CANCER EDUCATION DAY

Surveillance in AYA

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Overview

- Background
- **Familial Cancer Susceptibility Syndromes**
  - Hereditary Breast & Ovarian Cancer Syndrome (BRCA mutations)
  - Cowden Syndrome
  - Lynch Syndrome (hereditary non-polyposis colorectal cancer syndrome)
  - Familial adenomatous polyposis (FAP)
  - Hereditary Leukemia and Hematologic Malignancies Syndrome
  - Li Fraumeni Syndrome
  - Von Hippel-Lindau
  - Multiple Endocrine Neoplasia (MEN)
  - FAMM Syndrome – Melanoma
- BRCA
- Hodgkin's lymphoma
- AYA Cancer Survivors

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What causes cancer?

- **Lifestyle** : smoking, high fat diet, exercise, EtOH, hormone therapy
- **Genetics:** BRCA, Li Fraumeni, FAMM, HMMS
- **Family history :** increased risk, unknown cause
- **Certain viruses:** HIV (lymphoma / sarcoma)
- **Environmental exposures:**
- **Certain cancers**: Chronic Lymphocytic leukemia → squamous cell carcinoma
- **Chemotherapy / radiotherapy**
- The **interaction** between all of the above

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Familial Cancer Susceptibility Syndromes

- Birt-Hogg-Dubé Syndrome
- Breast/Gynecologic Cancers, Hereditary
- Carney-Stratakis Syndrome
- Colon Cancer, Hereditary Nonpolyposis or Lynch Syndrome
- Epidermodysplasia Verruciformis
- Fanconi Anemia Basal Cell Nevus Syndrome, Gorlin Syndrome, Gorlin-Goltz Syndrome, or Nevoid Basal Cell Carcinoma Syndrome
- Bloom Syndrome
- Brooke-Spiegler Syndrome
- Cowden Syndrome and *PTEN* Hamartoma Tumor Syndromes
- Dyskeratosis Congenita (Zinsser-Cole-Engman Syndrome)
- Epidermolysis Familial
- Cylindromatosis Bullosa
- Melanoma, Hereditary
- Muir-Torre Syndrome
- Multiple Familial Trichoepithelioma
- Oculocutaneous Albinism
- Rothmund-Thomson Syndrome
- Werner Syndrome
- Xeroderma Pigmentosum

The presence of a positive family cancer history is one of the strongest and most well accepted indicators of an underlying cancer genetic susceptibility syndrome.

Cowden Syndrome

- Autosomal dominant
- Small, non-cancerous growths / hamartomas of the skin and mucous membranes including GI tract and brain: usually present by age 20; by age 30 have some of the muco-cutaneous signs
- Increased risk of developing benign and malignant tumors of the breast, uterus, renal and thyroid
- 25% with a mutation in the germline PTEN gene
  - Use Cleveland Clinic score to determine who should get the test
  - If PTEN positive --> offer increased intensity cancer screening
    - < age 18 : annual thyroid US and skin exam
    - Adults : annual thyroid US and skin exam
    - Women start age 30: annual mammo +/- MRI breast / TV US
    - Colonoscopy : start age 35 : frequency depends on results
    - Biennial renal imaging : start age 40

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4525048/pdf/zlj2537.pdf
https://www.ncbi.nlm.nih.gov/books/NBK1488/

Lynch syndrome (hereditary Non-polyposis Colorectal Cancer Syndrome)

- Early onset of colorectal cancer and endometrial cancer as well as extra-colonic cancers
- Mutation in DNA mismatch repair genes : MLH2, MSH2, MSH6, PMS2
- A variant of the Lynch syndrome called Muir Torre Syndrome is associated with increased risk for certain skin tumors
- Guidelines:
  - In view of the observation of (advanced) CRC detected between 2 and 3 years after surveillance **colonoscopy**, the recommended interval for mutation carriers is 1–2 years
  - Gyne surveillance less well defined: Surveillance of the endometrium by **gynaecogical examination, transvaginal ultrasound and aspiration biopsy starting from the age of 35–40 years** may lead to the detection of premalignant disease and early cancers and should be offered to mutation carriers. The pros and cons should be discussed

