Inequality of Breast Cancer: Why Patients Get Different Treatments

Satellite Conference and Live Webcast
Wednesday, June 26, 2019
1:00 – 3:00 p.m. Central Time

Produced by the Alabama Department of Public Health
Video Communications and Distance Learning Division

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Breast cancer statistics

Genetic testing

Models for risk assessment: Tyrer Cuzik, Gail

Receptors in breast cancer

BREAST CANCER STATISTICS

- 1 in 8 women get breast cancer
- 12.4% population lifetime risk
- 10% of women with breast cancer have a family history
- 7 out of 8 will not get breast cancer
- 87.3% population will never get breast cancer
- 90% of women that get breast cancer do not have a family history

PROBABILITY OF DEVELOPING BREAST CANCER BY AGE+

•Birth to 49 years	•2.0 % (1 IN 51)
•50-59 years	•2.3 % (1 IN 43)
•60-69 years	•3.5 % (1 IN 29)
•≥ 70 years	•6.7 % (1 IN 15)
•BIRTH TO DEATH	•12.4 % (1 IN 8)

RISK OF DEATH FROM BREAST CANCER:

Findings at diagnosis	Distribution	5 year Mortality
Localized to breast	62%	1%
Regional	31%	15%
Metastatic	6%	73%

RISK OF BEING ALIVE WITH BREAST CANCER:

Findings at diagnosis	Distribution	5 year survival
Localized to breast	62%	99%
Regional	31%	85%
Metastatic	6%	27%

GENETICS??

- I have breast cancer – Do I carry the gene?
- Cancer runs in my family – we must have a bad gene!
- If I have one cancer, does that mean I will get another type of cancer?

OUTLINE

- Identify guidelines for referring patients for cancer genetic counseling
- Discuss panel testing

GENETICS IN CANCER

- 5-10% of all malignancies are due to highly penetrant hereditary cancer predisposition syndromes
- Over 602 genes have been identified as associated with increased risk of cancer development

http://cancer.sanger.ac.uk/census#cl_analysis

HEREDITARY CANCER SYNDROMES MOST COMMON/STUDIED

- Hereditary Breast and Ovarian Cancer Syndrome (BRCA1 and BRCA2)
  - Incidence: 1 in 300 (*BRCA1*) to 1 in 800 (*BRCA2*)
  - Ashkenazi Jewish (1 in 40)
- Hereditary Nonpolyposis Colorectal Cancer aka Lynch Syndrome (MLH1, MSH2, MSH6, PMS2 and EPCAM)
  - Incidence: 1 in 440

RARE HEREDITARY CANCER SYNDROMES WITH NCCN GUIDELINES

- Li-Fraumeni Syndrome (TP53)
  - Sarcomas, breast cancer, adrenocortical carcinomas, leukemia, many types of brain tumors, melanoma, cancers of the lung, GI tract, genitourinary tract, thyroid, ovaries, uterus

RARE HEREDITARY CANCER SYNDROMES WITH NCCN GUIDELINES

- Cowden Syndrome (PTEN)
  - Breast cancer, endometrial cancer, follicular or papillary thyroid cancer, GI hamartomas or ganglioneuromas, colon cancer, renal cell carcinoma
  - Lifetime risk of endometrial carcinomas of 13–19 %

RARE HEREDITARY CANCER SYNDROMES WITH NCCN GUIDELINES

- Case reports of in CS patients reports only endometrioid type
- Peutz-Jegher (STK11)
  - Breast, colon, small bowel, gastric, ovarian/cervical/uterine, testicular, pancreatic cancers

INDICATIONS FOR REFERRAL TO GENETIC COUNSELOR

NCCN GUIDELINES

Most current

- Genetic/Familial High-Risk Assessment: Breast and Ovarian
  - Version 3.2019-January 18, 2019
- Genetic/Familial High-Risk Assessment: Colorectal
  - Version 1.2018-July 12,2018

INDICATIONS FOR REFERRAL TO GENETIC COUNSELOR

- Personal OR family history of:
  - Cancer* diagnosed at a young age (<50)
  - Multiple primary cancers in the same individual
  - Cancer* in 2 or more close relatives
  - Combination of certain cancers* in a family

