Update in Cancer Genetics
BCCCP Annual Meeting

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Beaumont Cancer Genetics Program
5/2/2012

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Genetics is Everywhere

Peering Into the Future

Genetic testing is transforming medicine—and the way families think about their health. As science uncovers the intricate secrets of DNA, we face difficult choices and new challenges.

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Lung-Cancer Patients May Gain From a Simple, Five-Gene Test

Researchers Find Which Candidates Most Need Chemo

Associated Press

Scientists in Taiwan have developed a simple, five-gene test aimed at identifying which lung-cancer patients may benefit from chemotherapy, as similar tests now do for people with breast cancer and lymphoma.

The experimental test needs to be validated in larger groups of patients, so widespread use remains uncertain, said Dr. Shen-Chieh Hwu, director of the International Institute of Molecular Medicine in Taipei. However, it is already winning praise for its possible use in everyday hospital settings instead of in limited situations by people with special genetic training.

This has the potential to be extremely helpful,” said Dr. Thomas M. Jenson, chair of medical oncology at Vanderbilt University Medical Center and former president of the American Society of Clinical Oncology, the world’s largest group of cancer specialists.

“While no test is perfect and understanding genetic signatures may be helpful in allowing us to treat a patient correctly, those who are not responsive to current drugs and would be better off trying an experimental therapy, he said.

The study was paid for by the National Science Council of the Republic of China and the Taiwan Health and Welfare Department. It found that the test could identify about 70% of lung cancer patients who would benefit from chemotherapy.”
Cancer Etiology:

- ~5-10% of cases have a strong hereditary component
- ~15-20% are “familial” or multifactorial
- ~70-75% are sporadic
### Estimated New Cases*

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>186,320</td>
<td>182,460</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>114,690</td>
<td>100,330</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>77,250</td>
<td>71,560</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>51,230</td>
<td>40,100</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>35,450</td>
<td>30,670</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>34,950</td>
<td>28,410</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>33,130</td>
<td>21,650</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>25,310</td>
<td>7,250</td>
</tr>
<tr>
<td>Leukemia</td>
<td>25,180</td>
<td>21,260</td>
</tr>
<tr>
<td>Pancreas</td>
<td>18,770</td>
<td>19,090</td>
</tr>
<tr>
<td>All Sites</td>
<td>745,180</td>
<td>692,000</td>
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</table>

*Estimated New Cases data 2011*

### Estimated Deaths

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>90,810</td>
<td>71,030</td>
</tr>
<tr>
<td>Prostate</td>
<td>28,860</td>
<td>40,480</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>24,260</td>
<td>25,700</td>
</tr>
<tr>
<td>Pancreas</td>
<td>17,500</td>
<td>16,790</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>12,570</td>
<td>15,520</td>
</tr>
<tr>
<td>Leukemia</td>
<td>12,460</td>
<td>9,370</td>
</tr>
<tr>
<td>Esophagus</td>
<td>11,250</td>
<td>9,250</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>9,950</td>
<td>7,470</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>9,790</td>
<td>5,840</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>8,100</td>
<td>5,650</td>
</tr>
<tr>
<td>All Sites</td>
<td>294,120</td>
<td>271,530</td>
</tr>
</tbody>
</table>

*Estimated Deaths data 2011*
Breast Cancer

- 200,000 new cases diagnosed yearly
- ~40,000 deaths per year
- Lifetime risk: 12.6% for invasive breast cancer

Risk Factors:
- Familial/Genetic
- Age, Reproductive history
- Environmental Factors → thoracic RT<30 yrs, HRT
- Other Factors → atypia, breast density, BMI, LCIS
SEER Data: Decrease in Breast Cancer Mortality
How Much Breast and Ovarian Cancer Is Hereditary?

