National Cancer Institute

Cancer Epidemiology in Fanconi Anemia

FA Camp 2010

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

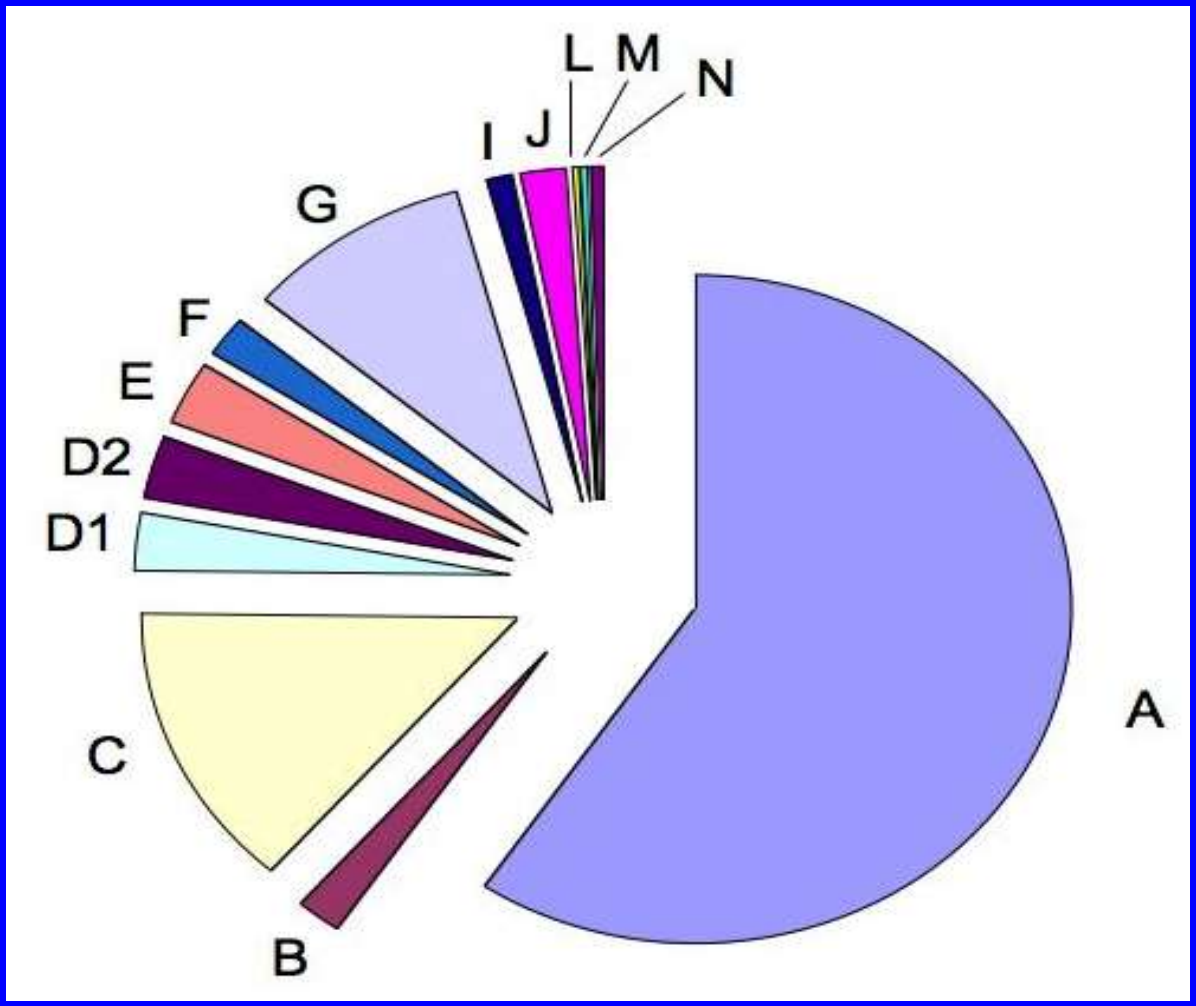
Resources

	Source	N
Retrospective:		
	Literature case reports	2000
Retrospective/prospective:		
	North American Survey (NAS)	145
	German FA Registry (GEFA)	182
	Israeli FA Registry (ISFAR)	66
	NCI FA Cohort (NCI)	66

Biases

- Volunteerism
- Selection (publication, enrollment)
- Information (incomplete records, self-report)
- Survival

13 FA Genes



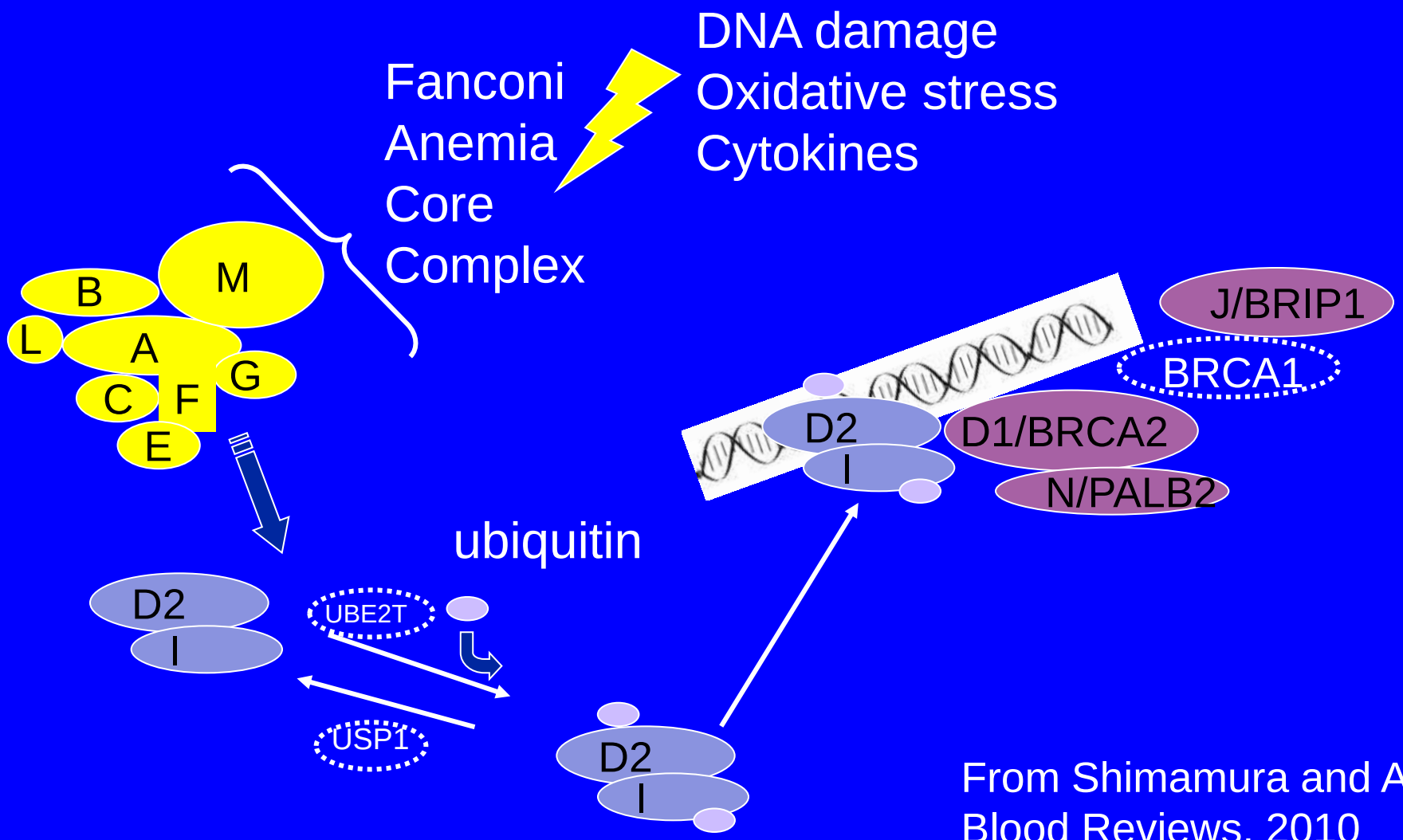
Data from Leiden Open Variation Database, http://chromium.liacs.nl/LOVD2/FANC/home.php

FA Complementation Groups/Genes

Group	Locus	cDNA	Exons	AA	%
A	16q24.3	5.5	43	1455	~70
B	Xp22.31	2.8	10	859	Rare
C	9q22.3	4.6	14	558	~10
D1/BRCA2	**13q12.3**	**11.4**	**27**	**3418**	**Rare**
D2	3p25.3	5	44	1451	Rare
E	6p21-22	2.5	10	536	~5
F	11p15	1.3	1	374	Rare
G/XRCC9	9p13	2.5	14	622	~10
I/KIAA1794	15q25-26	4.5	38	1328	Rare
J/BACH1/BRIP1	**17q22.3**	**4.6**	**20**	**1249**	**Rare**
L/PHF9/POG	2p15-16.1	1.7	14	375	Rare
M/Hef	14q21.3	6.5	22	2014	Rare
N/PALB2	**16p12.1**	**3.5**	**13**	**1186**	**Rare**

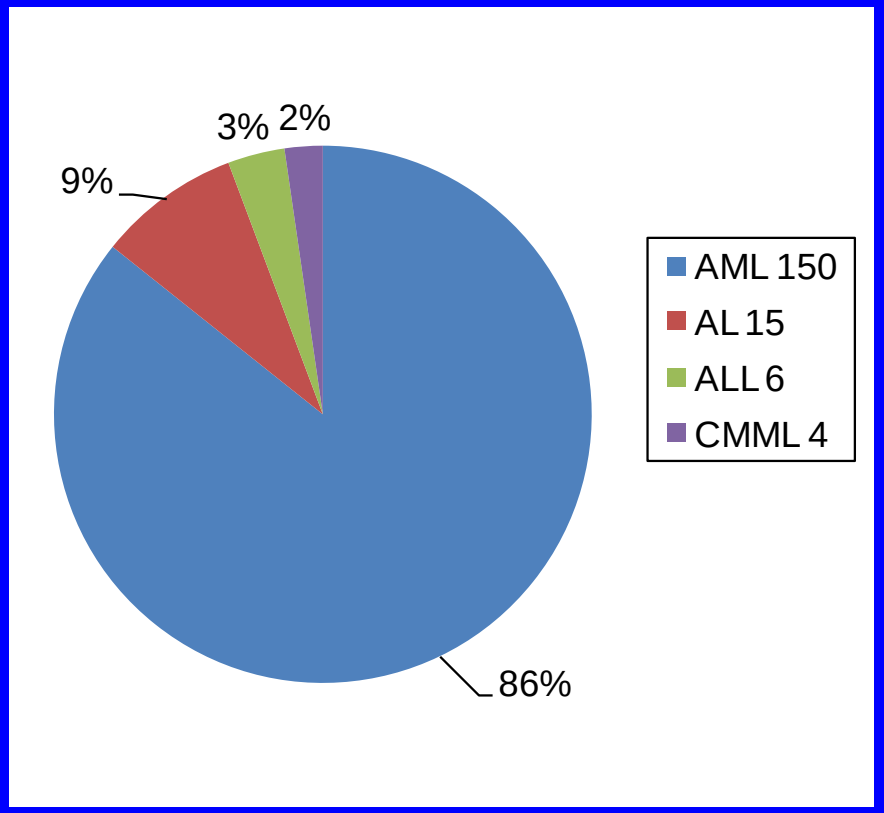
D1 = BRCA2; J = BRIP1, BRCA1 interacting protein; *N = PALB2,* partner and localizer of *BRCA2*

