Hodgkin lymphoma; XRT=radiation therapy; t-MN=therapy-related myeloid neoplasm; t-ALL=therapy-related acute lymphoblastic leukemia; BM=bone marrow; PB=peripheral blood; LBL=lymphoblastoid cell line; CR=complete remission; Y=yes; N=no

Table 4

Somatic mutations in 9 therapy-related leukemia cases after breast cancer



*UPIN 12 carries an inherited *BRCA1* mutation.

Black=frameshift, small insertions/deletions, or nonsense mutations; Striped=splice site mutation; Gray=missense mutation

Abbreviations: abn 5/7=abnormalities of chromosome 5 and/or 7; t=translocation