*Particularly breast, gastrointestinal, melanoma, uterine, renal, thyroid, urinary tract, sarcoma

INDICATIONS FOR REFERRAL TO GENETIC COUNSELOR

- Single case of:
  - Ovarian cancer
  - Sarcoma
  - Medullary thyroid cancer
  - Retinoblastoma
  - Wilm's tumor
  - Adrenocortical carcinoma
  - Choroid plexus carcinoma
  - Pheochromocytoma/Paraganglioma
- Multiple (>10) adenomas
- Hamartomatous polyps, juvenile polyps or serrated polyps (any number at any age)

*Particularly breast, gastrointestinal, melanoma, uterine, renal, thyroid, urinary tract, sarcoma

TOP 10 CANCER MOST LIKELY TO BE DUE TO GERMLINE MUTATION

1. Adrenocortical carcinoma (LiFraumeni and BWS)
2. Carcinoid tumors (MEN I)
3. Diffuse gastric cancer (Hereditary Diffuse Gastric Cancer)
4. Fallopian tube (BRCA)
5. Leiomyosarcoma (HLRCC, Lynch, Rb)
6. Medullary thyroid carcinoma (MEN 2)
7. Paraganglioma/pheo (MEN 2, VHL, NF1, PGL)
8. Renal cell carcinoma- chromophobe, hybrid oncocytotic, oncocytoma histology (Britt-Hogg-Dube)
9. Sebaceous carcinoma (Lynch)
10. Sex cord tumor with annular tubule (PJS)

Banks et al. Familial Cancer 2013;12:1-18.

- What is panel testing ?
  - Testing several genes for changes at one time
- Why is panel testing performed?
  - Genetic testing for breast cancer usually tests for mutations in BRCA1 and BRCA2 genes; there are at least 10 other genes that predispose a patient to breast cancer.

HEREDITARY CANCER PANELS*

- Multiple labs offering similar but different panels
  - High risk breast cancer panels (5-7 genes included)
  - Expanded breast cancer panels (17-23)
  - **Breast/ovarian cancer panels (21-23)**
  - **Gynecological (ovarian/uterine) cancer panels (9-24)**
  - High risk Colorectal cancer panels (7-12)
  - Expanded colorectal cancer panels (16-22)
  - Renal cancer panels (12-19)
  - Brain/CNS cancer panels (17)

*As of 7/10/15

HEREDITARY CANCER PANELS*

- Pancreatic cancer panels (13-16)
- Malignant Melanoma panels (2-4)
- Lymphoma/leukemia panels (13)
- Prostate cancer panels (5)
- Paragangliomas /pheochromocytomas panels (9-12)
- Hereditary cancer panels (25-61 genes)
  - *University of Washington: AKT1*, *APC*, *ATM*, *ATR*, *AXIN2*, *BAP1*, *BARD1*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK4*, *CDKN2A*, *CHEK1*, *CHEK2*, *CTNNA1*, *FAM175A* (Abraxas), *FH*, *FLCN*, *GALNT12*, *GEN1*, *GREM1*, *HOXB13*, *MEN1*, *MLH1*, *MRE11A*, *MSH2* (+*EPCAM*), *MSH6*, *MUTYH*, *NBN*, *NF1*, *PALB2*, *PALLD*, *PIK3CA*, *PMS2*, *POLD1*, *POLE*, *POT1*, *PRKAR1A*, *PRSS1*, *PTCH1*, *PTEN*, *RAD51B*, *RAD51C*, *RAD51D*, *RB1*, *RET*, *RINT1*, *RPS20*, *SDHB*, *SDHC*, *SDHD*, *SLX4*, *SMAD4*, *SMARCA4*, *STK11*, *TP53*, *VHL*, and *XRCC2*

*As of 7/10/15

INFORMED CONSENT: RISKS & LIMITATIONS OF GENETIC TESTING

- Not all mutations are detectable
  - Negative result in your patient is only fully informative *if* ***a*** mutation has been identified in another family member
  - Ie, negative results does not always mean the cancer is not genetic
- Uncertain significance of some variants (mutations)
- Unproven efficacy of most interventions
- Emotional impact and need to inform family members

GETTING TESTING COVERED

- AL Medicaid does not cover genetic testing
  - Contact labs to find one that is willing to perform testing for free for Medicaid patients
- Medicare only covers genetic testing in individuals affected by cancer and meet criteria
  - Invitae will test unaffected Medicare for free (at this time)
- Many of the main labs will offer significant financial assistance
  - Myriad, Ambry, Invitae, GeneDx
  - Look for patient assistance applications online

INDICATIONS FOR REFERRAL TO GENETIC COUNSELOR

OR

When should the provider order genetic testing????