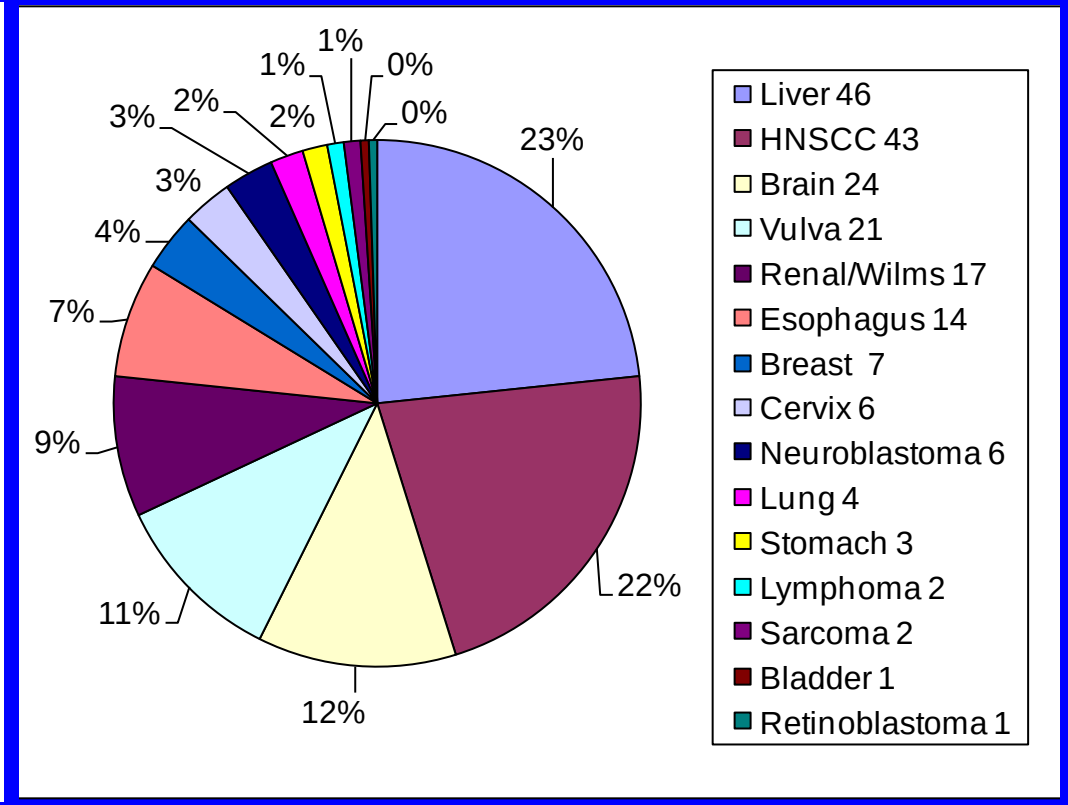
FA/BRCA DNA Repair Pathway



From Shimamura and Alter, Blood Reviews, 2010

FA Literature: Cancer Types 1927-2009



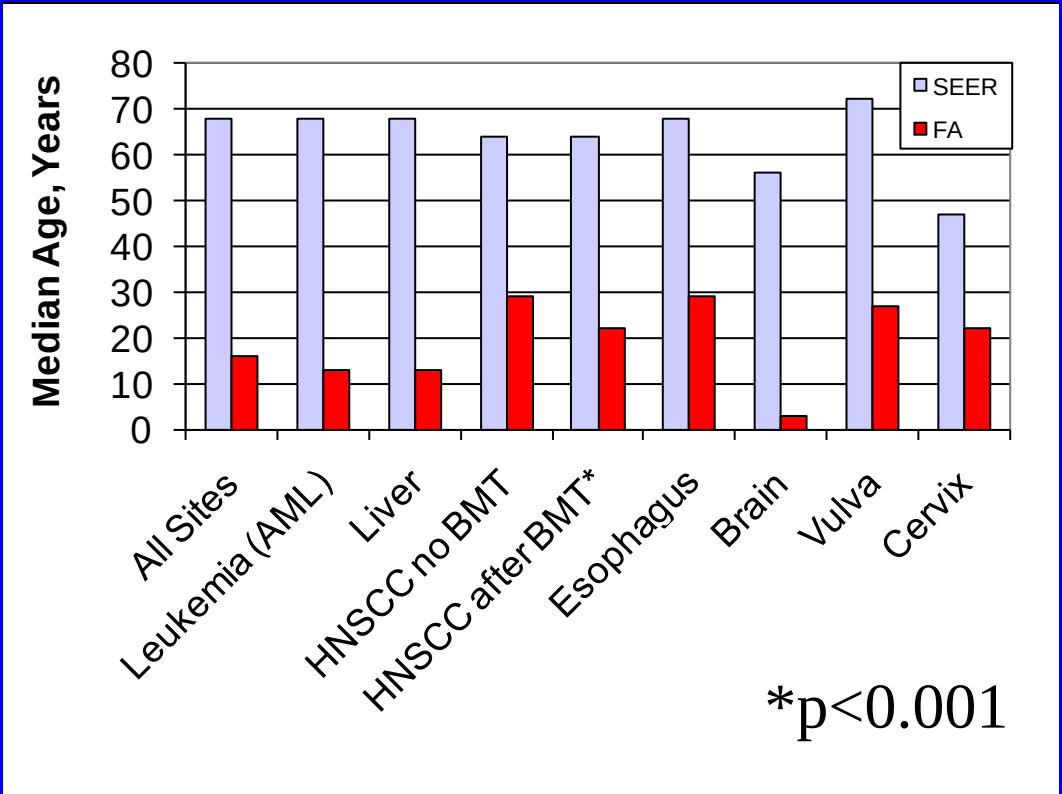


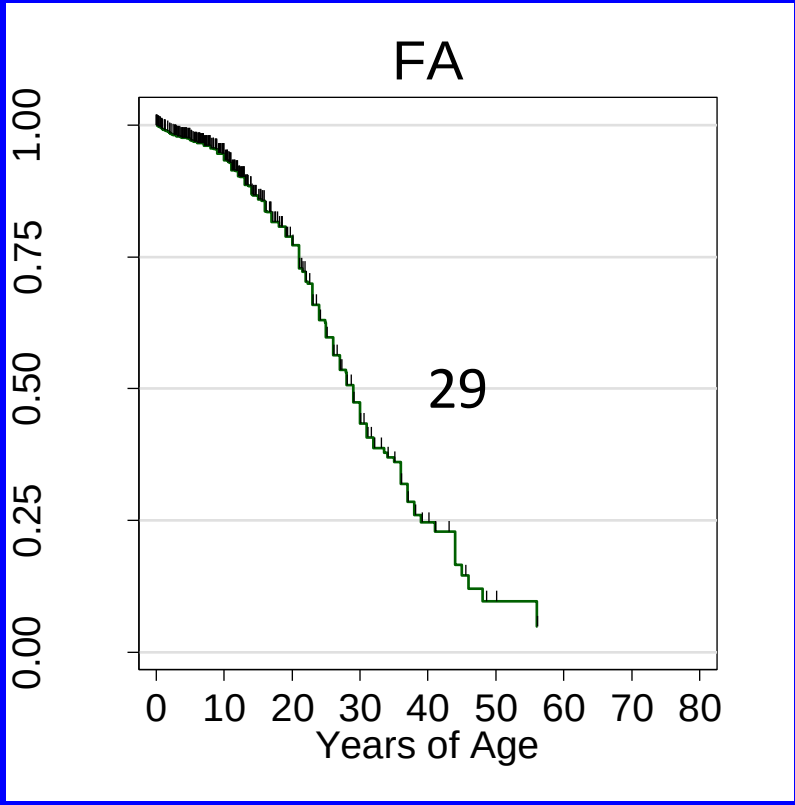
175 leukemias and 197 solid tumors in 320/2000 patients; 26 had 2-4 cancers.

Major Cancers in FA

- Leukemia: AML, ALL
- Liver: adenomas, carcinomas
- HNSCC: head and neck squamous cell carcinomas
- Brain Tumors: medulloblastoma
- Gynecologic: vulva, anus, vagina, cervix
- Kidney: Wilms, renal
- Esophagus: SCC
- Breast

FA Literature: Cancer Sites, Median Ages





Cancers in FA are at very young ages

Median survival free of cancer = 29 years

FA Literature: Multiple Solid Tumors

1st Ca	2nd Ca	3rd Ca	N
Vulva	Cervix		3
Cervix	Vulva		1
Vulva	Tongue		1
Colon	Vulva		1
Tongue	Cervix	Breast	1
Sarcoma	Vulva	Liver Adenoma	1
Breast	Breast		1
Tongue	Liver HCC		1
Liver HCC	Esophagus		1

1st Ca	2nd Ca	3rd Ca	N
Gingiva	Esophagus		1
Larynx	Bladder	Nasopharynx	1
Hypopharynx	Esophagus	Liver HCC	1
Tongue	Esophagus		1
Lip	Palate		1
Wilms*	Brain Medullo		4
Wilms*	Neuroblastoma	Brain	1
Neuroblastoma	Wilms		1
Neuroblastoma	Wilms	Brain	1

**D1/BRCA2* or *N/PALB2*

FA Literature: Solid Tumors + Leukemia

1st Ca	Age	2nd Ca	Age	3rd Ca	Age	Gene
T-ALL	4.9	AML	6.3	Wilms	6.6	*D1/BRCA2*
Wilms	0.5	AML	1.5			*D1/BRCA2*
Wilms	0.6	Brain	6	ALL	10	*D1/BRCA2*
Neuroblastoma	1.4	AML	1.7			*D1/BRCA2*
AML	0.9	Wilms	0.9	Brain	1	*N/PALB2*
Neuroblastoma	0.7	AML	2			*N/PALB2*
AML	0.5	Brain	1.2			-
Retinoblastoma	1.3	AML	1.9			-
Wilms	0.5	AML	5			-
Cervix	22	AML	28			-
Breast	37	Breast	45	AML	50	A

Combinations of Malignancies

- Vulva, cervix
- HNSCC, Gyn
- HNSCC, esophagus
- HNSCC, liver
- Cervix, AML
- Breast, AML
- Wilms; medulloblastoma; neuroblastoma; AML (*D1/BRCA2; N/PALB2*). All <6 yo

Leukemia post-BMT

Indication	Type	Yrs	Patient	Sib Donor
AA	ALL	1.5		1
MDS	AML	2.4	1	
MDS	AML	3.3	1	
AA	AML	1.5	-	
AA	AML	10	1	
AA	AML	0.2	1	
MDS	AML	4	1	
AA	AML	2.8		1

Tumors after SCT

- Tongue, buccal, lip, gingiva alone = 14
- Tongue + cheek = 2
- Tongue + vulva = 1
- Tongue + anus = 1

Observed/Expected Ratio (O/E)

- O = number of cases observed
- E = number of cases expected in the general population, adjusted for age, sex, and birth cohort
- An estimate of the relative risk of cancer in untransplanted patients with FA

Risk of Cancer by O/E Ratio

	FA Cohorts			
Parameter	**NAS**	**GEFA**	**ISFAR**	**NCI**
Number of Patients	145	182	66	66
Person-Years	2000	2818	814	1207
All Cancers	52x	44x	71x	39x
All Solid Tumors	51x	26x	50x	37x
Oral Cavity/Pharynx	706x	240x	986x	831x
Vulvar	4317x	2411x	3701x	2098x
AML	785x	868x	175x	326x
MDS	8559x	4559x	11683x	4910x

North American Survey;

