FANCONI Anemia: Solid Tumor Surveillance Discussion

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Discussion

- **# 1024 PD : Surveillance of adolescents and young adult patients with Fanconi Anemia (FA): Awareness of diagnosing solid tumors at a young age**

  Balmaña et al.

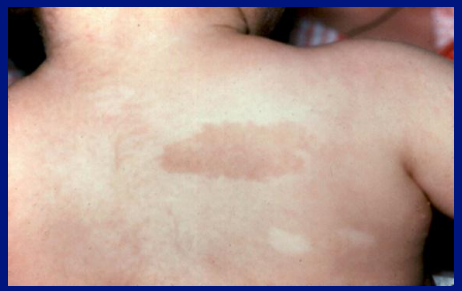
Fanconi Anemia

The underlying disease

Fanconi Anemia

Características principales

- First described by Guido Fanconi (1927)
- Inhereted disease (AR, X-linked)
- Incidence: 1/350.000 newborn
- Heterogeneous range of phenotype
- 60 -70% present congenital defects
  - Finger anomalies, skeletal defects (hip, ankle,…)
  - Renal anomalies
  - Hiperpihmentation, “café au lait” stains,..
  - Microcephaly, mental retardation,…
  - hypogonadism
  - Other

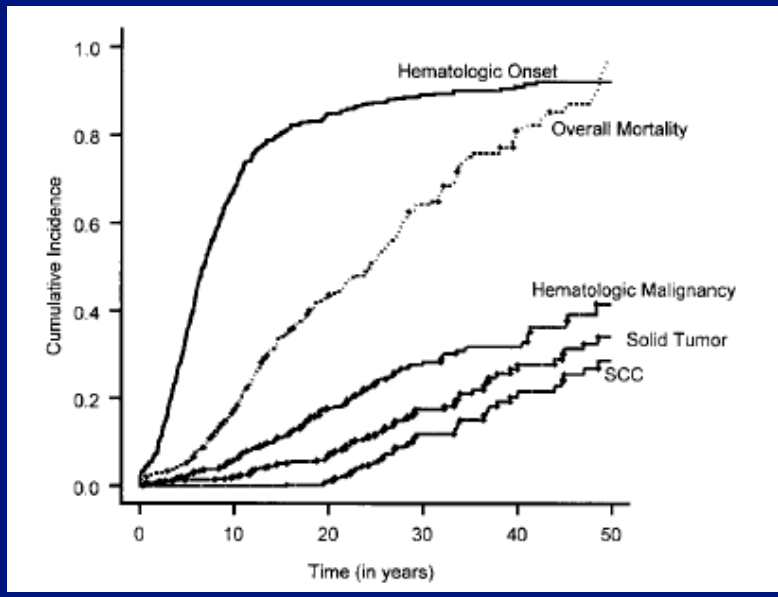


Fanconi Anemia

- Median age at diagnosis of 7 years (range: 0 – 50 y)
- Bone marrow disfunction:

  90 % of patients
- Increased risk of tumors
  - **MDS/AML**
  - Solid tumors

Disease Course



Kutler, Blood 2003

Fanconi Anemia

Increased sensitivity to DNA Cross linking agents (Mitomicin C, Diepoxibutane)

