

Biology Response Controversies and Advances
in **BRCA** related ovarian cancer

Lessons learned and future directions

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BREAST-CANCER BREAKTHROUGH

WEDNESDAY, SEP. 14, 1994

“The gene found today -- BRCA1 -- may also raise the risk of contracting ovarian cancer”.

Mutation testing - Evolution from Genetic Counselling to a greater understanding of the biology of Ovarian cancer

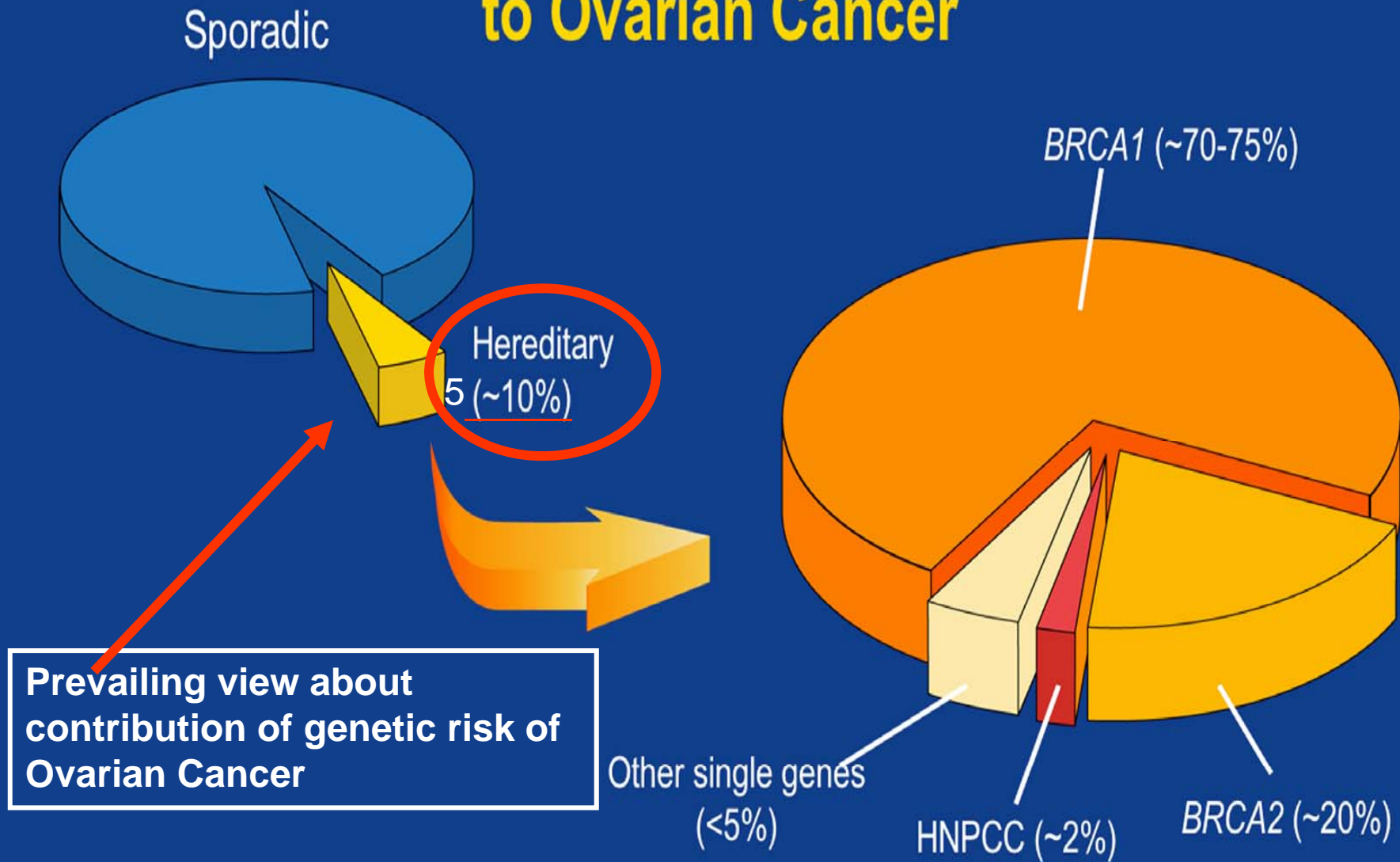
Lessons Learned

- The importance of a family history
- The contribution of BRCA mutations to ovarian cancer
- Revised criteria for referral for genetic testing and the emerging role for rapid testing
- Understanding that ovarian cancer is not one disease- pathological insight- NEW models
- Ovarian cancer is not “ ovarian cancer” in BRCA mutation carriers

Lessons Learned

- The futility of screening
- Risk reduction and prevention of ovarian cancer- What works and when to do BSO
- BRCA as a prognostic factor
- BRCA- and drug sensitivity and resistance- mechanisms and insights
- Targeted treatments- PARP inhibitors – emerging new paradigm for BRCA related ovarian cancer

Causes of Hereditary Susceptibility to Ovarian Cancer



Ovarian Cancer

Population BRCA1 and BRCA2 mutation frequencies and cancer penetrance: a kin-cohort study in Ontario, Canada -1171 patients

- 14% of epithelial ovarian cancers due to germ-line mutations in BRCA 1 or 2
- 18% of women with high grade serous cancers had BRCA mutations
- 21% of women ages 40-50
- Ethnic variations*
- Family history*

Ethnicity and BRCA Mutations

- 208 Ashkenazi women with ovarian cancer unselected for age or family history
- A total of 86 founder mutations were found among the 208 patients (**41.3%**)
- 57 in *BRCA1* (43 in 185delAG and 14 in 5382insC)
- 29 in *BRCA2* (6174delT).