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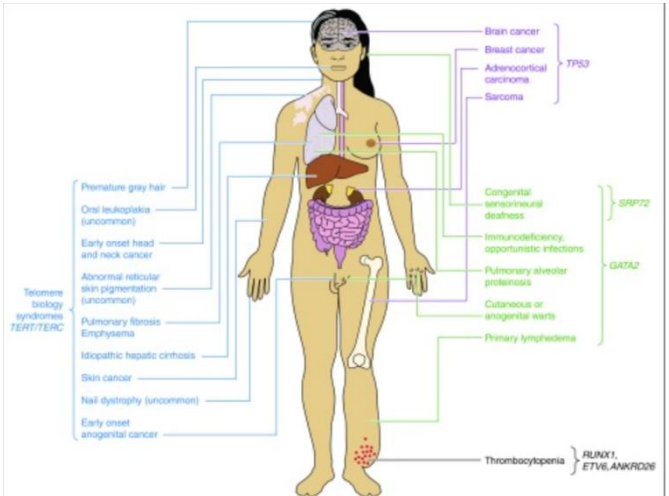
https://gut.bmj.com/content/gutjnl/62/6/812.full.pdf

Hereditary Leukemia and Hematological Malignancies Syndromes (HMMS)

- 5 – 10% of all leukemia cases are hereditary
- Leukemia patients with a family history of this disease should be considered for genetic testing
- RUNX1 , GATA
- Lucy Godley, MD PhD, Chicago – talking at the Windsor Cancer Research Group conference at 9 am on Sat Am Zoom – on this topic
- Taking a good pedigree



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Familial Melanoma Syndromes

- 5 – 10% of melanoma arise in multiple-case families
- Most don't have as of yet, detectable susceptibility genes
- Risk Factors: light skin, dyplastic nevus syndrome (autosomal dominant), familial atypical multiple mole-melanoma syndrome; CDKN2A gene (40% of families with > 3 melanomas); family history doubles risk

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CDKN2A Syndrome

- 50% increase of other cancers
  - Gastro-intestinal RR2.4
  - Pancreatic RR 7.4 – RR 47.8
  - Wilms RR 40.4
  - Lung 3.04
  - Breast RR 2.19
  - Astrocytoma

- Multiple other genes that cause cancer syndromes : telomere revers transcriptase ; POT1 ; BRCA-1 BAP1 ; DNA repair gene Xeroderma pigmentosa ; PTEN hamartoma syndrome ; MGMT ; others

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Management of High Risk Individuals

- Examination at 10 years and semi-annual examinations until nevi are considered stable, then annual exams; use photography to monitor
- Follow standard rules for biopsy : ABCDE
- CDKN2A pancreatic screening: not standardized : annual screen with CD19-9 + endoscopy; if symptomatic → ERCP +/- CT : can consider only if family history

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When to refer a melanoma to genetics

- *The American College of Medical Genetics and Genomics and the National Society of Genetic Counselors recommend that an individual with any of the following* ***characteristics be referred for a cancer genetics consultation*****:**

- A personal history of three or more primary melanomas.
- A personal history of melanoma and pancreatic cancer.
- A personal history of melanoma and astrocytoma.
- Three or more cases of melanoma and/or pancreatic cancer in FDRs.
- Melanoma and astrocytoma in two FDRs.

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Li Fraumeni

- PT53 mutation
- 100% chance of cancer lifetime
  - Sarcoma
  - Breast cancer
  - Lung cancer
  - Leukemia
  - Brain tumor
  - Adrenal gland

