BRCA Testing in Ovarian cancer  Arabic Approach

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Know:BRCA

Knowing your BRCA gene mutation risk can save your life
Development of cancer
Familial vs Hereditary Cancer Risk

- Familial patterns are seen in several types of cancer

  Generally confer a modest increase in risk such as 2x

  Not attributable to a defect in a single gene, but rather to a combination of genetic alterations known as SNP’s (single nucleotide polymorphisms)
Familial vs Hereditary Cancer Risk

- Hereditary cancer indicates that cancer risk is attributable to an inherited mutation that disrupts gene function.

  Often a much higher relative risk compared to average, and a tendency to occur at younger age.

  The affected genes are typically DNA repair genes (ie, tumor suppressor genes).
Molecular profiling of Serous OVCA

Goodman et al 2014
Germline mutations in ovarian cancer

1915 unselected Ovarian Carcinoma
(GOG 218, GOG 262)
Norquist, JAMA 2016

18% carried a germline mutation:
- 15% in BRCA1 or BRCA2
- 3% in BRIP1, RAD51C, RAD51D, PALB2, BARD1
- 0.4% in a MMR gene
Cancer Risk in Carriers

Anteil erblich bedingter Eierstockkrebsenerkrankungen

Eierstockkrebs ca. 20 % 1:5
Estimated Cumulative Risks of Breast and Ovarian Cancer in Mutation Carriers

- OVCA: Peak incidence
- BRCA1: 41-70y, BRCA2: 51-70y

Kuchenbaecker, JAMA 2017
Inheritance

- Autosomal dominant inheritance pattern
- Women and men equally affected
- 50% chance of inheriting mutation
- Vertical transmission
- Most mutations lead to truncated proteins
Function of BRCA1

- DNA damage response
- Checkpoint control
- Mitotic spindle assembly
- Sister chromatid decatenation
- Centrosome duplication

Yang, JAMA 2017
Function of BRCA2

- Regulation of RAD51 protein
- RAD51 required for double-strand break repair by homologous recombination

Yang, JAMA 2017
Function BRCA1/BRCA2

DNA DAMAGE

ATM/ATR

H2AX

Nibrin

NFBD1

S3BP1

MRN COMPLEX

Nibrin/Mre11/Rad50

Non-Homologous End Joining Repair

HOMOLOGOUS RECOMBINATION REPAIR

BRCA1

BRCA1/BARD1

BRCA2

FANCD2

CHK2

Rad51

MMR protein signaling complex
Prevalence of BRCA1/2 mutations

- General US population 1:400

- Ashkenazi Jews:
  - 1:40 - 1:50
  - 3 Founder mutations in 90% (BRCA1 185delAG, 5382insC, BRCA2 6174delT)

- > 2000 different mutations

Purpose for Genetic Testing in Oncology

- Identify patients at significant risk for second cancers
- Modify current treatment plan to reduce the likelihood of second cancer
- Implement cancer risk management strategies to
  - Reduce the likelihood of a second cancer
  - Find second cancers at an earlier, more treatable stage
- Surveillance Strategies
- Identify family members at hereditary risk before the first cancer
How Many Cancer patients should Undergo Genetic Testing?

• When current NCCN guidelines are applied to large groups of cancer patients, the following approximate percentage of patients will be appropriate for genetic testing:

  • Ovarian 100%  NCCN2008
  • Breast >30%  NCCN2018
  • Colorectal >25%  NCCN2015
  • Endometrial >70%  NCCN2015
  • Prostate >25%  NCCN2017

• Zhang et al. Gynecol Oncol2011; Eisenbraun et al. Community Oncol,2010;
• Boland et al. Gastroenterology,2010; Kerber et al Familial Cncer 2005;
„Automatics“ FOR BRCA Testing

- Breast cancer by age 45 (invasive or DCIS)
- ANY epithelial OVCA, regardless of age or family history
- ANY male breast cancer
- Triple negative breast cancer by age 60
- Breast cancer in jewish. Woman
- Metastatic HER2-neg breast cancer (NCCN2018)
- Famils history of BRCA cancer ( 3 cancers within 3 degrees)
- First degree family members of any of the above
• The linguistic approach is a relaxed definition and it includes all populations speaking the Arabic language and living in a vast area extending from south of Iran in the east to Morocco in the west including parts in the south-east of Asia Minor, East, and West Africa.

• The political definition of Arabs is more conservative as it only includes those populations residing in 23 Arab States, namely: Algeria, Bahrain, Comoros, Djibouti, Egypt, Eritrea, Iraq, Jordan, Kuwait, Lebanon, Libya, Mauritania, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, United Arab Emirates (UAE), and Yemen.
Arab gene geography

- Genetic disorders are not equally distributed over the geography of the Arab region

- Nearly, one-third of the genetic disorders in Arabs result from congenital malformations and chromosomal abnormalities

- High fertility rates together. Consanguineous marriages increase the rates of genetic and congenital abnormalities

- Approximately 35% of genetic diseases in Arabs do not have a defined molecular etiology
BRCA in arab world

- The proportion of BRCA1 and BRCA2 mutations could be higher in Arab women.

- In Morocco, a large number of distinct polymorphisms and unclassified variants in BRCA2, BRCA1 were described for the first time.

- In Algerian women, four of 11 familial cases were associated with BRCA1 alterations.

- In Tunisia, the prevalence of breast cancer is calculated to be between 16% and 38%. There, four novel unclassified BRCA1 mutations have been identified.

• In Lebanon 38 BRCA1 sequence variants, many of which are novel were revealed.

• Other unclassified BRCA1 variants, p.Phe486Leu and p.Asn550His, were detected in Saudi patients.

BRCA in arab world

- This seems to extend to Arab Diasporas

Shatavi et al J Clin Oncol. 2013
Cumulative Cancer Risk in BRCA1

Breast cancer

Cumulative risk (%)

Ovarian cancer

Age

- Average pathogenic BRCA1 variants
- BRCA1 R1699Q main analysis
- General population
Tools

- Implementation of simple questionnaire to personal and family cancer history
Testing procedure

- Blood sample of 5-10 ml (EDTA tube), DNA extracted from white blood cells
- Time till getting the result: 2 weeks
- Expenses:
  - Complete gene analysis: 3300 Euro
  - Carrier testing: 330 Euro
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Development of cancer

The Development of Cancer

SPORADIC CANCER

2 normal genes → 1 damaged gene → 1 normal gene → 2 damaged genes → Tumor develops

1 damaged gene → 1 normal gene → 2 damaged genes → Tumor develops
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Cancer Risk in Carriers of Germ Line Mutations in BRCA1 & BRCA2

Presented by Judy Carter at 2018 ABCD Annual Meeting

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Ghazi et al., glo. Card sci prac 2014
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