Popular misconceptions

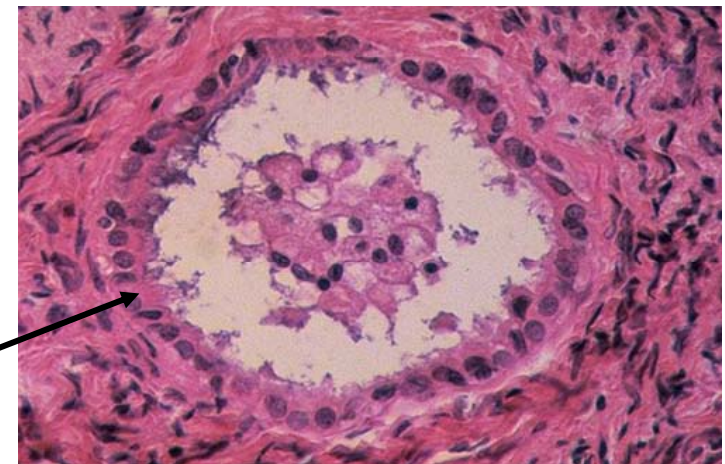
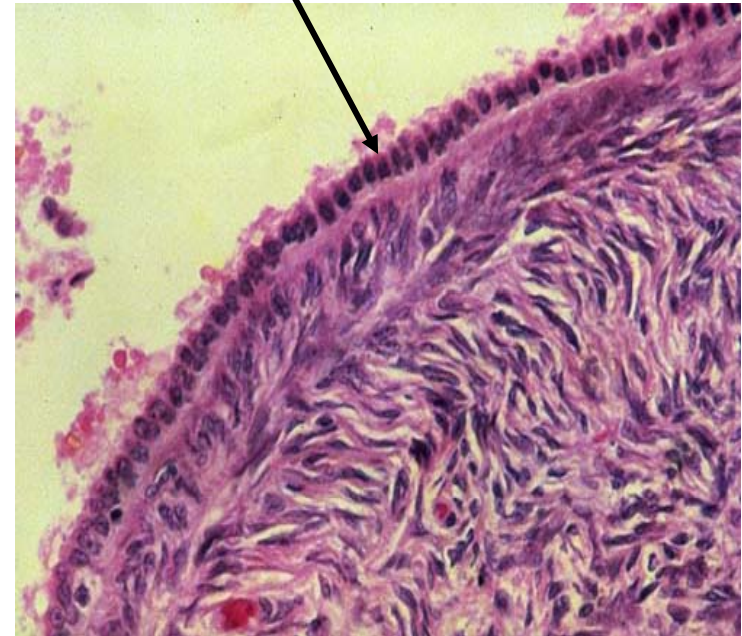