German FA Registry;

Israeli FA Registry;

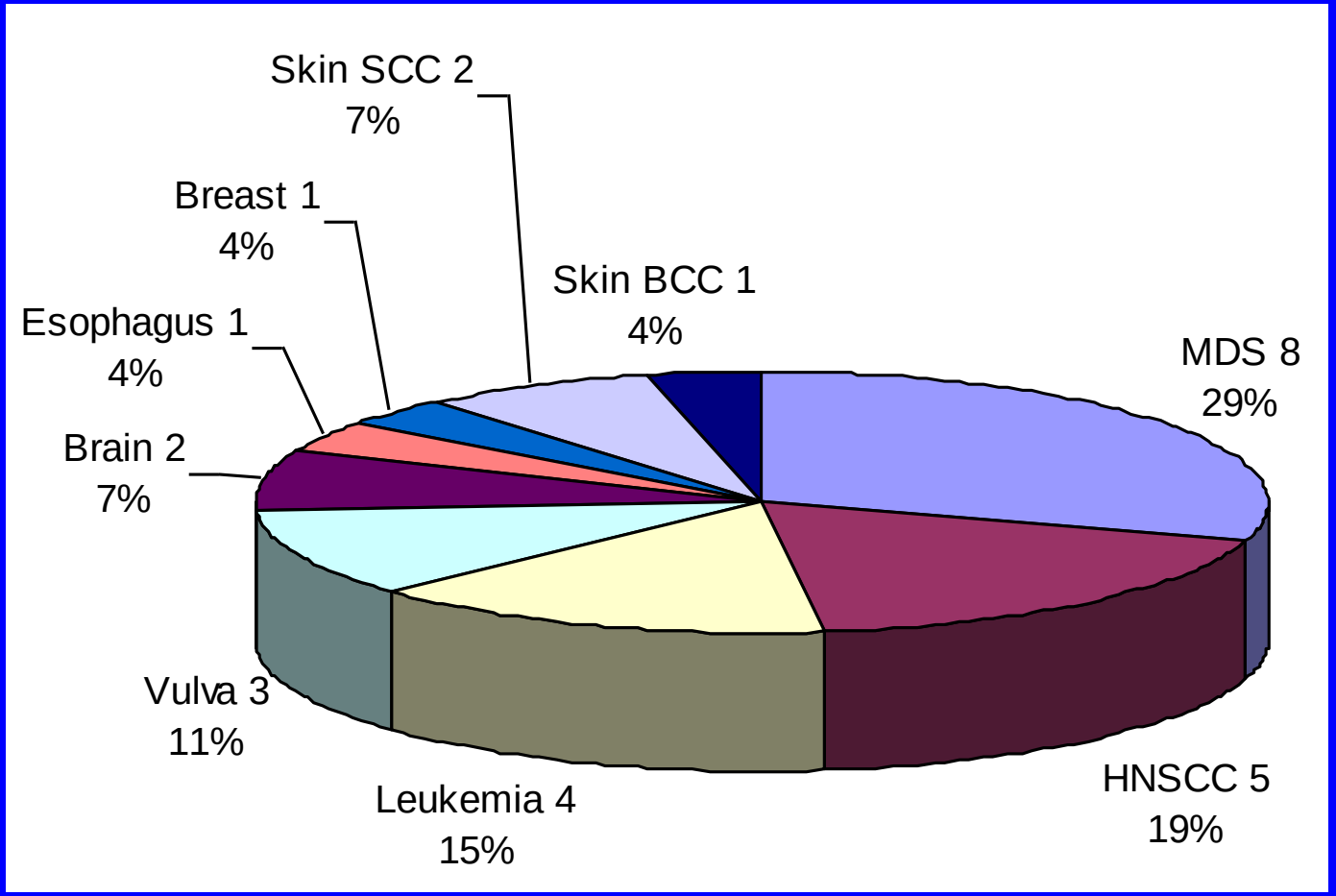
National Cancer Institute

Alter *et al*, BJH 2010

Risk of Cancer by O/E Ratio

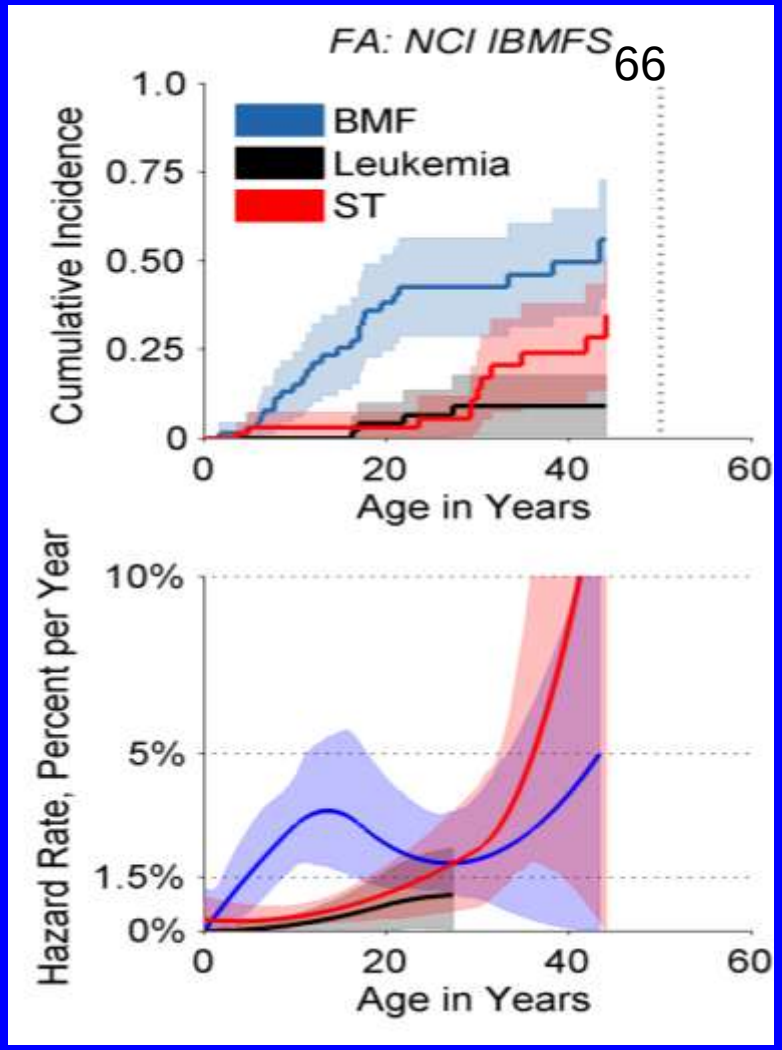
	FA Cohorts				
Parameter	**NAS**	**GEFA**	**ISFAR**	**NCI**	**Overall**
Number of Patients	145	182	66	66	**459**
Person-Years	2000	2818	814	1207	**6839**
All Cancers	52x	44x	71x	39x	**~50x**
All Solid Tumors	51x	26x	50x	37x	**~40x**
Oral Cavity/Pharynx	706x	240x	986x	831x	**~700x**
Vulvar	4317x	2411x	3701x	2098x	**~3000x**
AML	785x	868x	175x	326x	**~500x**
MDS	8559x	4559x	11683x	4910x	**~7000x**

All Cancers in NCI Cohort



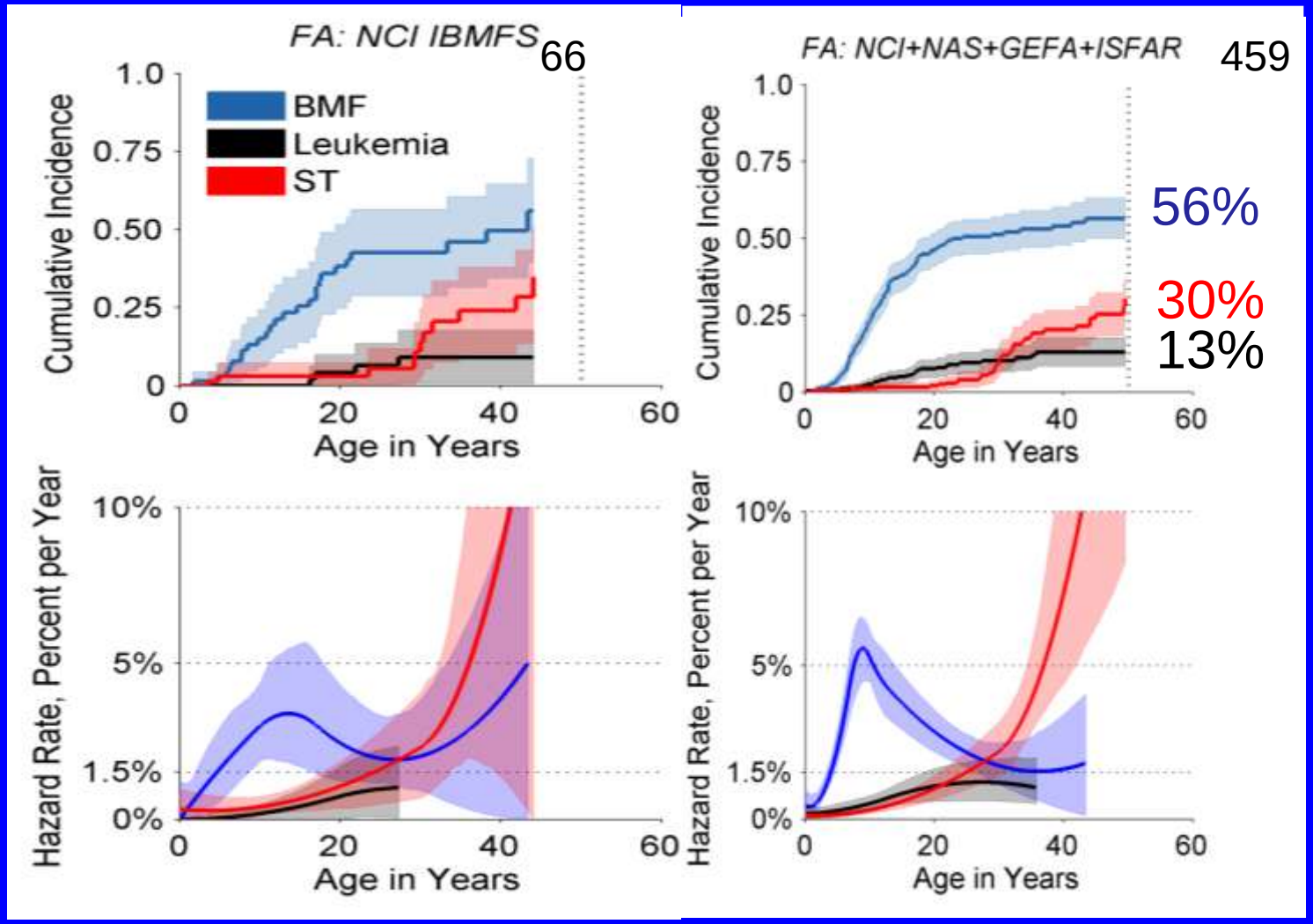
(MDS), HNSCC, AML, Gyn, Brain, Esophagus, Breast, Skin