Breast cancer
- Sporadic
- Family clusters
- Hereditary

Ovarian cancer
- ~10% hereditary
## Hereditary Breast Cancer Genes:

<table>
<thead>
<tr>
<th>GENE</th>
<th>Syndrome</th>
<th>RR of Breast Ca</th>
<th>Ca Risk by 70 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High penetrance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>HBOC</td>
<td>14-32 X</td>
<td>39-87%</td>
</tr>
<tr>
<td>BRCA2</td>
<td>HBOC</td>
<td>10-19 X</td>
<td>26-91%</td>
</tr>
<tr>
<td>P53</td>
<td>Li-Fraumeni</td>
<td>1.5-6.0 X</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>PTEN</td>
<td>Cowdens</td>
<td>2-4 X</td>
<td>25-50%</td>
</tr>
<tr>
<td>STK11/LKB1</td>
<td>Peutz-Jeghers</td>
<td>15 X</td>
<td>45-54%</td>
</tr>
<tr>
<td>CDH1</td>
<td>Hereditary Diffuse Gastric Cancer</td>
<td>3.25 X</td>
<td>39%</td>
</tr>
<tr>
<td><strong>Low-Moderate Penetrance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATM</td>
<td>Ataxia-Telangiectasia</td>
<td>3-4 X</td>
<td>n/a</td>
</tr>
<tr>
<td>CHEK2</td>
<td>Li-Fraumeni Variant</td>
<td>2 X women;</td>
<td>n/a</td>
</tr>
</tbody>
</table>

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BRCA 1 & 2 Genes

- Breast Cancer Gene 1 (1994)
  - Chromosome 17q21 – 5.6kb/22 exons
  - Chromosome 13q12 – 10.2kb/26 exons
- Number of mutations reported >1200
- Autosomal dominant inheritance
- Both genes normally function as tumor suppressor genes
BRCA1-2 Mutations Increase the Risk of Cancer More Than Other Factors

Relative risk of breast cancer

- BRCA1-2 mutation
- Early menarche
- Late age at birth of 1st child
- Benign breast disease
- Hormone replacement therapy
- Alcohol use
- Family history
# BRCA1/2 Mutations: Lifetime Cancer Risks

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer to age 80</td>
<td>55-87%</td>
<td>50-80%</td>
</tr>
<tr>
<td>Ovarian cancer to age 80</td>
<td>20-44%</td>
<td>up to 27%</td>
</tr>
<tr>
<td>Male breast cancer</td>
<td>&lt;6%</td>
<td>6-8%</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Slight incr.</td>
<td>20%</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>2-4%</td>
<td>3-6%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Min incr.</td>
<td>Slight incr.</td>
</tr>
</tbody>
</table>
Cancer Risk Estimates for \textit{BRCA1} and \textit{BRCA2} Mutation Carriers from Unselected Families

Cumulative risk of breast (\textbullet) and ovarian (\textblacksquare) cancer

Fig 1: \textit{BRCA1} mutation carriers

Fig 2: \textit{BRCA2} mutation carriers


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BRCA1 vs BRCA2 Risks of Breast and Ovarian Cancers

NEJM 2007;357(2)154

Figure 1. Probability of Breast Cancer and Ovarian Cancer during a 10-Year Period.
Data were adapted from Chen and Parmigiani.10
BRCA1 and BRCA2 Mutations in the Ashkenazi Jewish Population

An estimated 1 in 40 Ashkenazi Jews carries a BRCA1 or BRCA2 mutation.

BRCA1

185delAG
Prevalence = \(~1\%\)

5382insC
Prevalence = \(~0.15\%\)

BRCA2

6174delT
Prevalence = \(~1.5\%\)

BRCA1&2: Function

- Tumor Suppressor Genes
- Maintain genomic stability
  - Repair of double-stranded DNA breaks
    - Through recombination with undamaged homologous strands (Homologous Recombination)
    - Mutations interfere with DNA repair → accumulation of chromosomal abnormalities
- Associated with Fanconi Anemia genes
Features That Indicate Increased Likelihood of Having BRCA Mutations

- Multiple cases of early onset breast cancer
- Ovarian cancer (with family history of breast or ovarian cancer)
- Breast and ovarian cancer in the same woman
- Bilateral breast cancer
- Ashkenazi Jewish heritage
- Male breast cancer
Family History of Hereditary Breast and Ovarian Cancer

**Hereditary**
- Two or more women with breast cancer before age 50 or ovarian cancer at any age
- One woman with breast cancer before age 50 or ovarian cancer at any age, plus Ashkenazi ancestry

