

# Pre-gestational Genetic Diagnosis A Promising Prevention Strategy

ESGO-19, Nice, France

**Uziel Beller, MD**

**Professor and Chairman  
Department of Gynecology  
Shaare Zedek Medical Center  
Hebrew University of Jerusalem, Israel**



# Mortality from Ovarian Cancer..

- Has not changed over the past three decades and remains **the highest** of all gynecological cancers.
- Aggressive surgery, chemotherapy and biological tailored treatments had an impressive effect on **median survival** but the cure rates remain disappointingly low

# Female Cancer - 2010 Global

| <b>Cancer</b>          | <b>Global</b>    |
|------------------------|------------------|
| <b>Breast</b>          | <b>1,383,000</b> |
| <b>Cervix</b>          | <b>530,000</b>   |
| <b>Uterus</b>          | <b>287,000</b>   |
| <b>Ovary</b>           | <b>225,000</b>   |
| <b>Ovary Mortality</b> | <b>140,000</b>   |

**“An ounce of Prevention is worth a  
pound of cure”**

**Benjamin Franklin (1706-1790)**

**Are we, care takers, ready to move to  
Cancer Prevention  
scientifically, medically & conceptually ?**

# **Genetic Predisposition to Cancer**

## **Personalized Cancer Medicine**

**Genetic and Genomic changes i.e. mutations, copy number of individual genes or subsets of genes, chromosomal aberrations - translocations, insertions, deletion inversions, expression patterns and epigenetic changes which, alone or in combination, increase the individual's risk to develop cancer during lifetime.**

**Genomics – based “personalized medicine” widely hailed yet very limited evidence based applications for medicine.**

**Most genomic scientific discoveries did not move into practice and “lost in translation”**

**Hereditary Breast & Ovarian Cancer i.e.**

**BRCA 1/2 & other genes are an exception.**

# Four successive phases for translation Implementation of Genomic Medicine

Khoury et al. Genet Med. 2008

- a) **Discovery of a gene related to a particular disease and developing a **reliable** genetic test.**
- b) **Development of clinical guidelines based on the health value of genetic test; **cancer risk in carriers i.e. RR****

- c) **Moving evidence – based guidelines**  
i.e. how to **implement genetic testing.**
- d) **Evaluating the “real world”, health outcome of implementing a genetic intervention.**  
**Genetic screening and related change in mortality.**

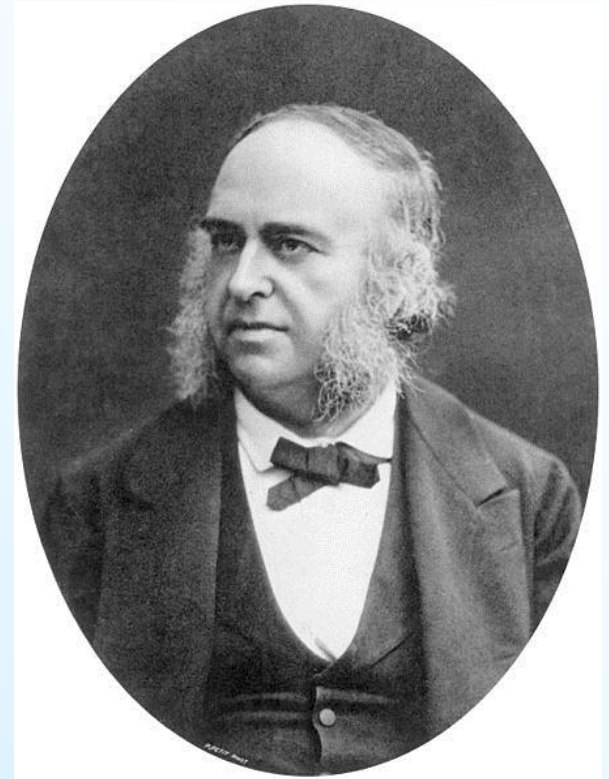


# Paul Broca (1824-1880)

Founder of neurosurgery

**1866; Trait des Tumeurs**

**“A daughter may be born long before her mother and maternal grandmother develop breast cancer, the daughter to develop it, herself, many years later..”**



# The purpose of the testing

- To identify patients with specific disease characteristics & potential **personalized** treatments (PARP inhibitors)
- To reach & identify **family members** to whom early detection & prevention measures could be offered
- **Unborn as well?**

**Theoretically, if ...**

**24%** genetic predisposition to ovarian cancer could be identified **and all preventive measures accepted**, there is a potential for **33,600** lives saved...