NCI FA Cohort: First Adverse Event



Alter *et al*,
BJH 2010

All FA Cumulative Incidence and Cause-specific Hazards



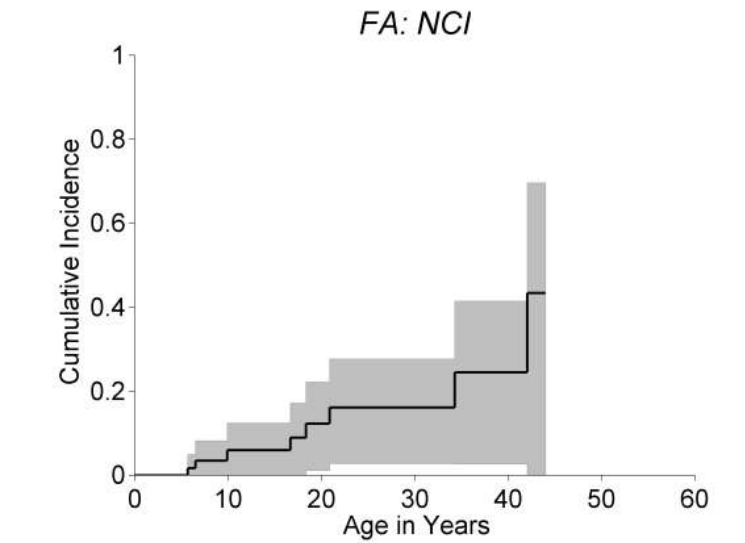
Alter *et al*, BJH 2010

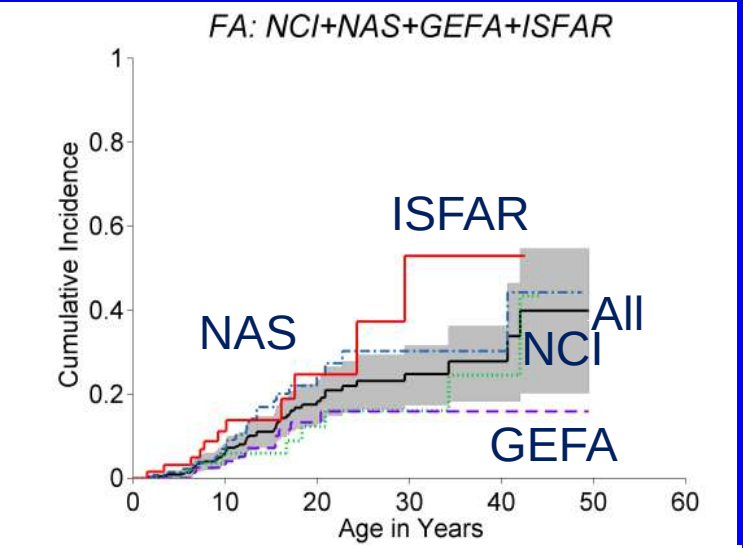
Current Risk Estimates, Competing Risks for First Adverse Event

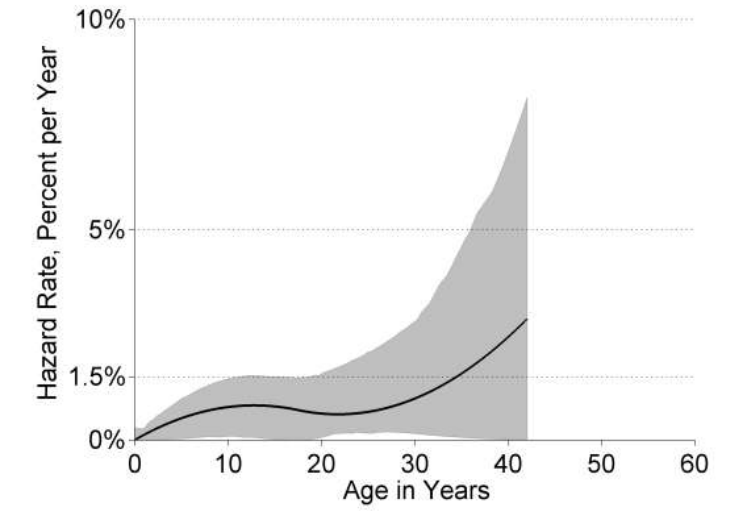
- Bone Marrow Failure: 50%
- Solid Tumors: 30%
- Leukemia (AML): 10-20%
- Total: 90-100%

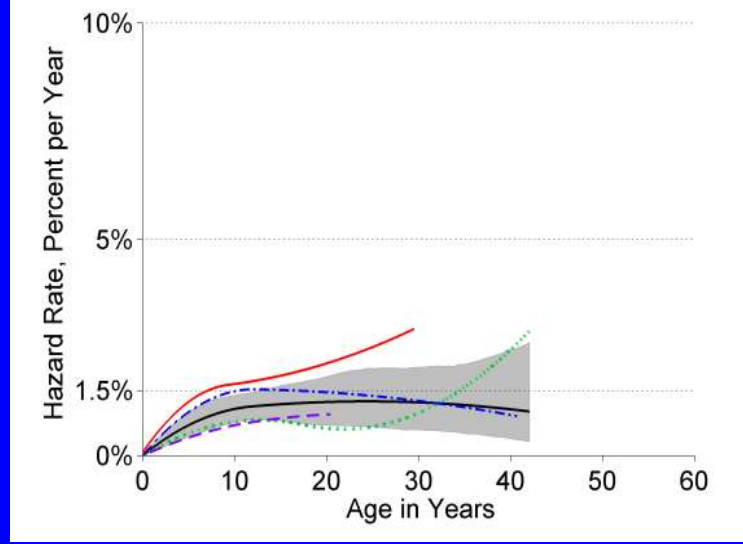
By about age 50

MDS in FA







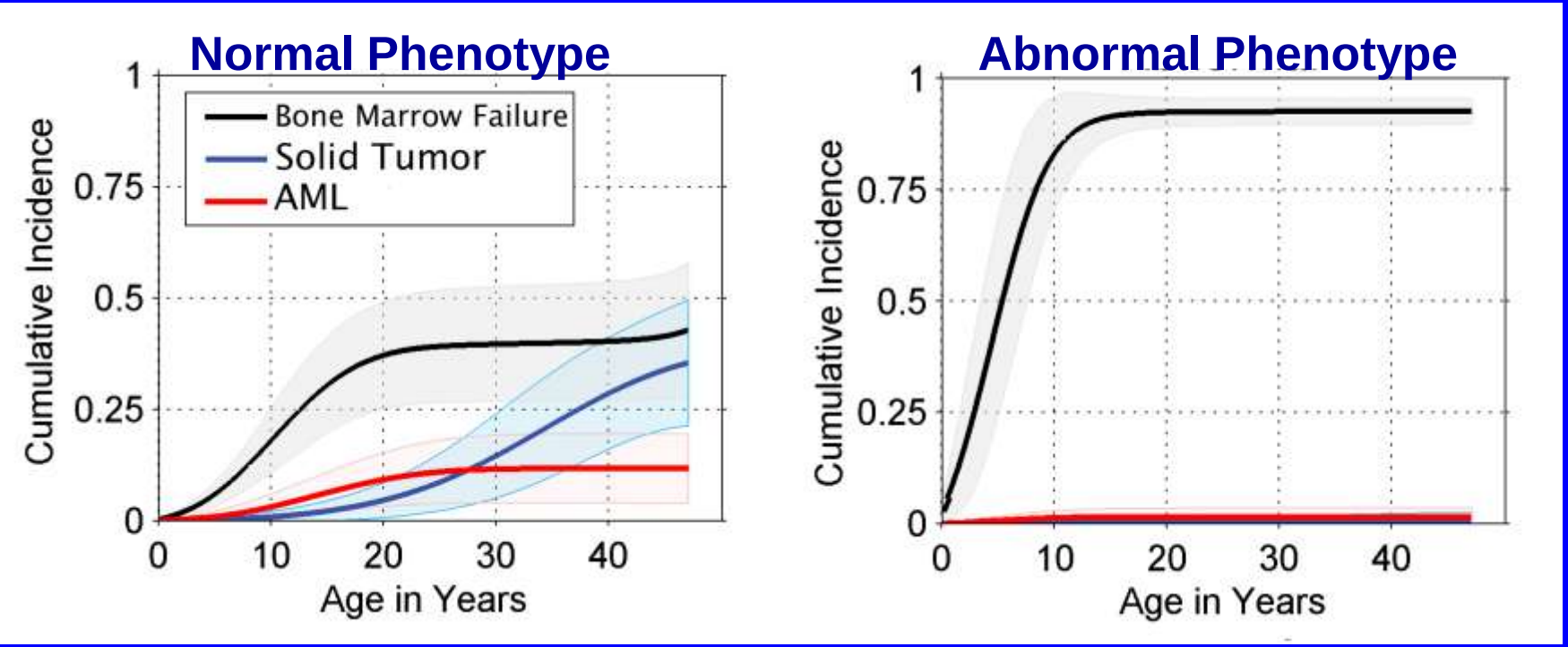


Alter *et al*, BJH 2010

Phenotype

- Does the physical appearance predict the first adverse outcome?

Fanconi Anemia: Phenotype/Outcome



Components of abnormal phenotype = radii, development, heart/lung, renal, hearing, head.

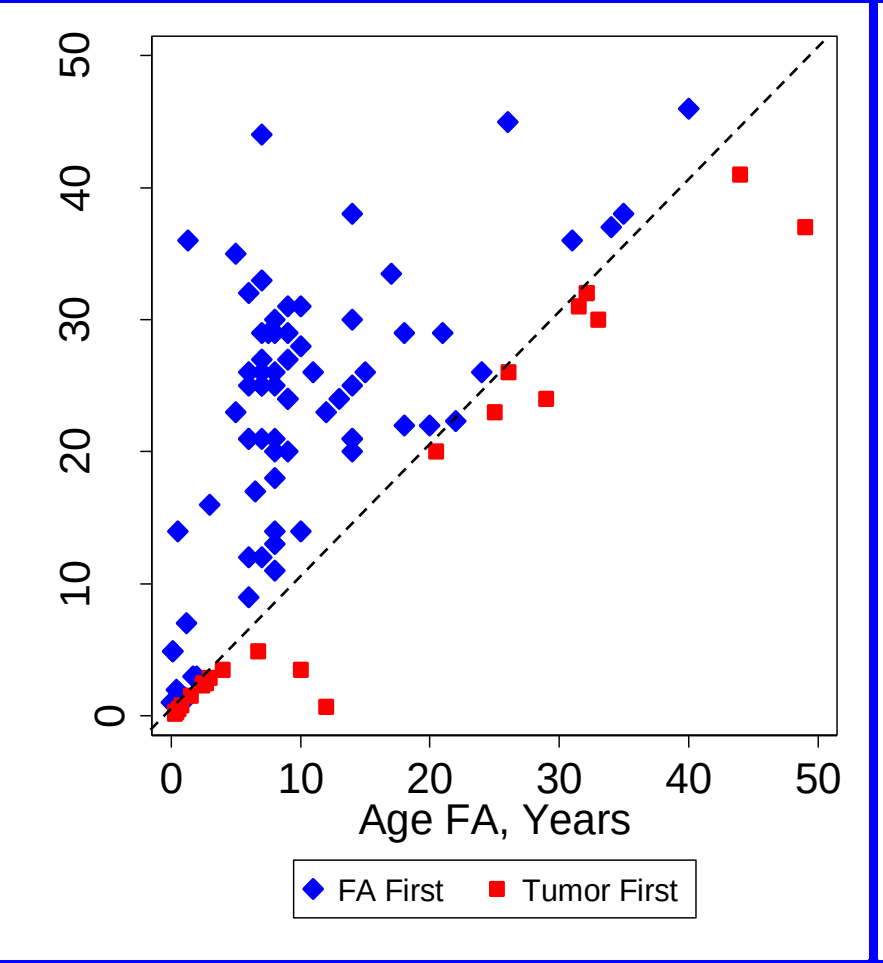
Phenotype predicts age and incidence of marrow failure and solid tumors.