**Sporadic**
- None of the breast cancer is diagnosed before age 60
- No ovarian cancer
- No clear pattern on one side of family or other
Clinicopathological Findings in Mutation Carriers: Breast Cancer

- **BRCA1**:  
  - Medullary histology more common  
  - High rate of ER/PR negativity (70% ER/PR negative)  
  - High nuclear grade  
  - Basaloid cell type by microarray  
  - erbB-2 positivity less common

- **BRCA2**:  
  - No “typical” phenotype  
  - ER/PR profile similar to sporadic cases (70% ER/PR+)
-Prognosis similar to sporadic breast cancer-
Clinical Questions

- Is there a genetic predisposition to breast cancer in this family?
- Should this patient undergo genetic testing?
- Which gene test(s) should be ordered?
- Can her risk of cancer be lowered?
- What are the implications of risk-reducing interventions for her health?
- Should other family members be tested?
- Are there insurance ramifications of genetic testing?
Consensus Guidelines Regarding Genetic Testing for Hereditary Cancer

- ASCO
- USPTF
- ACS
- NCCN
- NSGC

- Uniform guidelines issued regarding pre and post-test counseling
- Recognition of cancer syndromes
- Management recommendations
American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility

Robson, M et al JCO 28(5) 2/10/10

- Education and training of physicians
- Pre-test/post-test counseling
- Access to clinical trials
- Informed consent
- DTC
- Federal oversight/standards for accuracy, validity, quality of genetic/genomic tests
Genetic Predisposition Testing Is a Multistep Process

Identify at-risk patients
Provide pretest counseling
Provide informed consent
Select and offer test
Disclose results
Provide posttest counseling and follow-up

Interpreting Test Results

- Positive for a deleterious mutation

- No mutation detected
  - Mutation previously identified in the family – “true negative”
  - No known mutation in family – “uninformative negative”

- Variant of uncertain clinical significance (VUS)
Management Options for *BRCA1/2* Mutation Carriers

- Increased Surveillance
- Prophylactic Surgery
- Chemoprevention
Increased Surveillance
# Surveillance for Breast Cancer

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Age to begin</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast self-exam</td>
<td>18 yrs</td>
<td>Monthly</td>
</tr>
<tr>
<td>Clinical breast exam</td>
<td>25 yrs</td>
<td>6 months to a year</td>
</tr>
<tr>
<td>Mammography</td>
<td>25 yrs</td>
<td>Yearly</td>
</tr>
<tr>
<td>MRI</td>
<td>25 yrs</td>
<td>Yearly</td>
</tr>
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</table>

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Efficacy of MRI and Mammography for Breast Cancer Screening in Women with a Familial or Genetic Predisposition

- 1909 high risk women, including 358 BRCA1/2 mutation carriers
- **Sensitivity, specificity**
  - Clinical Exam – 18%, 98%
  - Mammography – 33%, 95%
  - MRI – 79%, 90%
- MRI detected smaller lesions
- MRI – twice as many additional exams and three times as many biopsies

NEJM 2004
MRI Screening

- ACS guidelines for Breast Cancer Screening with MRI
  (March/April ‘07 CA: A Cancer Journal for Clinicians)

- BRCA mutation carriers (& 1º relatives)
- Lifetime risk 20-25% or more
- Li-Fraumeni, Cowden (& 1º relatives)
Prospective, multicenter trial

Women with familial increased risk for breast cancer

Screening Protocol:

- CBE, mammo, U/S, MRI
EVA Trial (cont)

- MRI proved most important screening test
  - Cancer yield with MRI higher than mammogram, U/S, or both
  - Confirms prior data on importance of MRI

- MRI alone preferred for women <30 and BRCA+
  - Mammogram sensitivity low in BRCA1-associated cancer
  - Lower radiation exposure

- Addition of U/S or CBE did not contribute to earlier diagnosis
Surveillance for Ovarian Cancer

- Semi-annually, starting at age 25-35:
  - CA-125
  - Pelvic exam
  - Transvaginal ultrasound with Doppler

- No data showing that surveillance lowers mortality from ovarian cancer
Screening for Other Cancers