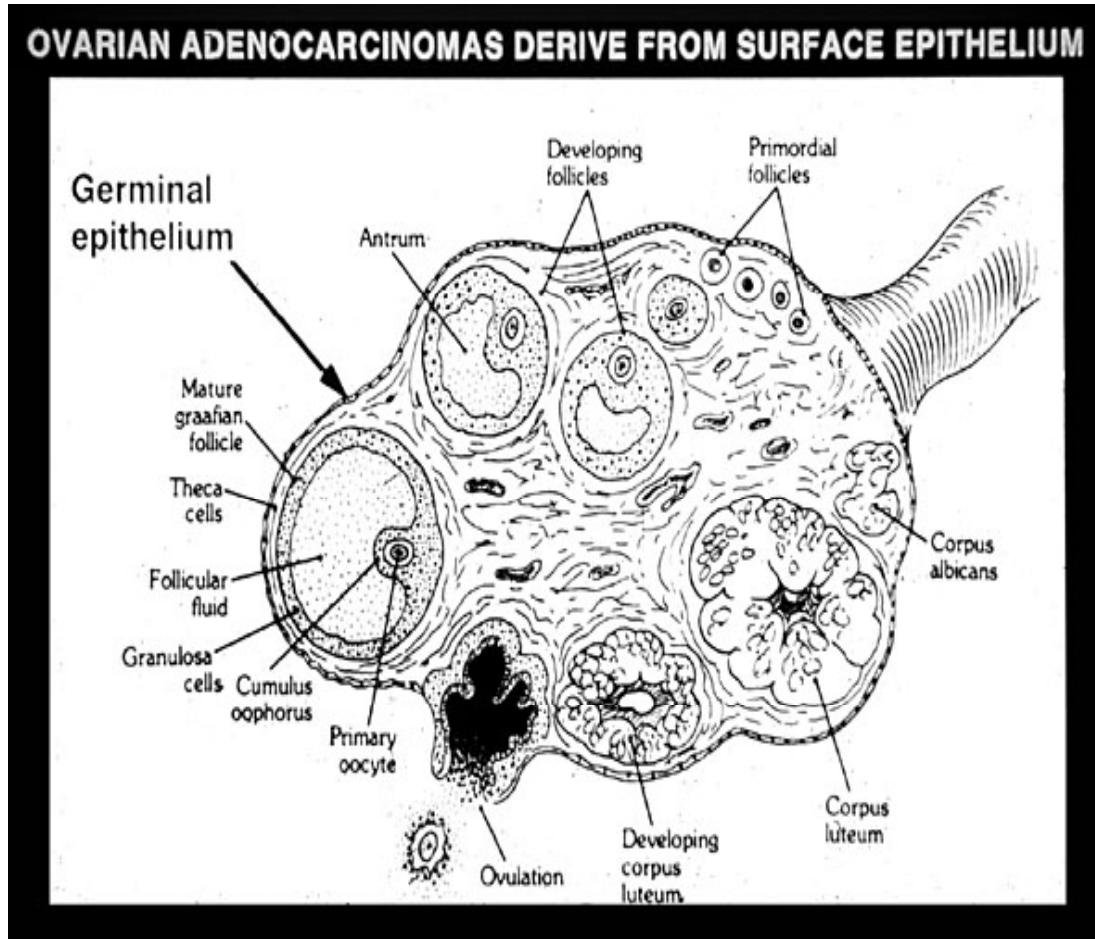
That have directed screening of ovaries particularly in BRCA related ovarian cancer