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Li Fraumeni Screening

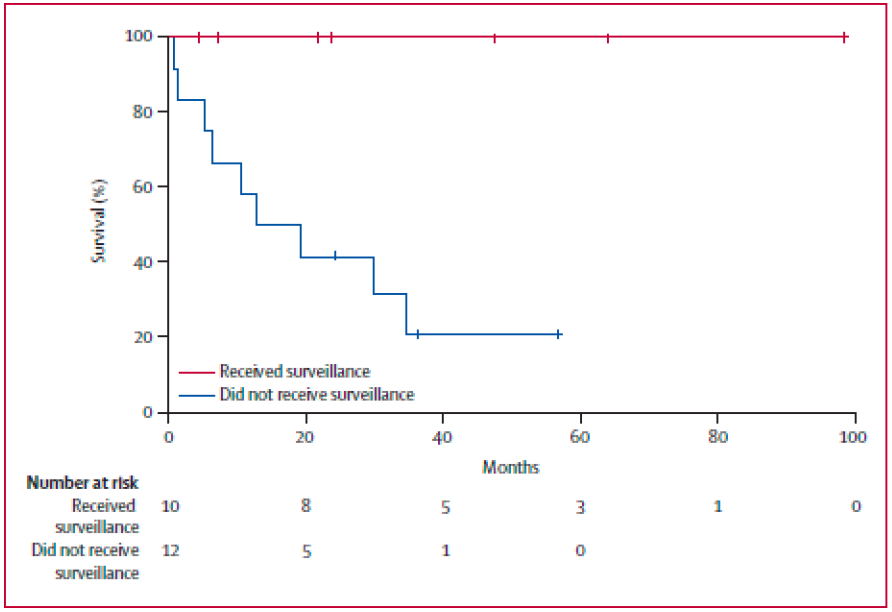

***Figure*: Survival of *TP53* mutation carriers in surveillance and non-surveillance groups followed prospectively since 2004**

n=cancer diagnoses (each neoplasm counted individually for patients with multiple cancers). Curves are marked (+) at the point at which patients were censored.

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Panel 1*: Surveillance strategy for individuals with germline *TP53* mutations

Children

Adrenocortical carcinoma

- Ultrasound of abdomen and pelvis every 3–4 months
- Complete urinalysis every 3–4 months
- Blood tests every 4 months: β-human chorionic gonadotropin, alpha-fetoprotein, 17-OH-progesterone, testosterone, dehydroepiandrosterone sulfate, androstenedione

Brain tumour

- Annual brain MRI

Soft tissue and bone sarcoma

- Annual rapid total body MRI

Leukaemia or lymphoma

- Blood test every 4 months: complete blood count, erythrocyte sedimentation rate, lactate dehydrogenase

Adults

Breast cancer

- Monthly breast self-examination starting at age 18 years
- Clinical breast examination twice a year, starting at age 20–25 years, or 5–10 years before the earliest known breast cancer in the family
- Annual mammography and breast MRI screening starting at age 20–25 years, or at earliest age of onset in the family
- Consider risk-reducing bilateral mastectomy

Brain tumour

- Annual brain MRI

Soft tissue and bone sarcoma

- Annual rapid total body MRI
- Ultrasound of abdomen and pelvis every 6 months

Colon cancer

- Colonoscopy every 2 years, beginning at age 40 years, or 10 years before the earliest known colon cancer in the family

Melanoma

- Annual dermatological examination

Leukaemia or lymphoma

- Complete blood count every 4 months
- Erythrocyte sedimentation rate, lactate dehydrogenase every 4 months

*In addition to regular assessment with family physician with close attention to any medical concerns or complaints.

Von Hippel Lindau

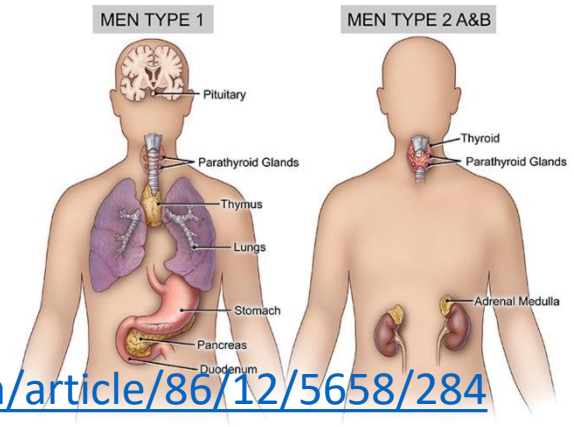
- Hemangioblastomas / angiomas
  - In the retina, areas of the brain, spinal cord
  - Other cancers in the adrenal gland, kidney, pancreas
  - High risk of kidney cancer
  - Have a mutation in the VHL gene
  - Lifetime risks:

retinal angiomas	up to 92%
renal cell carcinoma	up to 80%
cerebellar hemangioblastoma	up to 85%
epididymal cystadenoma (males)	up to 60%
spinal hemangioblastoma	up to 50%
pheochromocytoma	up to 30%
endolymphatic sac tumour	up to 11%

