Exploring Hereditary Syndromes

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Disclosures

- I have no disclosures

Objective

- Following this lecture, participants should be able to discuss testing criteria for and management of common hereditary cancer syndromes

Overview

- All cancers develop because of a pathogenic mutation in one or more genes
- Mutations can be somatic, de novo, germline[1,2]
- Germline (hereditary) mutations can increase the risk for multiple malignancies and are passed down through families

Hereditary Breast and Ovarian Cancer Syndrome (HBOC)

HBOC

- 5-10% of all breast cancers are linked to a genetic cause[3]
- BRCA1/2
- ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53
- Autosomal dominant

Testing criteria

- Personal history of breast cancer:
  - Age <50y
  - Any age:
    - Aid in treatment decisions
    - Triple negative
    - Multiple primaries
    - Male breast cancer
    - Ashkenazi Jewish ancestry
- Family history:
  - Close blood relative with:
    - Male breast cancer
    - Breast cancer <50y
    - Ovarian cancer
    - Pancreatic cancer
    - Metastatic prostate cancer; high risk prostate cancer
  - >3 diagnoses of breast and/or prostate cancer on the same side of the family

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Cancer Risks

BRCA1

- **Breast:** >60% (up to 88%); contralateral breast- 40%[4,5]
  - Male breast up to 1.2%[6,7]
- **Ovarian:** 40-60%[8]
- **Pancreatic**: <5%[7]
- **Prostate**: 7-26%[9,10]
- **Uterine**: reported

BRCA2

- **Breast**: >60%; contralateral breast- 25%[4,5]
  - Male breast up to 7%[6,7]
- **Ovarian**: 13-29%[8]
- **Pancreatic**: 5-10%[7]
- **Prostate**: up to 60%[9,10]
- **Melanoma**: increased

Positive Result Management

- Breast awareness starting at age 18
- Clinical breast exam starting at age 25
- Annual breast MRI starting at age 25
- Annual screening mammogram starting at age 30
- Discuss risk reducing mastectomy

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Management con't

- Ovarian
  - CA 125 and pelvic US are no longer mentioned as screening tools in NCCN, only used for preoperative planning
  - Total hysterectomy/bilateral salpingo-oophorectomy (BSO), ages 35-40 for BRCA1, 40-45 BRCA2
  - Clinical trials regarding bilateral salpingectomy at earlier age, then bilateral oophorectomy later
  - Oral contraceptives and intrauterine devices for ovulation suppression to decrease the risk of ovarian cancer[11-13]

Management con't

- Pancreatic
  - For patients with BRCA1/2 mutation and first or second degree relative with pancreatic cancer, patients should undergo pancreatic cancer screening on clinical trial.
  - Annual MRI/magnetic resonance cholangiopancreatography (MRCP) and/or annual endoscopic ultrasound (EUS)
- Prostate
  - Prostate screening at age 40
- Melanoma
  - No established guidelines
  - Annual skin exam, limit sun exposure

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A few more things…

- Other high-risk genes:
  - CDH1 (Hereditary diffuse gastric), PALB2, PTEN (Cowden), STK11 (Peutz-Jeghers), TP53 (Li-Fraumeni)
- Moderate risk genes:
  - ATM, BARD1, CHEK2, NF1, RAD51C, RAD51D

Variant of Uncertain Significance (VUS)

- A VUS is a change, or variant, in the gene that has never been seen before or because of conflicting or incomplete information in the medical literature, its association with cancer risk is unknown.
- No testing for family members
- ClinVar

Lynch Syndrome

Testing Criteria

- An individual with a Lynch Syndrome (LS) related cancer
  - <50y
  - Synchronous or metachronous LS cancer
  - 1st or 2nd degree relative with LS cancer at <50y
  - 2 or more 1st or 2nd degree relative with LS cancer, regardless of age
- MMR deficiency

- Family history of:
  - 1st degree relative with colorectal or endometrial cancer <50y OR a synchronous or metachronous lLS cancer at any age
  - 2 or more 1st or 2nd degree relatives with LS cancer, 1 being diagnosed <50y
  - 3 or more 1st or 2nd degree relative with LS cancer, regardless of age

NCCN guidelines v2.2023 “Genetic/Familial High Risk Assessment: Colorectal”

Cancer Risk

- Cancer risks vary with LS
- MLH1 and MSH2 are the most common
- MLH1 is highest risk, PMS2 is lowest risk

- Colorectal, endometrial, ovarian, renal pelvis, ureter, bladder, gastric, small bowel, pancreas, biliary tract, prostate, brain, skin
- Insufficient data to support an increased risk of breast cancer

Management

- Colonoscopy every 1-2 years
- Total hysterectomy/BSO
  - Ultrasound, endometrial biopsy, and CA125?
- Consider urinalysis (UA) annually
- Upper endoscopy every 2-4 years
- Pancreatic cancer screening
- Annual prostate specific antigen (PSA)
- Dermatologic exam annually

- Colonoscopy every 1-3 years
- Consider total hysterectomy/BSO
- Consider UA annually
- Upper endoscopy every 2-4 years
- NO pancreatic screening (unless family history dictates)
- Consider PSA annually
- Dermatologic exam every 1-2 years

NCCN guidelines v2.2023 “Genetic/Familial High Risk Assessment: Colorectal”

But what about aspirin?