- **Early stage ovarian cancers are chronologically early in their natural history**
- **That the favourable outcome of women with stage 1 ovarian cancer is related to early diagnosis**

Origin of “Ovarian Cancer”

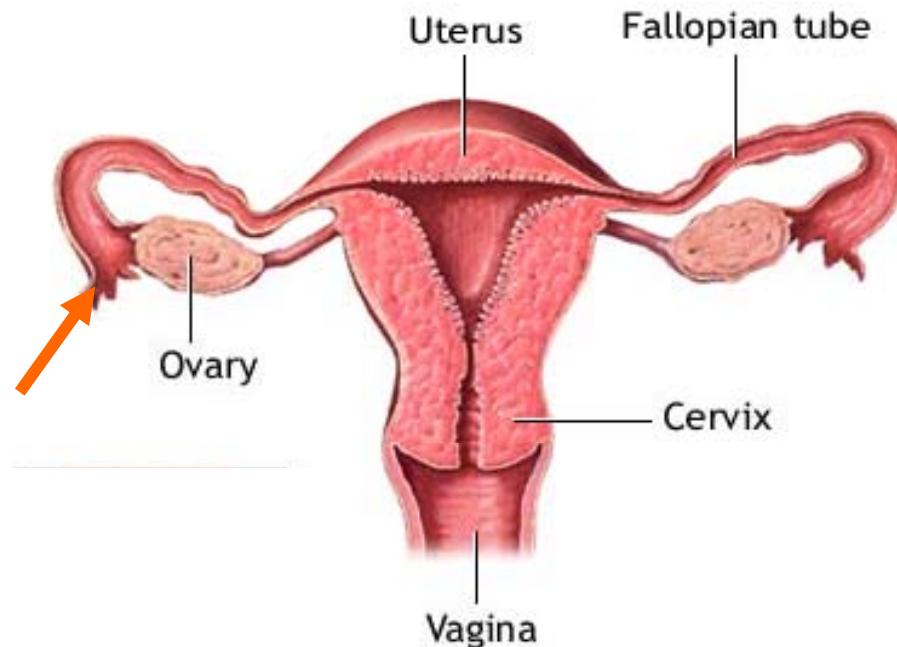
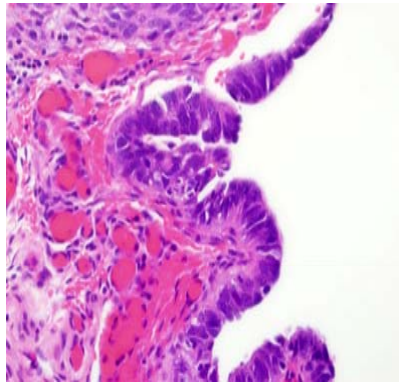
Implications for Screening and Management of women at increased risk

The prevailing paradigm



Prophylactic BSO

Unique opportunity to observe the early events of serous carcinogenesis in BRCA mutation carriers



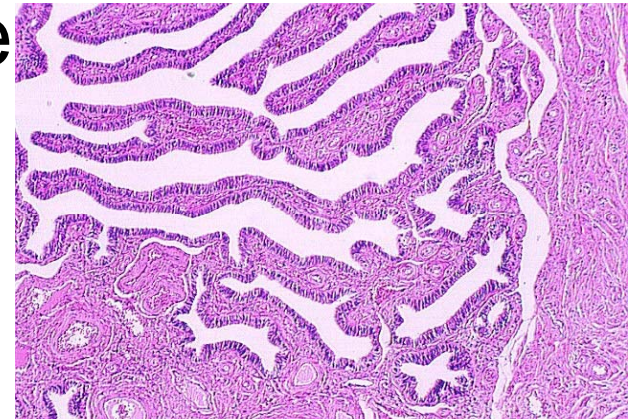
ADAM.