DNA Repair Genes & Syndromes

Fanconi Anemia

FANCA, -B, -C, -D, -E, -F, -G, -I -J -L, -M, -N

Xeroderma pigmentosum

XPA - XPG

Bloom Syndrome

BLM

Ataxia telangiectasia

ATM

CROMOSOMAL INSTABILITY

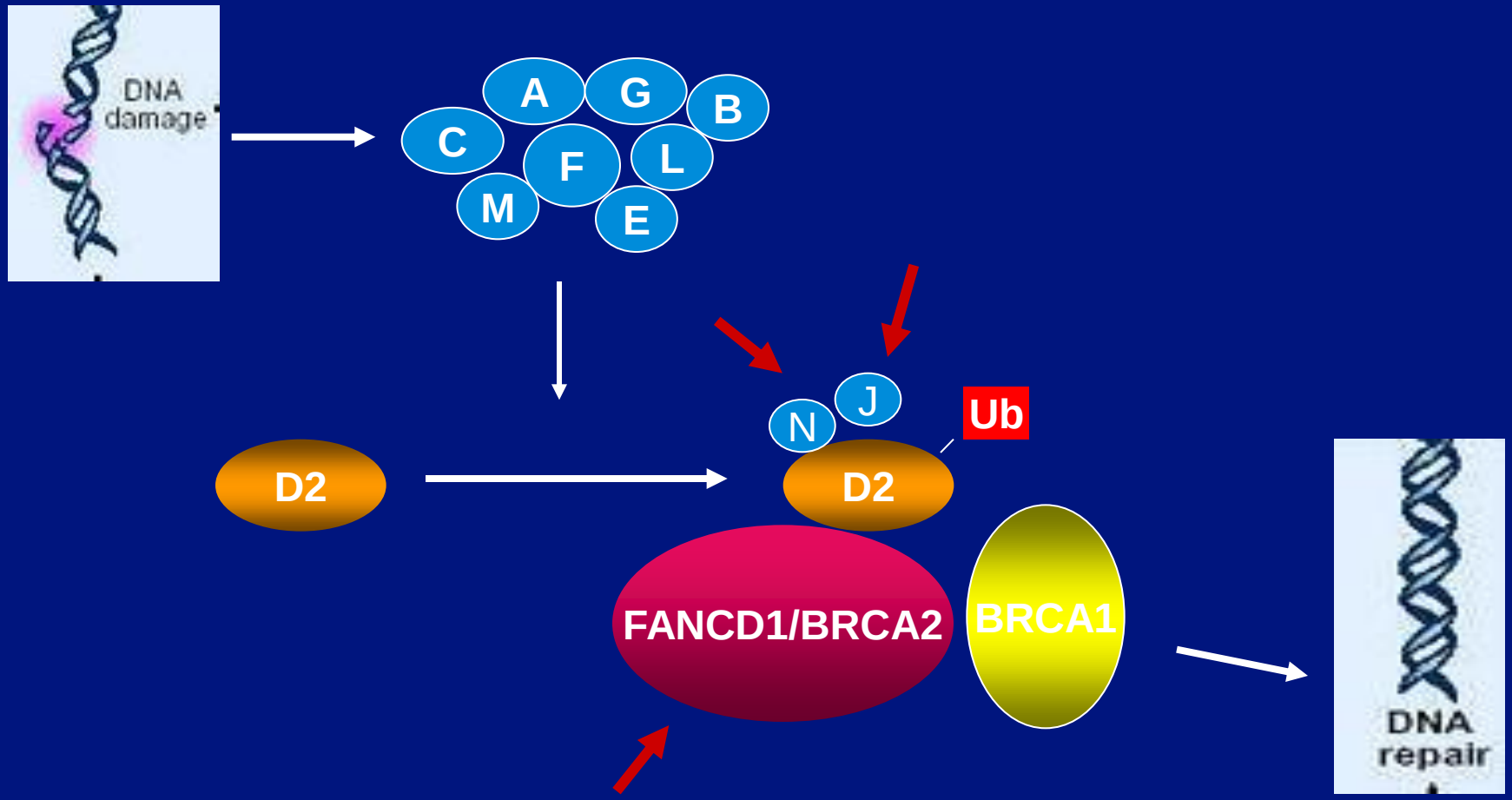
Hereditary colorectal cancer

MSH2, MSH6, MLH1, PMS1, PMS2

Heredidary Breast and ovarian carcinoma

BRCA1 – BRCA2

The Fanconi anemia/BRCA pathway



The Fanconi anemia/BRCA pathway

BRCA2 ←

Table 1. Characteristics of the 13 Genes in Fanconi's Anemia.*

Gene	Prevalence	Position on Chromosome	Size of Protein Product (kD)	Activity
FANCA	66%	16q24.3	163	Core complex member; required for FANCD2–FANCI ubiquitination
FANCB	2%	Xp22.31	95	Core complex member; required for FANCD2–FANCI ubiquitination
FANCC	10%	9q22.3	63	Core complex member; required for FANCD2–FANCI ubiquitination
FANCD1	2%	13q12–13	380	HR mediator; FANCN interactor; functions downstream of ubiquitination