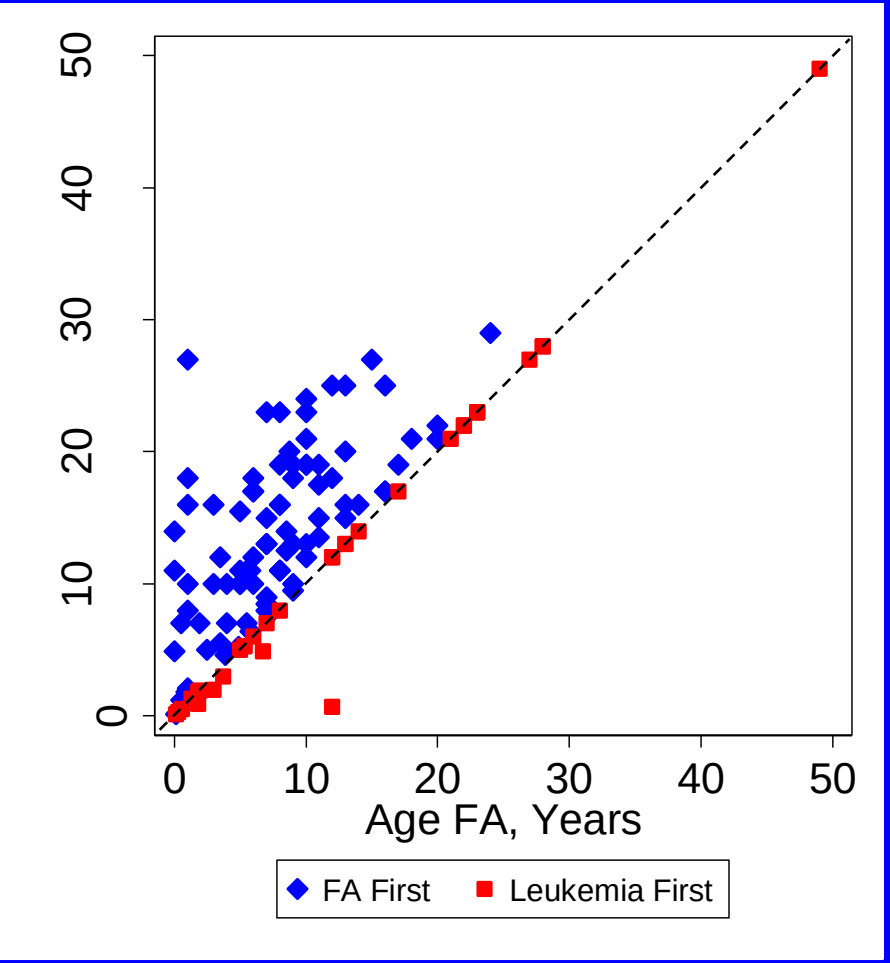
Rosenberg *et al*, Blood 2004

Other Predictors

- Age?

Cancer Diagnosis before FA





Solid tumor or leukemia preceded the diagnosis of FA in 35%.

Diagnosis of FA before Cancer

- Aplastic anemia
- Birth defects
- Family history

Diagnosis of FA after Cancer

- Clinical suspicion based on phenotype
- Family history
- FA-type cancers, atypically young, no risk factors
- Unrecognized marrow failure
- Absence of marrow involvement (e.g. somatic mosaicism)

Conclusions

1. Mosaicism may occur from reversion of an FA mutation, with selective growth advantage from the revertant cell.
2. All siblings of an FA patient should be tested for FA, no matter their age or their potential roles as donors.
3. Affected individuals should not be stem cell donors for siblings with FA.
4. Asymptomatic “non-penetrant” persons with FA are at risk of late onset bone marrow failure, myelodysplastic syndrome, acute leukemia, and solid tumors.

Possible Causal Factors for Cancer in FA

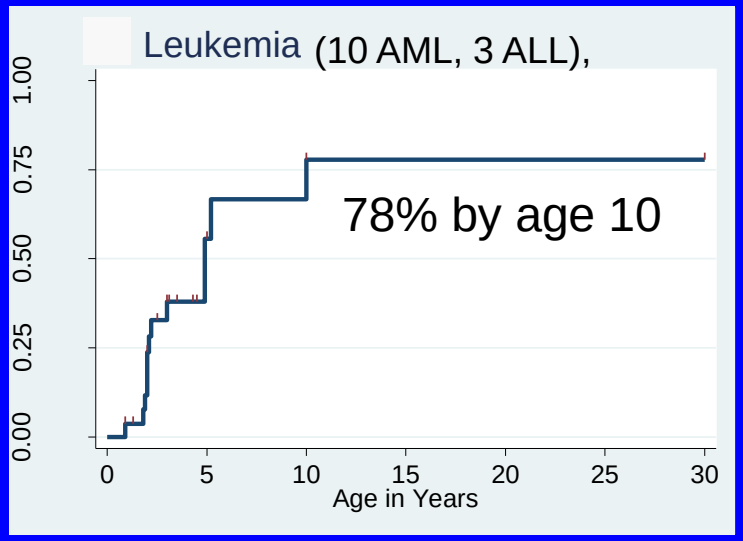
- Genetics
- Stem cell transplant - GVHD, XRT
- HPV
- Immunodeficiency
- Tobacco
- Alcohol
- Dental XRays
- Oral trauma (braces)

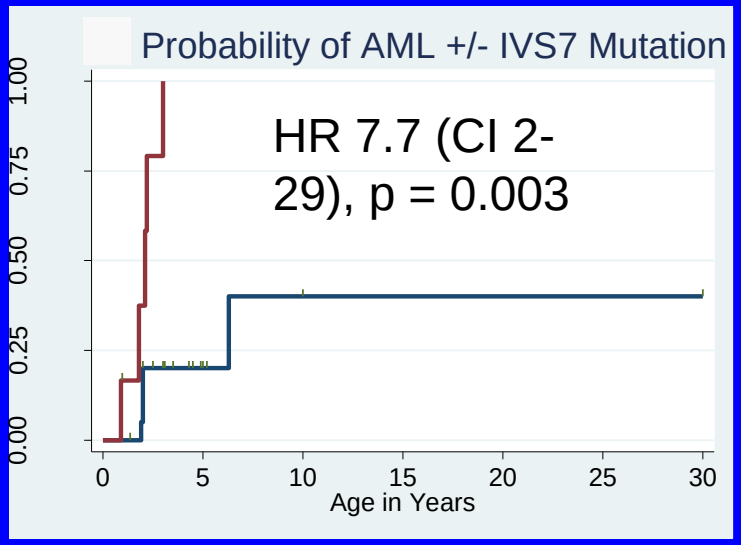
Genetics

VACTERL-H Association

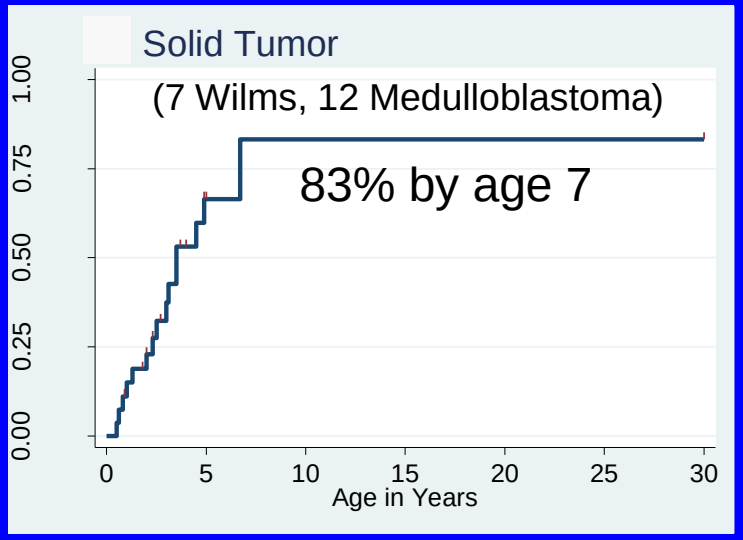
- At least three of:
  - vertebral anomalies
  - anal atresia
  - cardiac anomalies
  - tracheo-esophageal fistula
  - esophageal atresia
  - radial limb anomalies
  - renal anomalies
  - plus hydrocephalus

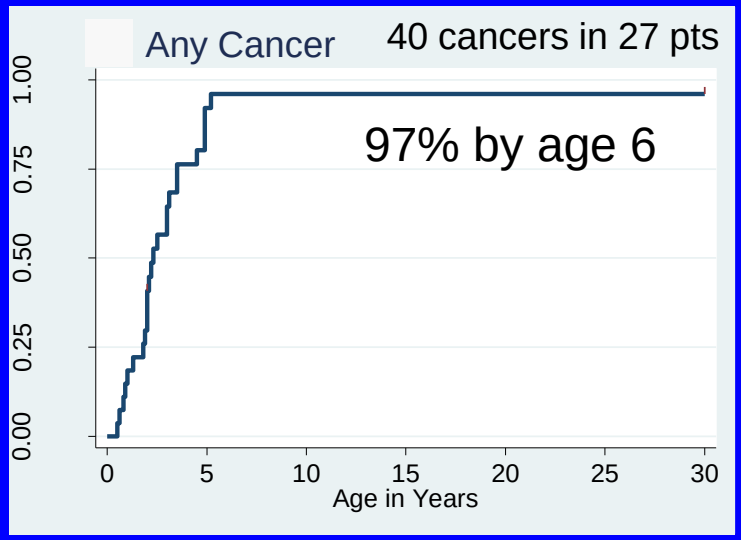
Genotype/Phenotype/Outcome: 27 FA with Biallelic Mutations in *BRCA2*