# United States Preventive Services Task Force

**There is no existing method of ovarian cancer screening that helps reduce deaths**

**Sept, 2012**

**“Maybe” Stage shift**

# Preventive measures

**Oral contraception**

**Risk Reducing BSO**

**Risk Reducing Bilateral Salpingectomy**

**Prenatal Diagnosis (CVS, Amniocentesis)**

**Pre-gestational Genetic Diagnosis (PGD)**

- **Should we intervene by preventing the birth of BRCA  $\frac{1}{2}$  or other genetic deleterious mutation carriers?**
- **A very complicated medical, ethical, legal and emotional issue.**

# Hereditary Breast and Ovarian Cancer: Y do we forget about dad?

**Barry Rosen et al**  
**The Lancet Oncology**  
**October 25, 2010**

**...be aware & careful !!**

# Pre-Conception new dilemmas facing a couple with a BRCA mutation

- **Should/can we prevent another BRCA carrier?**
- **Do all carriers carry the same risk for Breast/Ovarian cancer?**
- **Does our family history make a difference?**
- **What is involved in such a decision?**
- **Do these treatments endanger our baby?**



# More questions..

- **Can we select sex at the same time?**
- **What should we do with male embryos who carry the mutation?**
- **What if “they” find a cure for cancer in 20 years?**
- **Can it harm the mother?**
- **How much does it cost & Can we afford all this?**

# The “parents to be” are also influenced by a long list of variables

- **Personal/family experience with Breast/Ovarian cancer**
- **Previous pregnancies prior to revealing the carrier state**
- **Who is the carrier, he or she?**
- **Religious/Ethical beliefs**
- **Parents age and prior fertility problems**
- **Ability to understand this complex issues**

**The fact is..**

**Doctors, cannot answer all the questions and must only provide the current accurate knowledge available.**

**It may not be enough!**

**All choices have a downside!**

# Prenatal Preventive Measures

1. **Amniocentesis** : – **Late TOP**
  2. **Chorionic Villi Biopsy (CVS)**: – **Early TOP**
  3. **Pre-Implantation Genetic Diagnosis (PGD)** –  
**with IVF-ET** : **no abortion needed**
- **In fact interest in prevention grew with the introduction and availability of PGD**
  - **Freezing technology, delaying pregnancy**

# Pre-implantation Genetic Diagnosis



**Cutting edge technology in  
personalized preventive medicine**

# **BRCA mutation carriers do not have compromised ovarian reserve.**

Michaelson-Cohen R., Mor P., Srebnik N., Beller U.,  
Levy-Lahad E., Eldar-Geva T.

Int. J Gynecol Cancer, 2014 Feb; 24(2): 233-7.

# ***BRCA* mutation carriers show normal ovarian response in in vitro fertilization cycles**

Moran Shapira, B.Med.Sc., Hila Raanani, M.D., Baruch Feldman , M.D.,Ph.D.,  
Naama Srebnik, M.D., Sanaz Dreck-Haim, B.Sc., Daphna Manela, R.N.B.A.,  
Masha Brenghausen, Ph.D., Liat Geva-Lerner, M.D.,Ph.D., Eitan Friedman, M.D.,  
Efrat Levi-Lahad, M.D., Ph.D., Doron Goldberg, M.D., Tamar Perri, M.D.,  
Talia Eldar-Geva, M.D., Ph.D., Dror Meirow, M.D.

Fertil Steril 2015 .Aug 31.

# **Fertility treatments and invasive epithelial ovarian cancer risk in Jewish Israeli BRCA1 or BRCA2 mutation carriers**

Tamar Perri, M.D., Dror Lifshitz, M.D.,  
Siegal Sadetzki, M.D., M.P.H., Bernice Oberman, M.Sc.,  
Dror Meirow, M.D., Gilad Ben-Baruch, M.D.,  
Eitan Friedman, M.D., Ph.D., Jacob Korach, M.D

**Fertil Steril. May 2015, Vol. 103 Issue 5, 1305-1312**



# PGD in SZMC

Prof. T Eldar-Geva; MD PhD



**380 babies**

**Clinical  
Pregnancy rate  
per ET**

**37%**

## PGD for BRCA1/2 in SZMC 10/2009 – 12/2014

|          | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 1-6/2015* |
|----------|------|------|------|------|------|------|-----------|
| # cycles | 1    | 12   | 15   | 31   | 26   | 55   | 48        |

**\*2015 is not included in the statistics (no deliveries yet)**

**43 couples**

**5 women aged 38-41 had 16 OPU cycles – no pregnancy.**

## All subsequent data for 37 women aged <38 years at OPU (mean 30.5; range 26-37.5)

2 patients had PGD for other diseases in addition to BRCA (CF, FRAX).

**5 patients recovered from breast cancer.**

|                     |    |
|---------------------|----|
| BRCA1:              | 23 |
| BRCA2:              | 13 |
| BRCA 1+2:           | 1  |
| Male BRCA:          | 5  |
| IVF for infertility | 8  |

**All cycles (2009-2014) 123**

OPU cycles 85

Cryo cycles 38 (31% of cycles)

## ET cycles

95

Fresh ET

58 (68% of OPU)

Cryo

37 (97% of thawed-embryo cycles)

**Clinical pregnancies 31** (33% per ET; 36.5% cumulative per OPU)

Deliveries

26 ( 20 singletons, 6 sets of twins)

Babies

32

**21/37 women had live birth (57%)**

# A PATIENT HISTORY

**35 years old. G<sub>2</sub>P<sub>2</sub>, nursing**

- **Mother Diagnosed with Ovarian Cancer at age 34(!), died at age 36.**
- **Grandmother – Breast Cancer**
- **At age 16: BRCA<sub>1</sub> mutation carrier (1996)**
- **Followed and on OC.**
- **Achieved pregnancy 2010 with PGD. male BRCA<sub>1</sub> carrier**
- **RRBS 2011**
- **Second PGD : Healthy non-carrier baby girl 2012**
- **RRBO 12/2012**
- **RR Mastectomy pending**