FANCD2	2%	3q25.3	155	Ubiquitinated after DNA damage
FANCE	2%	6p21–22	60	Core complex member; required for FANCD2–FANCI ubiquitination; binds directly to FANCD2
FANCF	2%	11p15	42	Core complex member; required for FANCD2–FANCI ubiquitination
FANCG	9%	9p13	68	Core complex member; required for FANCD2–FANCI ubiquitination
FANCI	<2%	15q25–26	140	Ubiquitinated after DNA damage
FANCJ	<2%	17q22–24	140	Helicase; BRCA1 interactor; functions downstream of ubiquitination
FANCL	0.2%	2p16.1	43	Core complex member; required for FANCD2–FANCI ubiquitination; ubiquitin-ligase activity
FANCM	0.2%	14q21.3	250	Helicase; localizes the core complex to DNA; required for FANCD2–FANCI ubiquitination
FANCN	<2%	16p12.1	140	FANCD1 and BRCA1 interactor; functions downstream of ubiquitination

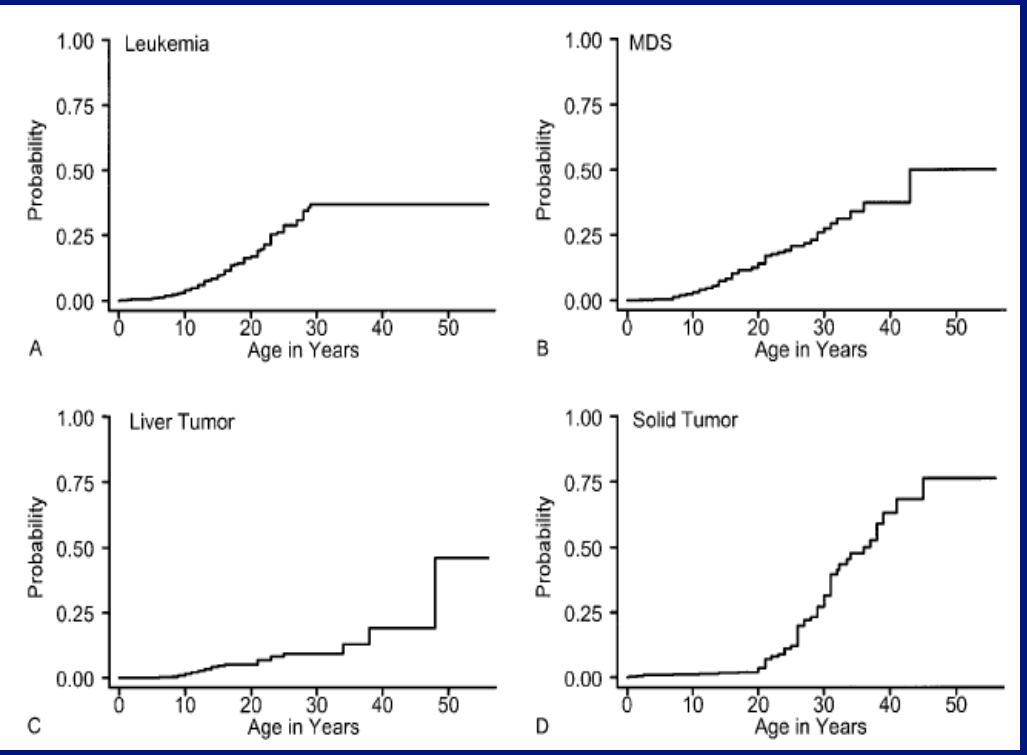
* HR denotes homologous recombination.