- Prostate – PSA, DRE at age 40 yrs
- Male breast – Breast Self Exam, Clinical Breast Exam, Mammogram if gynecomastia
- Pancreas – no data
  - Consider EUS in high risk families
Prophylactic Surgery
Bilateral Mastectomy in High Risk Women

- 639 high risk women
  - Landmark trial

- Prophylactic bilateral mastectomy

- 90% risk reduction in breast cancer risk

Hartmann et al, NEJM 99(340)77
Mastectomy Reduces Risk of Breast Cancer in *BRCA* Mutation Carriers

Bilateral Prophylactic Mastectomy Reduces Breast Cancer Risk in *BRCA1* and *BRCA2* Mutation Carriers: The PROSE Study Group

Timothy R. Rebeck, Tara Friebel, Henry T. Lynch, Susan L. Neuhausen, Laura van ’t Veer, Judy E. Garber, Gareth R. Evans, Steven A. Narod, Claudine Isaacs, Ellen Matloff, Mary B. Daly, Olufunmilayo I. Olopade, and Barbara L. Weber
Prophylactic Mastectomy

Rebbeck, et al JCO 2004;22(8)1055

- 483 Women with BRCA1/2 mutations
  - 105 – prophylactic mastectomy
  - 378 - controls
- F/U duration – 6 yrs
- 90% reduction in risk of breast cancer
  - 95% reduction if also had oophorectomy <40 years
Deciding on Prophylactic Mastectomies

Cancer Free, but Weighing a Mastectomy

By AMY HARMON

CHICAGO — Her latest mammogram was clean. But Deborah Lindner, 33, was tired of constantly looking for the lump.

Ever since a DNA test had revealed her unusually high chance of developing breast cancer, Ms. Lindner had agonized over whether to have a mastectomy, a procedure that would reduce her risk by 90 percent.

She had stared at herself in the mirror, imagining the loss of her familiar shape. She had wondered, unable to ask, how the man she had just started dating would feel about needing that also.

Deborah Lindner, 33, faced family tumult as she considered surgery after a genetic test revealed a high breast cancer risk.

A Lindner family chart showing the path of breast and ovarian cancer in relatives, and those who had died.

THE DNA AGE
Changing the Odds

learned early that they are genetically prone to breast cancer; and have the chance to act before it strikes.

As they seek to avoid the potentially lethal consequences of a mutant gene, many of them turn to relatives who share its burden. But at a moment when a genetic test has made family ties even more tangible, they are often at their most strained.
Prophylactic Oophorectomy

- Reduces risk of ovarian cancer by ~90% in women with BRCA mutations
  - More effective in BRCA1*
- Reduces risk of breast cancer by 50-75%
  - More effective in BRCA2*
- Replacement estrogen did not negate effect
- Strongly recommended after childbearing

*JCO 08;26(8)
Multicenter cohort study – PROSE

2482 women with BRCA1/2 mutations

Goal: estimate risk and mortality reduction
Benefits of risk-reducing surgery (RRSO)

- RRSO → reduction in all cause mortality (HR 0.40)
  - Reduction in breast cancer-specific mortality (HR 0.44)
  - Reduction in ovarian cancer-specific mortality (HR 0.27)

*JAMA. 2010;304(9):967-975*
HRT after RRSO in *BRCA* carriers

- Short term (2-3 yrs) HRT after oophorectomy in premenopausal women did not increase breast cancer risk
- Safe option for patients with symptoms of estrogen deficiency

Rebbeck et al JCO 05;23(31).
Chemoprevention
Tamoxifen Chemoprevention

- NSABP-P-01 Trial
- 13,388 high risk women
  - Gail Model >1.67
  - Tamoxifen vs Placebo
- 49% reduction in breast cancer risk
- Decrease in osteoporotic fractures
- Increase in endometrial cancer, DVT, PE (if >50 y/o)

Fisher et al JNCI 90;1371, ‘98
NSABP-P-1 Trial – BRCA+ Patients

- 280 Cases of Breast cancer
- 19 patients (6.6%) had BRCA1/2 mutations
- Trend to protective effect of Tam in BRCA2 carriers
  - BRCA1 carriers more often ER-negative
    - Tamoxifen less effective