- CAPP2 trial evaluated using aspirin (600mg) daily vs placebo for 2-4 years.
- After 10 year follow up, patients who took aspirin for at least 2 years had a 35% reduction in the incidence of colorectal cancer [14,15]
- An observational study which included 1858 patient from the Colon Cancer Family Registry, examined the use of aspirin and ibuprofen in decreasing risk of colorectal cancer.[16]

- Optimal duration and dose of therapy is undetermined. CAPP3 trial is ongoing.

What else?

- APC, MUTYH, STK11, SMAD4, BMPR1A, AXIN2, CHEK2, GALNT12, GREM1, MBD4, MSH3, NTHL1, POLD1, POLE, PTEN, RNF43, RPS20, TP53

Hematologic genetic syndromes

- Familial myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML)
- DDX41, RUNX1, GATA2, DKC1, TERT, TERC
- Increased risk for MDS/AML at younger ages[17,18]

- Skin punch biopsy

Takeaways

- HBOC and Lynch are common hereditary syndromes; however, there are many hereditary syndromes, and more are emerging
- Guidelines are readily available, but remember to consider family history when screening
- Think PANEL TESTING

References

1. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990;61:759-767.
2. Vogelstein B, Kinzler KW. The multistep nature of cancer. Trends Genet 1993;9:138-141.
3. Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE. Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. *Lancet.* 1994;343:692–695. doi: 10.1016/S0140-6736(94)91578-4.
4. Berliner JL, Fay AM. Risk assessment and genetic counseling for hereditary breast and ovarian cancer: recommendations of the National Society of Genetic Counselors. J Genet Couns 2007;16:241-260
5. Eccles DM, Mitchell G, Monteiro AN, et al. BRCA1 and BRCA2 genetic testing-pitfalls and recommendations for managing variants of uncertain clinical significance. Ann Oncol 2015;26:2057-2065.
6. Terraf P, Pareja F, Brown DN, et al. Comprehensive assessment of germline pathogenic variant detection in tumor-only sequencing. Ann Oncol 2022;33:426-433.
7. Slavin TP, Banks KC, Chudova D, et al. Identification of incidental germline mutations in patients with advanced solid tumors who underwent cell-free circulating tumor DNA sequencing. J Clin Oncol 2018;36:JCO1800328
8. Offit K, Sharkey CM, Green D, et al. Regulation of laboratorydeveloped tests in preventive oncology: emerging needs and opportunities. J Clin Oncol 2022:JCO2200995
9. Walsh T, Casadei S, Coats KH, et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. JAMA 2006;295:1379-1388.
10. Kurian AW, Hare EE, Mills MA, et al. Clinical evaluation of a multiplegene sequencing panel for hereditary cancer risk assessment. J Clin Oncol 2014;32:2001-2009.

References

11. Narod SA, Risch H, Moslehi R, et al. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. N Engl J Med 1998;339:424-428.

12. Huber D, Seitz S, Kast K, Emons G, Ortmann O. Use of oral contraceptives in BRCA mutation carriers and risk for ovarian and breast cancer: a systematic review. Arch Gynecol Obstet 2020;301:875-884. Erratum in: Arch Gynecol Obstet. 2022;305:1627

13. Balayla J, Gil Y, Lasry A, Mitric C. Ever-use of the intra-uterine device and the risk of ovarian cancer. J Obstet Gynaecol 2021;41:848-853

14. Burn J, Gerdes AM, Macrae F, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet 2011;378:2081-2087

15. Burn J, Sheth H, Elliott F, et al. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial. Lancet 2020;395:1855-1863.

16. Ait Ouakrim D, Dashti SG, Chau R, et al. Aspirin, Ibuprofen, and the Risk of Colorectal Cancer in Lynch Syndrome. J Natl Cancer Inst 2015;107

17. Liew E, Owen C. Familial myelodysplastic syndromes: a review of the literature. Haematologica 2011;96:1536-1542.

18. Hahn CN, Chong CE, Carmichael CL, et al. Heritable GATA2 mutations associated with familial myelodysplastic syndrome and acute myeloid leukemia. Nat Genet 2011;43:1012-1017.