D'Andrea, N Engl J Med 2010

Fanconi Anemia

Solid Tumors Incidence

Secondary Tumors



Median Ages (Years) for Cancers in the FA Literature, 1927–2001

Cancer	General age[a]	FA age	FA range	FA no.
All sites	68	16	0.1–48	211
All solid tumors	—	26	0.2–45	68
Leukemia (AML)	68	14	0.1–29	116
Liver	68	13	6–48	37
Head and neck	64	28	13–41	26
Head and neck after BMT[b]	—	21[b]	11–33	12
Esophagus	68	27	20–36	9
Vulva/anus	72	27	20–37	10
Cervix	47	25	22–32	3
Brain	56	3	0.5–11	6
Breast	63	37	26–45	4

High risk
Young age

Alter BP. Cancer 2003; 15:425-440

Head and Neck Squamous Cell Carcinoma in 13 Patients With Fanconi Anemia After Hematopoietic Stem Cell Transplantation

Main Characteristics of 13 Fanconi Anemia Patients Diagnosed With HNSCC After HSCT

No. of Males	Median Age at Time of HSCT, Years*	Median Age at Time of Diagnosis of HNSCC, Years	Median Interval Between HSCT and HNSCC Diagnosis, Years	Tumor Location and TNM Classification	Surgery	Follow-up After HNSCC
9	9.7	20	10	Oral cavity (n=11; 85%) T1 (n=6; 46%)	10 (clear margins in 7)	2 patients alive between 9 and 23 mo after HNSCC

HNSCC indicates head and neck squamous cell carcinoma; HSCT, hematopoietic stem cell transplantation.

*All 13 patients received radiation-based conditioning with the bone marrow as the source of stem cells. Ten patients received transplants from related donors. All patients developed chronic graft versus host disease.