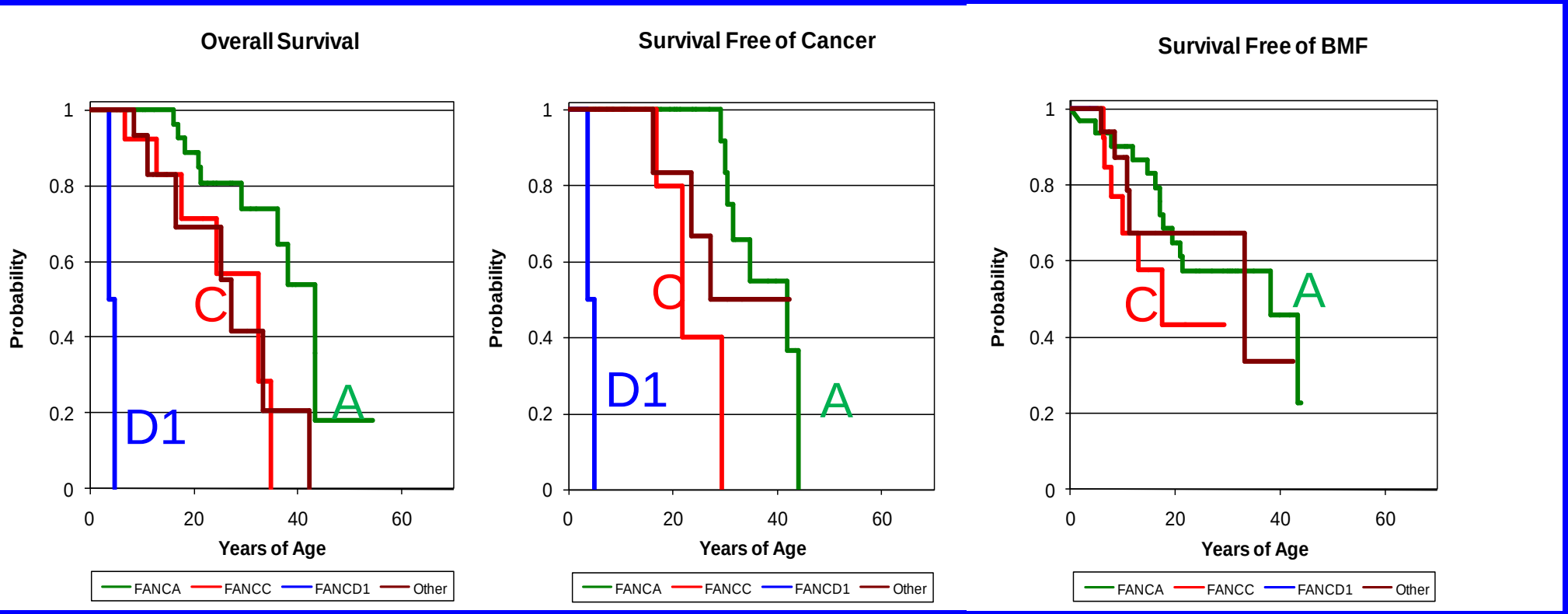
Alter: Br J Haematol, 2006





Alter, Brody, Rosenberg: J Med Genet, 2007

Outcome by FA Genotype



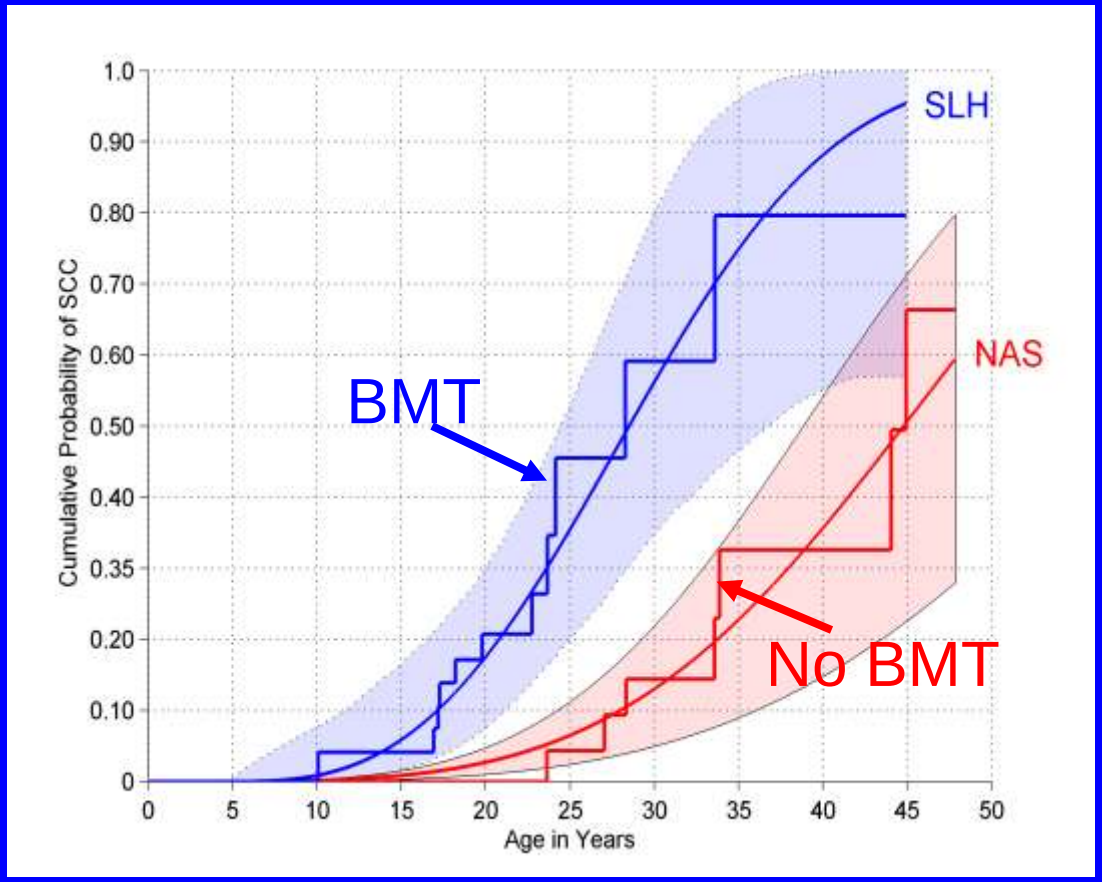
FANCD1/BRCA2 is the most severe, followed by *FANCC* and Other/unknown; *FANCA* is the mildest ; p<0.001

Alter *et al*, BJH 2010

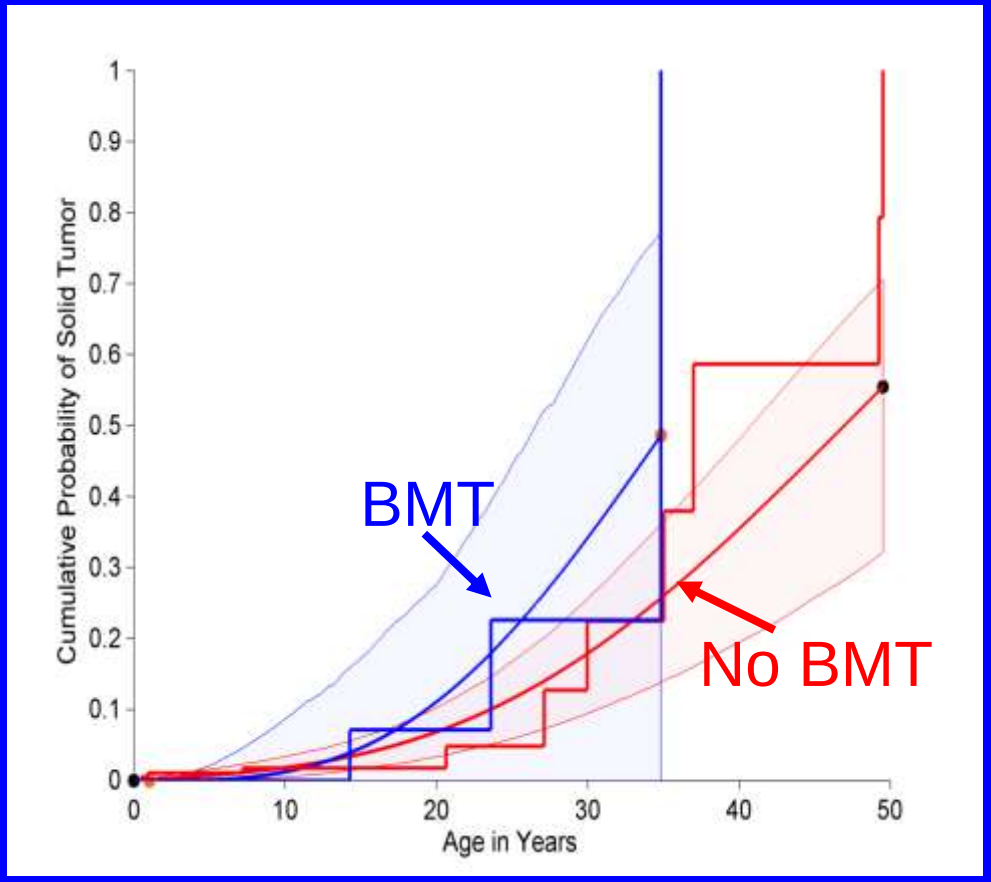
Transplant

Transplant and Head and Neck Cancer in Fanconi Anemia

NAS and Paris



GEFA



BMT increases risk of HNSCC 4-fold, and 16 years earlier.
All had GVHD. (Other reports include patients without GVHD.)

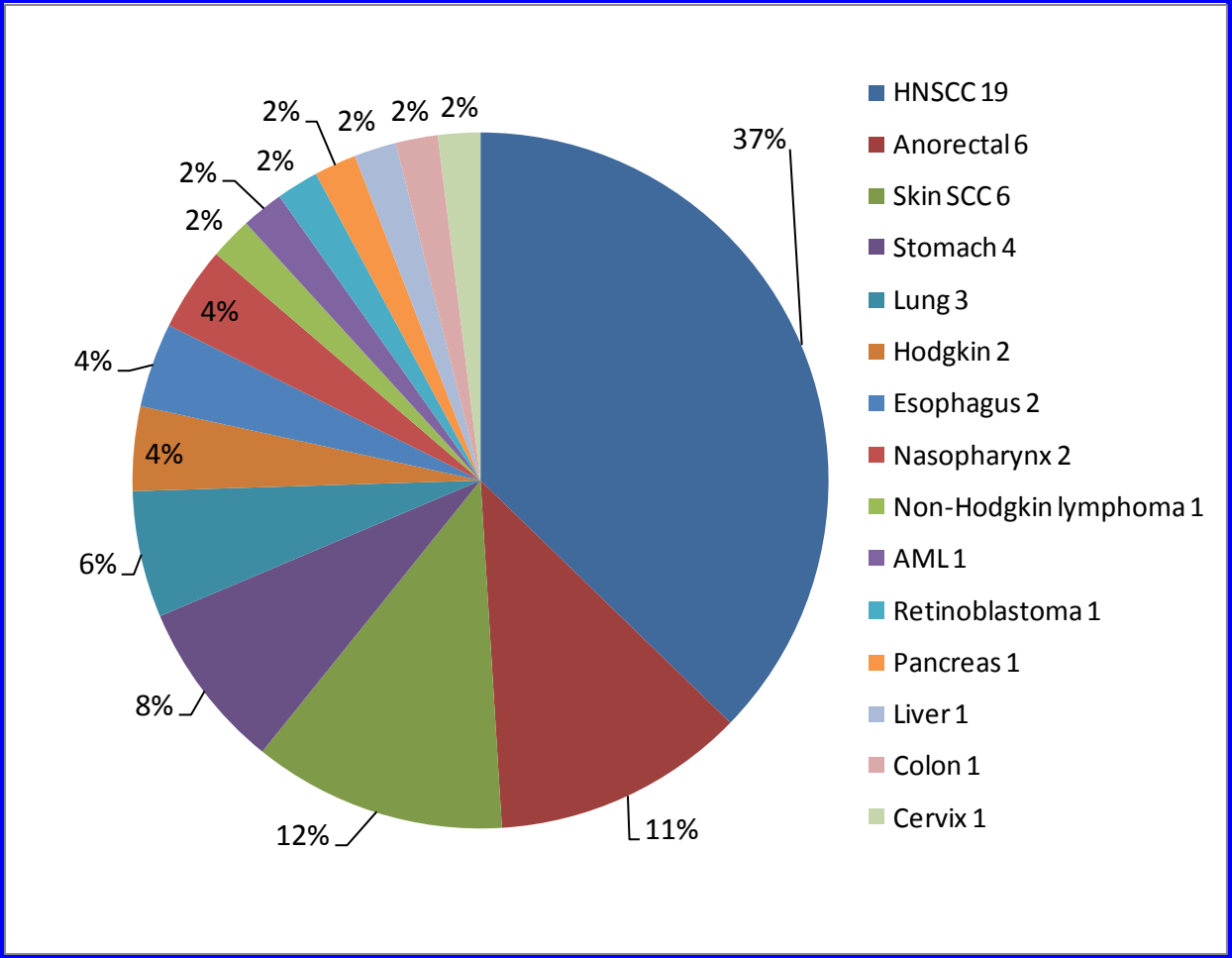
Human Papillomavirus (HPV)

HPV Vaccine for General Population

- FDA approved June 2006
- Age 9 to 26 years
- Females
- 16, 18, 6, 11 (Merck Gardasil)
- FDA approved for males WHEN?