King et al JAMA ‘01
Tamoxifen Lowers Contralateral Breast Cancer Risk in \textit{BRCA1/2} Mutation Carriers

- 491 women with breast cancer and \textit{BRCA1/2} mutation
- Risk of contralateral breast cancer $\rightarrow$ 40\% at 10 yrs
- Tam lowered contralateral breast cancer by up to 40\%

Narod et al JCO 04;22(12).
Chemoprevention of Breast Cancer: Future Directions

- Other SERMs: Raloxifene
  - STAR Trial - Tam vs Raloxifene in high risk women
    - Both drugs lower risk
    - Raloxifene – better side effect profile
    - FDA approved 9/07

- Aromatase Inhibitors
  - Arimidex - decreases contralateral breast cancers
    - Effective in tx of invasive breast cancers
    - Studies underway in DCIS
    - Benefit in BRCA carriers not known
Chemoprevention of Ovarian Cancer

Oral Contraceptives

- Up to 60% risk reduction for ovarian cancer in general population
- BRCA+ patients – similar benefit
- Breast Cancer Risk (?) → Minimal

NEJM 1998; 339:424-8
NEJM 2001;345:235-40
JNCI 2002;94:1773-9
Cancer Epidemiol Biomarkers Prev. 2005
Feb;14(2):350-6
Treatment of BRCA-related Cancers: Future Directions

- DNA repair defect
  - Cisplatin \(\rightarrow\) induces DNA breaks \(\rightarrow\) cell death

- PARP inhibitors
  - PARP (Poly-ADP Ribose polymerase)
    - Protein required for repair of ss-DNA breaks
  - Target DNA repair pathway to specifically kill malignant cells in BRCA carriers

- Phase III Clinical trials underway
BRCA Negative Patients: Are they high risk?

- BRCA True negative: Known mutation in family.
- Unknown ➔ no mutation seen in family
  - May still be high risk
Pedigree 2: True Negative
Pedigree 3: 
*BRCA* negative, but HIGH risk still
Breast Cancer Risk Assessment Models

- Gail Model
  - 1° relatives, reproductive history, atypia
- Claus
  - 1° and 2° relatives, age of diagnosis
- Tyrer-Cuzick
  - 1° and 2° relatives, age of diagnosis, hormonal factors
- BRACAPRO
  - Based entirely on probability that the individual carries a \textit{BRCA} mutation
High risk BRCA Negative pts Management

- High-risk surveillance for breast cancer:
  - MRI screening (ACS guidelines)/Mammo
    - > 20% risk
  - Clinical breast exams/BSE
  - Access to clinical trials

- Risk-reducing strategies:
  - Tamoxifen
  - Prophylactic mastectomies
The Search for Other Genes...
Easton et al Nature 6/07
Genome-Wide Association Study

- BRCA1/2 account for ~25% of all cases of hereditary breast cancer
- Genetic linkage studies have not shown other major breast cancer genes
- Hereditary breast cancer is “polygenic”
  - i.e. large # of loci, each with a small effect on breast cancer risk (CHEK2, ATM, PALB2)
- Recent technological advances:
  - Platforms to analyze thousands of SNPs
  - Putative novel genes associated with risk of breast cancer
    - FGFR2, TNRC9, MAP3K1, LSP1
Figure 2. Breast-Cancer Susceptibility Loci and Genes.
Cancer Genetics: Future Directions

- Low penetrance genes – *CHEK2, PALB2*
- Gene modifiers/SNPs
  - e.g. FGFR2 – 1.5 X increase in risk
- Targeted Therapies
  - Example: PARP inhibitors
- Optimal screening
- Chemoprevention
- Other: exercise, diet, BMI etc
Legislation on Genetic Discrimination

**GINA** = Genetic Information Nondiscrimination Act of 2008

*Legal protection against discrimination based on genetic information*

- Prohibits employment and health insurance discrimination *(both private & group insurances)*
- Prohibits insurers from requiring genetic testing; individuals cannot lose insurance due to testing

www.geneticfairness.org
Mutant Jeans