WHO GETS GENETIC TESTING?

- Patient with cancer – Medical Oncologist will arrange for testing if indicated
- Patient without cancer:
  - Primary provider must determine if genetics testing is a consideration
  - Primary provider must counsel patient on seeking testing

RISK ASSESSMENT TOOLS

- B-RST – Breast Cancer Genetics Referral Screening Tool
  - https://www.breastcancergenescreen.org
- Ibis (Tyrer Cuzick)
  - http://www.ems-trials.org/riskevaluator/
- Gail – Breast Cancer Risk Assessment Tool
  - https://bcrisktool.cancer.gov/

FACTORS FOR RISK ASSESSMENT

- Age
- Height and weight
- Race
- Age at menarche
- Age at first birth
- History of breast biopsy
- Family history

FAMILY HISTORY

- Primary family members
  - Mother
  - Sister
  - Daughter
- Secondary family members
  - Cousin
  - Aunt
  - Grandmother

PATERNAL FAMILY HISTORY

- PATERNAL FEMALE RELATIVES
- Father
- Paternal family member with genetic mutation

RISK ASSESSMENT TOOLS

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- Ibis (Tyrer Cuzick
- Gail – Breast Cancer Risk Assessment Tool

RISK ASSESSMENT TOOLS

- B-RST – Breast Cancer Genetics Referral Screening Tool
- Ibis (Tyrer Cuzick) – accurate for at least 19 years
- Gail – Breast Cancer Risk Assessment Tool

TYRER CUZICK

- Age at menarche
- Height
- Weight
- Age at menopause
- Age at parturition
- Prior breast biopsies and PATH
- Family history – who had breast cancer AND at what age
- Hormonal use
- Breast density

RISK ASSESSMENT TOOLS

- B-RST – Breast Cancer Genetics Referral Screening Tool
- Ibis (Tyrer Cuzick)
- Gail – Breast Cancer Risk Assessment Tool
  - Estimates the risk of developing invasive breast cancer in the next 5 years

RISK OF BREAST CANCER

- Population (average) risk (women with no risk factors): 12.7%
- Moderate risk: Greater than 12.7% but less than 20%
- High risk: 20% or greater

American Cancer Society Recommendations for the Early Detection of Cancer in Average-Risk, Asymptomatic Adults

- Women 40-54 years
  - Mammography starting at age 45, screened annually
  - Women should have the opportunity to begin annual screening between 40-44 years
- Women aged 55 years and older
  - Mammography – biennial screening or continue annually
  - Mammography – continue as long as life expectancy is 10 years or longer

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MODERATE RISK (LIFETIME RISK 12.7-20%)

- Mammographic screening – start at age 40
- Lifestyle behaviors
  - Alcohol – limit to no more than one drink per day
  - Lose weight – BMI >28 increases risk in a postmenopausal woman
  - Regular exercise – 30 minute brisk walks 5 times weekly
  - Vitamin D (1000 IU daily)
  - Healthy diet – limit red meat to 3 servings/week

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HIGH RISK (GREATER THAN 20% LIFETIME RISK)

- Enhanced screening: yearly breast MRI in addition to mammogram
  - Alternate mammogram and MR every 6 months
- Lifestyle behaviors
- Prevention
  - Tamoxifen – only therapy for PREMENOPAUSAL women
  - Raloxifen – more favorable than Tamoxifen
  - AI's – Exemestane and anastrozole
  - Surgery – not a candidate unless a BRCA mutation in family