Other Similar Syndromes?

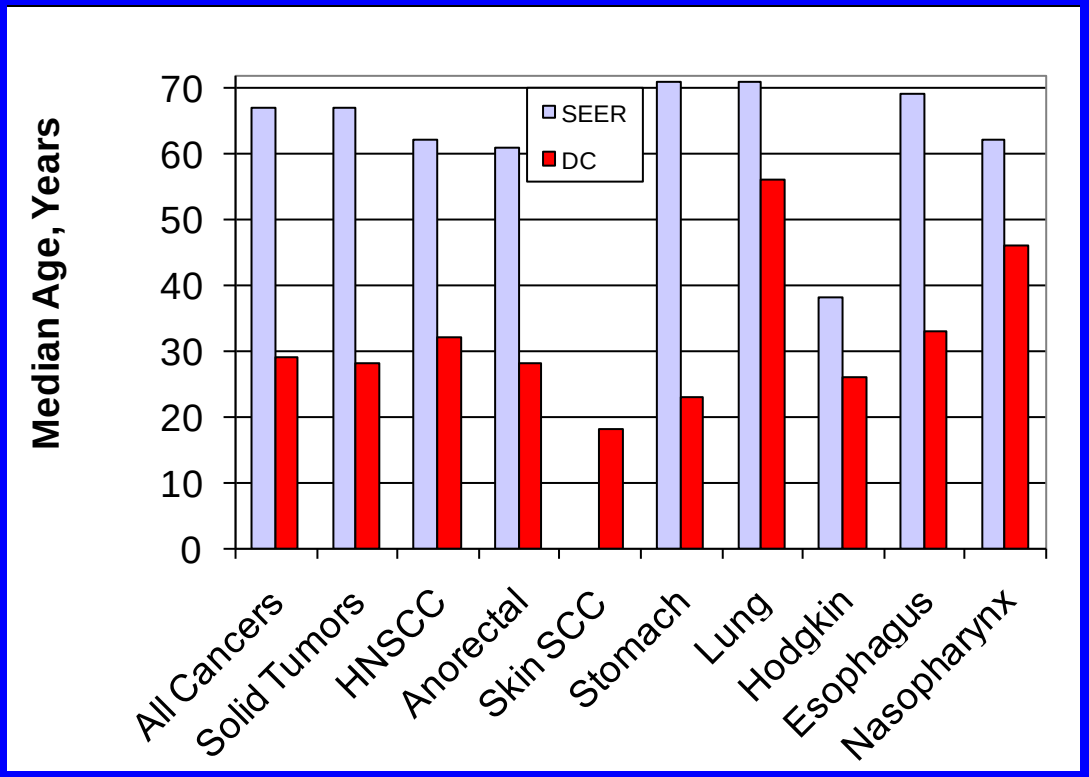
Dyskeratosis Congenita (DC) Literature: Cancer 1910-2009

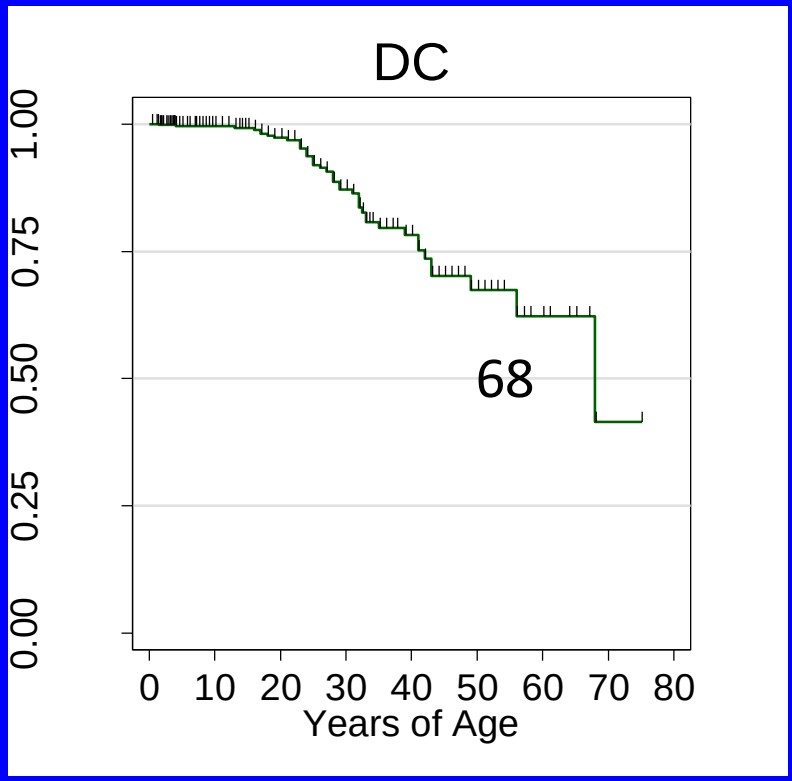


Spectrum of solid tumors in DC resembles that in FA.

51 cancers in 42/550 patients; 6 patients had 2-4 cancers

DC Literature: Cancer 1910-2009



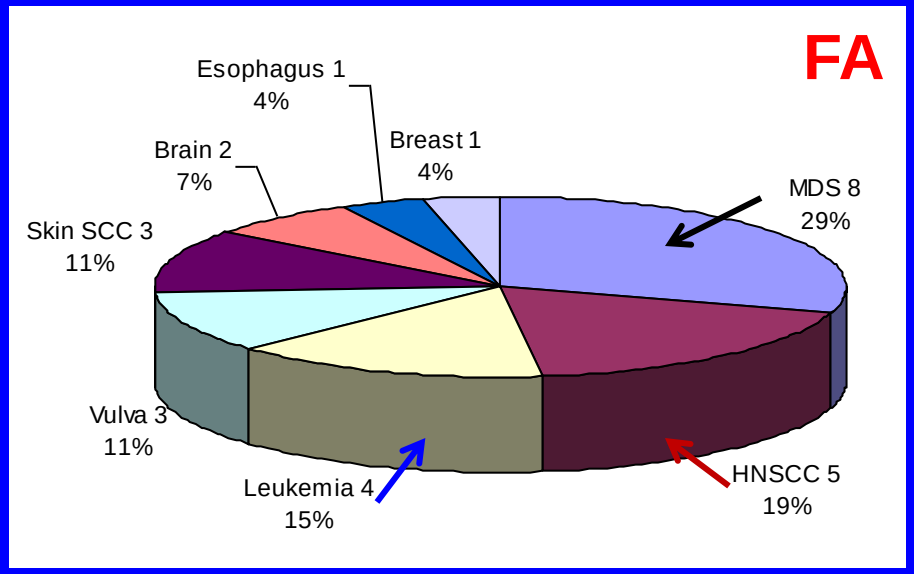


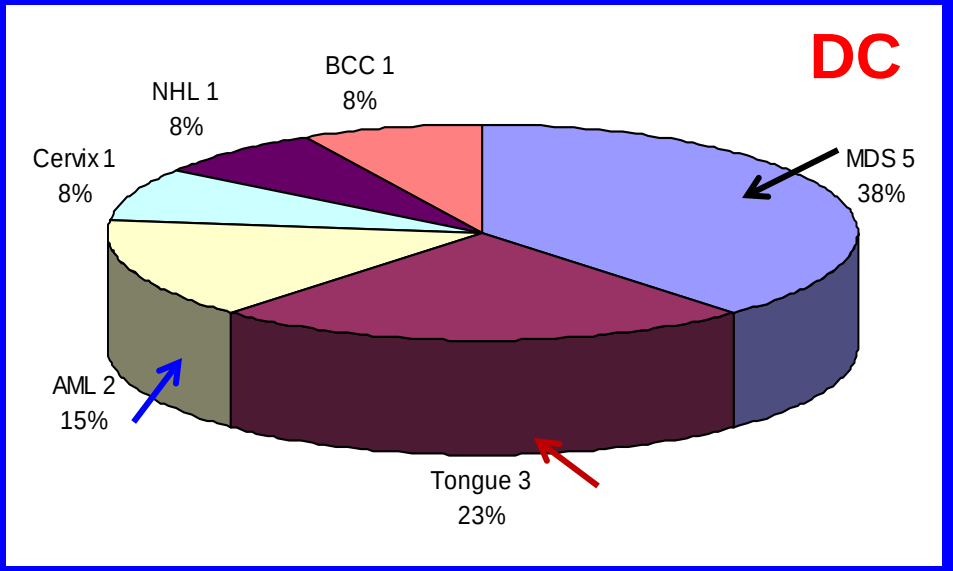
Median survival free of cancer = 68 years

DC tumors occur slightly later than FA tumors.

Alter *et al*, Blood 2009

FA and DC Cancer in NCI IBMFS Cohorts





FA and DC share MDS, HNSCC, and Leukemia

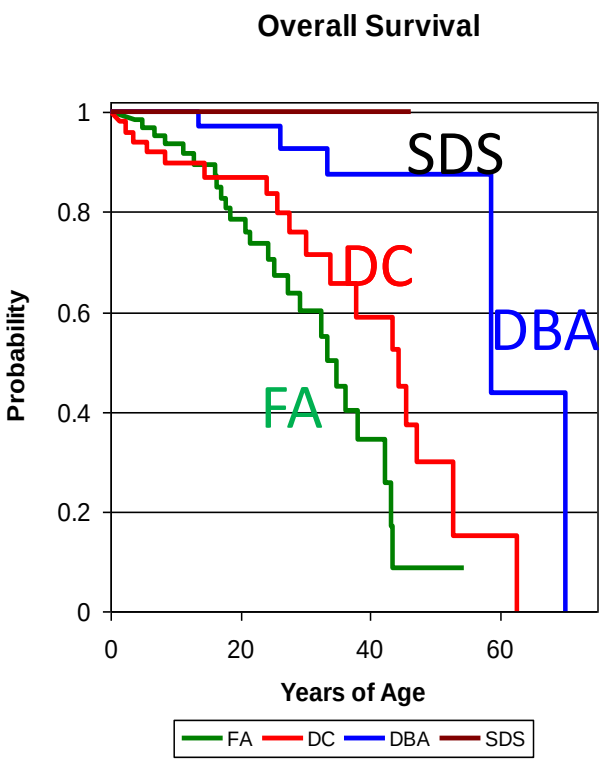
NCI IBMFS Cohort: Relative Risk of Cancer

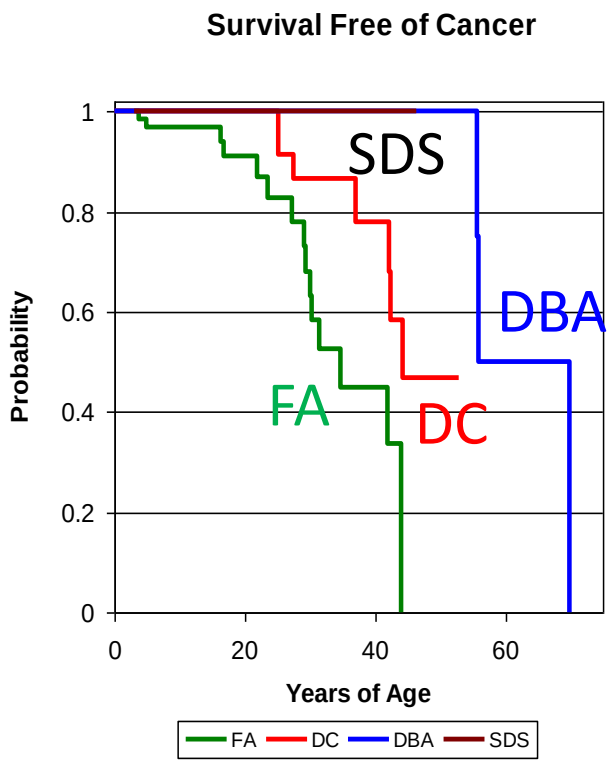
Parameter	FA*	DC*	DBA	SDS
Number	**66**	**55**	63	16
Person-Years	**1207**	**1266**	1387	253
All Cancers	**39x**	**10x**	3x	-
All Solid Tumors	**37x**	**7x**	4x	-
Tongue	**589x**	**897x**	-	-
AML	**326x**	**188x**	-	-
MDS	**4,910x**	**2,362x**	-	-