1. MRI of the brain stem, spine, and abdomen at ages 12, 15, and 18, with abdominal ultrasound in intervening years, followed by MRI every 2 years from age 20.
2. annual physical examination from 2 years of age
3. consider annual catecholamine assessment – plasma free metanephrines have the highest sensitivity
4. annual ophthalmologic review from 2 years of age
5. audiometry if symptomatic and consider baseline audiometry at age of school entry

Multiple Endocrine Neoplasia (MEN)

- Endocrine cancers
- MEN1 : A practical definition of MEN1 is a case with 2 of the 3 main MEN1-related endocrine tumors (parathyroid adenomas, entero-pancreatic endocrine tumors, and pituitary tumor).
- MEN2: medullary thyroid cancer (90%),pheochromocytoma (50%), multi-gland parathyroid tumor (30%)



https://academic.oup.com/jcem/article/86/12/5658/2849111

BRCA testing : who is eligible? Affected Individuals

1. Ashkenazi Jewish and breast cancer < age 50
2. Ovarian cancer at any age
3. Breast cancer age < 35
4. Male Breast Cancer
5. Triple negative breast cancer < age 60
6. Bilateral breast cancer if 1st < age 50
7. Breast ca + a family history of ≥2 HBOC –related cancers : breast, ovarian, prostate (Gleason ≥7), pancreatic

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Cancer Risks for BRCA carriers

Cancer type	Cancer risk in BRCA1 mutation carrier	Cancer risk in BRCA2 mutation carrier	General population cancer risk
Cumulative lifetime invasive breast cancer risk in women (by age 70)	57%	49%	~12%
Cumulative lifetime ovarian cancer risk (by age 70)	40%	18%	~1.3%
Cumulative lifetime breast cancer risk in men (by age 70)	increased (controversial)	6-7%	0.1%
Lifetime prostate cancer risk (by age 70)	n/a	2-6x increased risk	~14%

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Treatment Options for BRCA positive

- **Enhanced screening**: annual mammogram + MRI starting at age 25; controversy about routine TV US + Ca125 (have not been proven to increase survival)
- **Prophylactic surgery**: bilateral mastectomy & bilateral prophylactic salpingo-oophorectomy → 86% risk reduction of death from ovarian cancer, 56% reduction in death from breast cancer
- **Chemoprevention**: tamoxifen or raloxifene – not tested in this population, but may help in those who can't have surgery
- **Oral contraceptives** reduce risk of ovarian cancer by 50% in general population and in women with BRCA mutations

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Hodgkin's lymphoma: long term side effects / monitoring

- Fertility
- Infections: maintain flu shots
- Thyroid
- Heart disease
- Lung damage

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Hodgkin's lymphoma: long term side effects / monitoring

- Second cancers : up to 15% at 15 years
  - **Breast : if had XRT to breast area → MRI screening**
  - Thyroid: if had XRT to thyroid
  - Lung cancer : if had XRT to lung
  - *May be lower with current lower doses of XRT*
  - Leukemia/ MDS / lymphoma/ salivary gland/ liver / pancreatic/ bone

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AYA Cancer Survivors Chronic Comorbidities

- 2 – 3 fold increased risk for cardiomyopathy, stroke, premature ovarian failure, chronic liver disease, renal failure
- Increased risk of dyslipidemia, HTN, osteoporosis, avascular necrosis
- 40% of AYA cancer had ≥ 2 comorbidities at 10 years vs 20% those with no history of cancer
- Need for personalized survivorship plans for the AYA population

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Choa JCO 38; Sept 20,2020 p 3161

AYA Cancer Survivors Cancer Risk

- Increased risk of Breast Cancer in patients post stem cell transplant(SCT) (HR 2.6- 4.6) - higher if had SCT age < 30
- If had SCT age < 30 and those who had alkylating agents before SCT should be considered for enhanced breast cancer screening
- Less likely to get PPV vaccine post SCT

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McDonald et al. 38 (Sept 1, 2020) JCO
York 38 (Sept 1, 2020)

Question & Answer