Risk of head and neck squamous cell cancer in FA patients with and without BMT

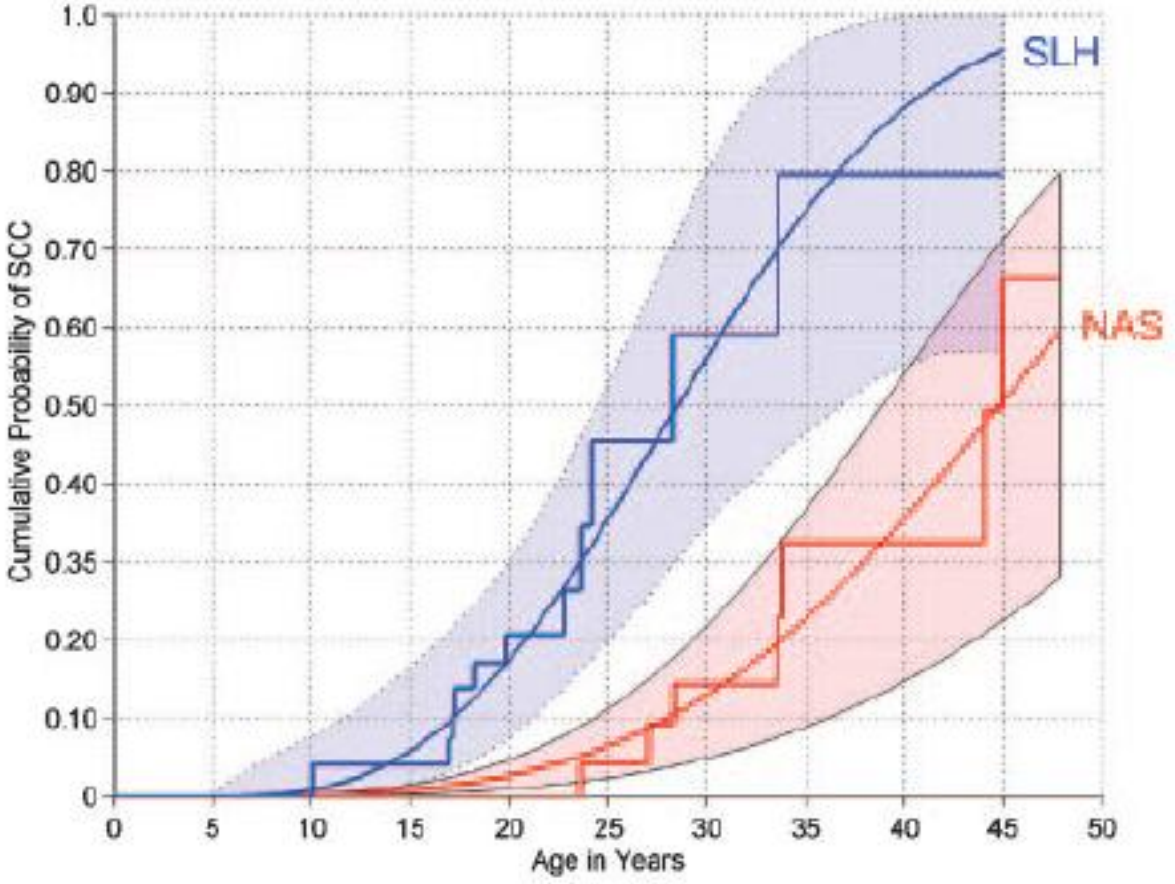


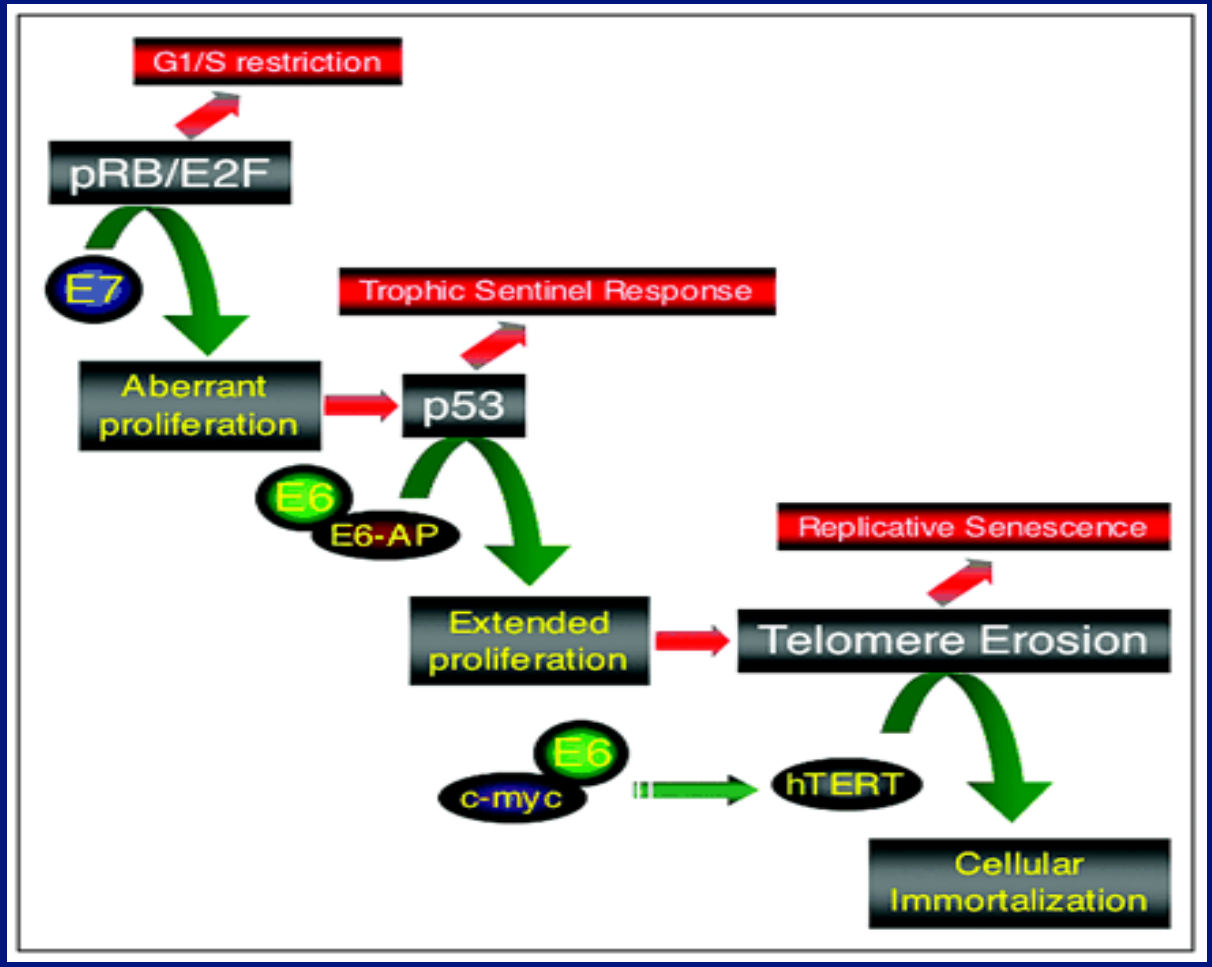
Figure 4. Hypothetical cumulative incidence curves for SCC in NAS and SLH.