RISK-REDUCING SURGERY – IN MUTATION CARRIERS

- Bilateral prophylactic mastectomy (risk reduction)
  - decreases risk of breast cancer greater than 90%
- Risk reducing salpingo-oophorectomy (RRSO)
  - Decreases breast cancer risk by 50%
    - BRCA1 – by age 35
    - BRCA2 – by age 40
  - Decreases ovarian cancer risk by 80%

CALCULATORS ARE NOT TO BE USED FOR PATIENTS WITH A PERSONAL HISTORY OF BREAST CANCER

BREAST CANCER

= breast cancer

= BREAST cancer

= breast CANCER

PATHOLOGY OF BREAST CANCER

1. Breast mass – biopsy is sent to pathology
2. Slides are made – pathology confirms diagnosis of cancer
3. Slides are stained to determine if there are certain receptors:
   - Estrogen
   - Progesterone
   - HER2

RECEPTORS

- Cell receptors – proteins found inside and on the surface of cells – normal breast and cancer cells
- Cell receptors receive messages from substances in the bloodstream, telling the cells what to do
- Cell hormone receptors: Estrogen (E), progesterone (P)
- If cells have hormone receptors, E and P attach and provide instructions to help cells grow and function
- Normal breast cells – E and P help growth
- Cancer cells – E and P stimulate growth of cancer
- 2/3 of breast cancers have receptors for Estrogen, Progesterone, or Both

HER2: HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2

- Gene that can play a role in the development of breast cancer
- HER2 gene makes HER2 proteins – these are receptors on breast cells
- Normal: HER2 receptors help control how a healthy cell grows, divides, and repairs itself
- 25% breast cancer: HER2 gene makes too many copies of itself (HER2 amplification), extra HER2 genes tell breast cells to make too many HER2 receptors (HER2 overexpression), and makes breast cells grow and divide in an uncontrolled way
- HER2 positive cancers grow faster, are more likely to spread and come back
- HER2 positive cancer cells have 40-100 X as many HER2 receptors on the cell surface

HER2

- Healthy breast cells – HER2 stimulates cell growth
- Breast cancer cells with too much HER2: cells grow and divide too quickly
- TOO much HER2 protein (receptors) is bad – cancer cells grow rapidly
- HERCEPTIN: blocks the HER2 receptors
  - HER2 positive – Herceptin is a effective drug
  - HER2 negative – Herceptin doesn't treat the cancer

HER2 POSITIVE BREAST CANCER – GOOD OR BAD?

- HER2 positive tumors
  - More aggressive
  - Increased risk of recurrence
  - More likely to metastasize (especially to the brain)
  - Found in younger women

BREAST CANCER -- INVASIVE

Hormone (ER/PR)	HER2
•Hormone positive	•HER2 positive
•Hormone negative	•HER2 negative

ER/PR/HER2

- Hormone positive means Estrogen positive, Progesterone positive, or both positive

- Hormone positive, HER2 negative
- Hormone positive, HER2 positive
- Hormone negative, HER2 positive
- Hormone negative, HER2 negative

CANCER TREATMENTS

- Receptor blockade – blocking the receptors on a cancer cell prevents hormones and HER2 from stimulating cell growth
- Hormonal therapy: Tamoxifen, Anastrazole (Arimidex), Letrozole (Femara) – block the effect of estrogen and progesterone on cancer cells, slowing or stopping growth
- Herceptin, Perjeta, Tykerb, Kadcyla: blocks HER2 receptors

TRIPLE NEGATIVE BREAST CANCER

- Estrogen negative
- Progesterone negative
- HER2 negative

TRIPLE NEGATIVE CANCER

- 10-20% of breast cancers are triple negative
- Hormones are not stimulating the cancer's growth, so cancer is not going to slow down by giving hormonal therapy
- HER2 is not stimulating cancer growth, so Herceptin-type drugs don't work
- Triple negative cancers are more aggressive than other types
- Triple negative cancers more likely to spread beyond the breast
- Triple negative cancers more likely to recur – return after treatment

WHO GETS TRIPLE NEGATIVE CANCER

- Anyone
- Younger people – more likely to be found in women younger than 50 years
- African American and Hispanic women
- People with BRCA1 mutation(70% of cancers in BRCA1 patients are triple negative