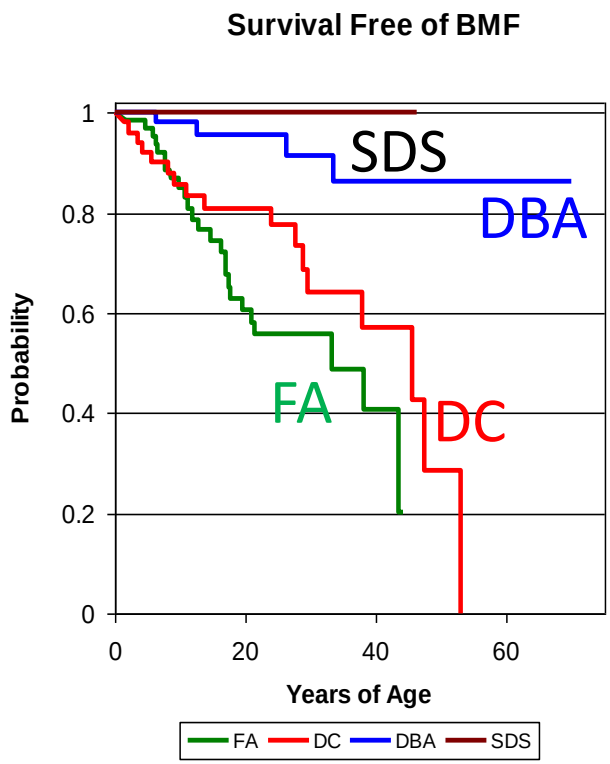
*Significant

Alter *et al*, BJH 2010

Outcome by Syndrome







FA is the most severe, followed by DC; DBA and SDS are milder ; $p<0.001$

Alter *et al*, BJH 2010

FA and DC

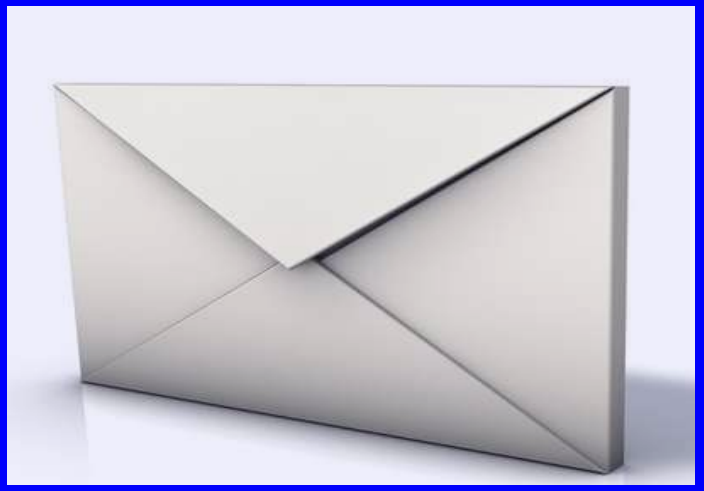
- The risk of SCC in FA and DC is extraordinarily high & tumors occur at very young or young ages.
- Epidemiologic patterns suggest the ***hypothesis*** that SCC in FA may resemble SCC in DC.
  - Laboratory studies are needed!
    - prove/disprove
    - explore molecular mechanisms
- Some “sporadic” cases may actually be undiagnosed FA or DC.

How many FA are there?

How many are at risk of cancer?

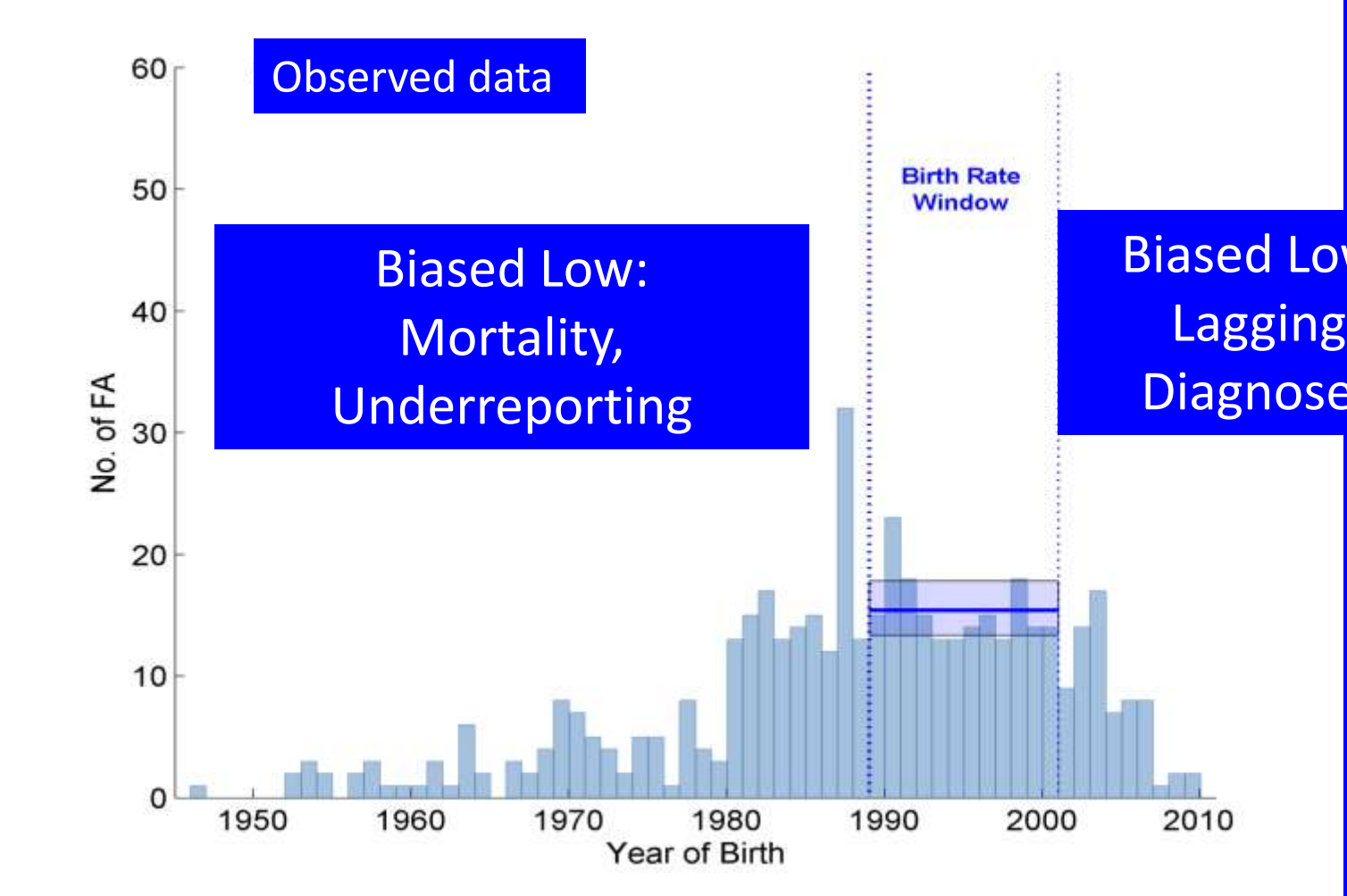
Prevalence of FA in the USA

- Back-of-the-envelope calculation using FARF data:



- Given estimates of the FA ***birth rate*** and ***survival curve***, calculate how many persons are living with FA in the US as of 2009, by age.

Number of FA known to the FARF



US FA Total and Cancer Risk

- Back-of-the-envelope approach:
  - ~600 persons with FA in the USA in 2010
    - Lower bound: ~360
    - Upper bound: ~900
  - ~55% of FA in 2010 are age >15 (160 – 400 persons)
- Conventional study designs have limited statistical power:
  - Joint studies of HNSCC in FA and DC may boost sample size.

USA and Other Countries

FA Adult Care Recommendations

- CBC q 4-6 mo
- BM aspirate/biopsy/chromosomes q yr
- Dental q yr
- Head and neck with laryngoscopy q yr
  - ***Self exam or mouth and neck, frequently***
- Gyn exam with Pap and HPV q yr
- Liver ultrasound q yr
- Consider esophageal endoscopy

Summary/Conclusions

- Patients known to have FA have a high risk of neoplasia
- Patients with atypical presentations of neoplasms may have undiagnosed FA
- The specific risk may depend on the specific gene and mutation
- Be cautious with term “pre-transplant” – some may be “non-transplant”.

www.marrowfailure.cancer.gov

cancer.gov

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Inherited Bone Marrow Failure Syndromes

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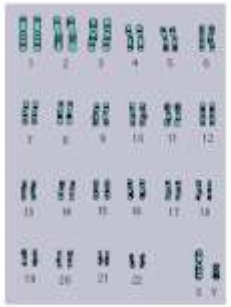

Etiologic Investigation of Cancer Susceptibility in Inherited Bone Marrow Failure Syndromes (IBMFS)

Inherited bone marrow failure syndromes (IBMFS) are rare disorders in which there is usually some form of aplastic anemia (failure of the bone marrow to produce blood), associated with a family history of the same disorder. Some of these conditions have typical changes in physical appearance or in laboratory findings which suggest a specific diagnosis. There are several well-described syndromes, which can be recognized by health care experts. There are also patients who are harder to classify, but who appear to belong in this category.

Patients with these syndromes have a very high risk of development of cancer (either leukemia or certain solid tumors). At the moment we cannot predict which specific patient with an IBMFS is going to develop cancer. The NCI IBMFS Cohort Study will enroll North American families in which at least one member has or had an IBMFS. We plan to:

- include individuals known to have an IBMFS as well as their first degree relatives (brothers, sisters, parents, and children);
- collect clinical information from study participants and their physicians;
- perform detailed physical examinations, x-rays and routine laboratory tests on those who are interested in traveling to the NIH to be seen in person by our team;
- attempt (on a research basis) identification of the specific genetic mutation that is associated with each family's disease;
- screen participants for early changes related to the specific cancers that occur in each syndrome;
- perform detailed research laboratory studies on blood and tumors collected from study participants, in an effort to understand the process by which cancers develop;
- monitor study participants in an ongoing fashion to determine the rate at which complications develop related to each disease, and to identify those complications more precisely;
- provide suggestions to study participants and their physicians regarding how to best take care of family members who are affected with a particular IBMFS; and
- offer genetic counseling, and an opportunity to learn the results of mutation testing, for those persons who decide that this information will be of use to them.

The Principal Investigator responsible for this study is Blanche P. Alter, MD, MPH. For further information regarding her credentials and experience, please see: http://dceg.cancer.gov/biographies/Alter.html

Our overall goal is to reach a better understanding of how cancers develop in persons with IBMFS, so that we may improve the health care which can be offered to persons with these disorders.

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