(prior BMT)

(no prior BMT)

Rosenberg PS. Blood 2005

Critical steps of high-risk HPV-induced carcinogenesis



Münger et al. J Virol 2004;78:11451

FA patients Surveillance
Vall D´Hebron Hospital Cohort

Vall D´Hebron Hospital Cohort

I. Characteristics of FA study population	
N	15
Female Male	7 (47%) 8 (53%)
Median current age	22 years (14-32)*
Mean age at FA diagnosis	6.2 years (SD±5,5)
Mean FA follow-up program	1.8 years (SD±11,1)
Compliance with surveillance Yes No NA	 7 (70%) 3** (30%) 5***
Consanguinity Yes No	 3 (13%) 12 (87%)

Vall D´Hebron Hospital Cohort

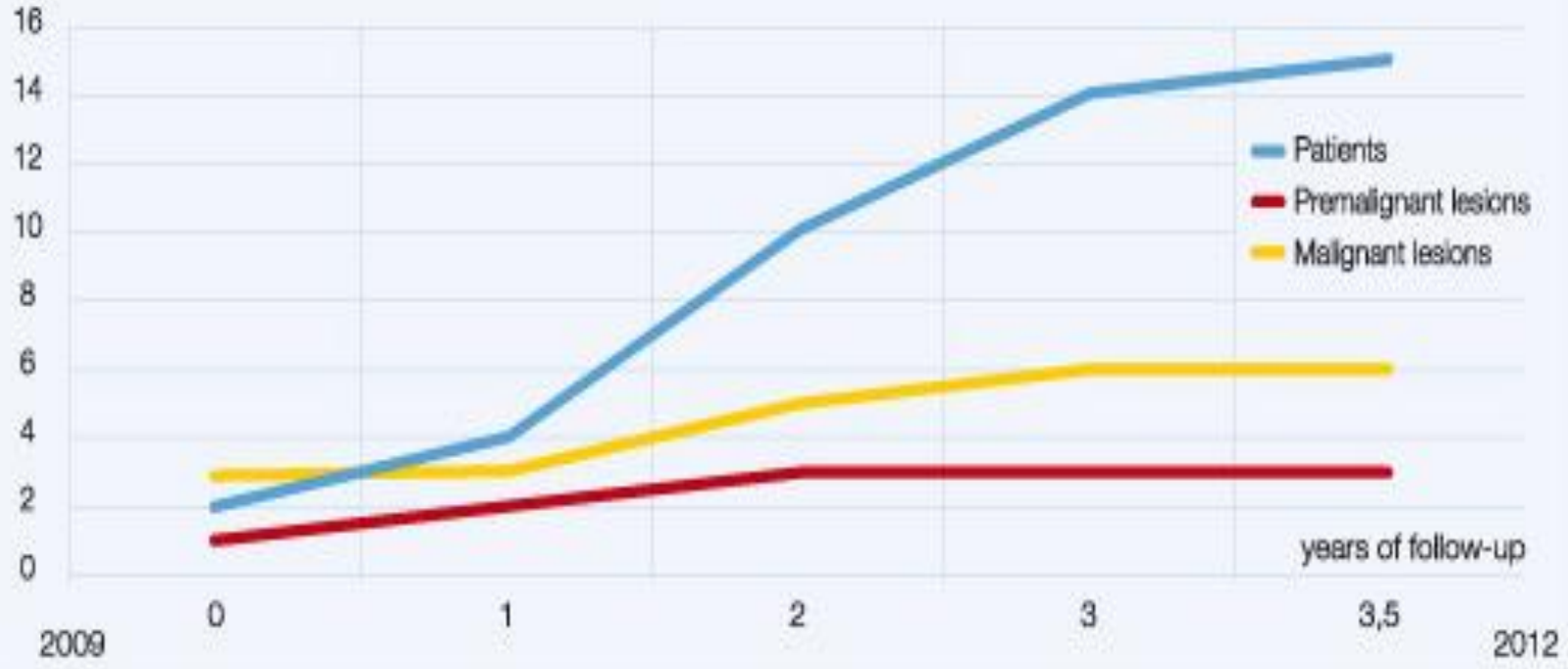
II. Clinical and genetic features of FA study population

N	15
Bone marrow transplantation	
Yes	8 (53%)
No	7 (47%)
Median age BMT	9 (6 to 20y)
Graft versus host disease	
Yes	4
No	4
HPV Vaccine in females	
Yes	5 (71%)
No	2 (29%)*
Mosaicism confirmed	
Yes	5 (33%)
No/na	10 (67%)
Genetic complementation group	
FANCA	9
Non-FANCA	2

Vall D´Hebron Hospital Cohort

III. Premalignant and malignant lesions in FA patients

Cummulative incidence of patients, premalignant and malignant lesions, during the FA follow-up program



Vall D´Hebron Hospital Cohort

Premalignant lesion or non-HNSCC	HNSCC	Age at diagnosis	TNM Stage	Treatment	Evolution	Last follow-up
Squamous dysplasia of the tongue	Lingual**	24 y HNSCC	pT2N1Mx	Surgery+Rx	LR at 4y, died at 5y	2010
-	Epiglotis	3y	pT4N1Mx	Surgery+Rx	Free of disease a 3 months	2012
BCC jaw, forehead, shoulder	x	21, 22, 22y	-	exeresis	Alive	2012
BCC abdomen, arm squamous	x	26, 27y	-	exeresis	Alive	2012
dysplasia of the tongue		32y	-	exeresis		
Cervical squamous dysplasia GI*	x	25y	-	exeresis	Alive	2012

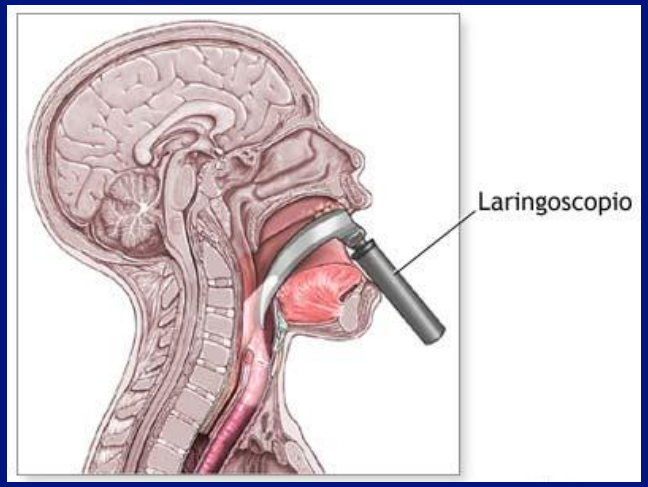
Implications

Implications

- Close surveillance needed
  - Should the follow-up be different based on prior BMT?
- Avoiding tobacco and alcohol
- Education
- HPV vaccination (?)

Follow-up in adult Fanconi Anemia patients

- High risk clinics at the Medical Oncology department
- ENT surgery clinic
- Maxillofacial
- Gynecology
- Genetics
- Pediatric and Adult Hematology



Surveillance protocol in the High Risk Clinics

SURVEILLANCE	FREQUENCY
- Symptoms survey - Physical examination - Health education - Specific recommendations - Papilloma virus vaccine	Every 6-12 months

Implications

- Close surveillance needed
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HPV infection in FA patients

Table 3 Risk of HPV infection in the study population

Group	*OR*	*95% CI*		*OR*[a]	*95% CI*[a]	
Group I	8.08	0.88	74.59	7.76	0.83	72.29
Group II	5.63	0.60	52.37	5.00	0.50	49.88
Group III	9.55	1.02	89.22	11.27	1.01	125.41
Group IV	1.00	–		1.00	–	

CI, confidence interval; OR, crude odds ratio. OR[a], OR adjusted for age.

Thanks

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