The Fallopian Tube

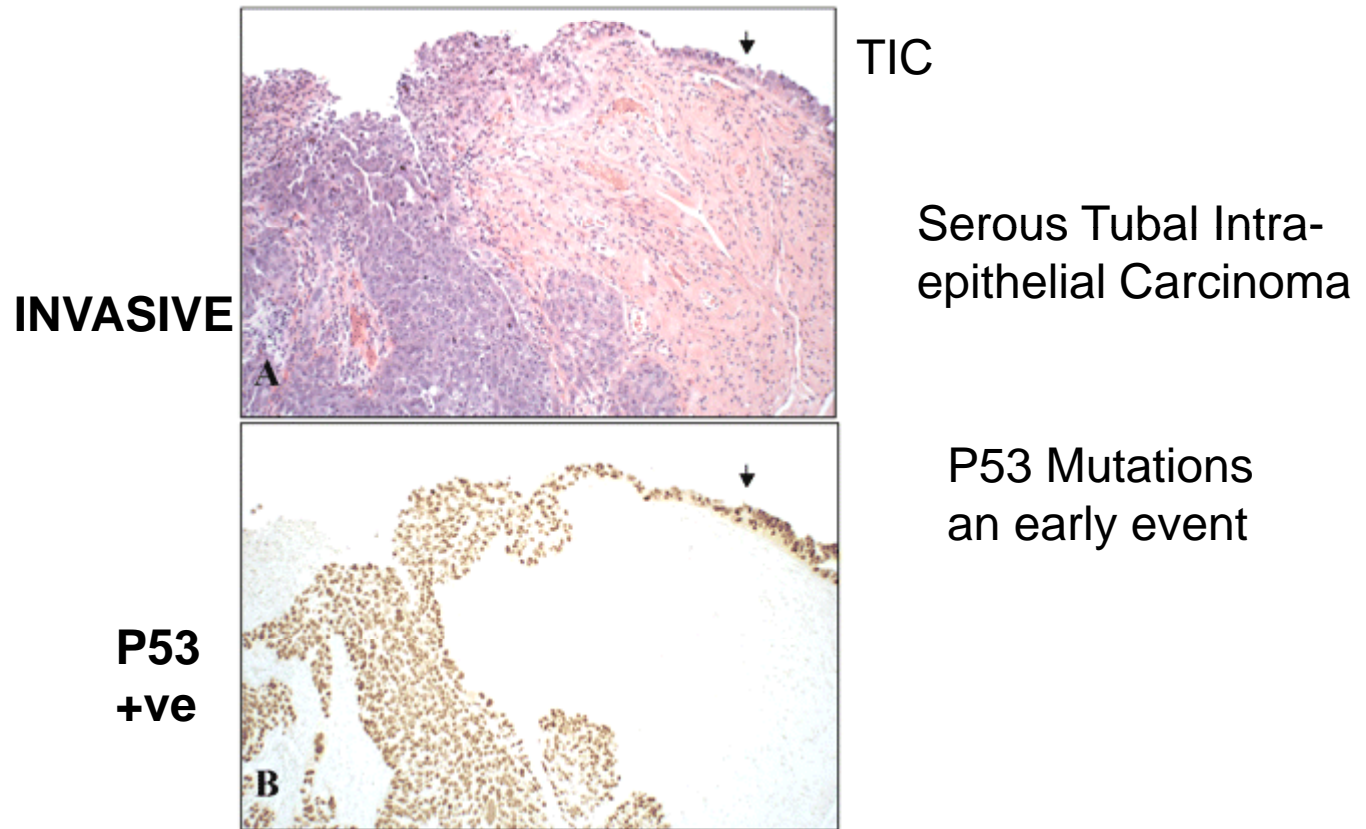
- 2-17% of women with BRCA mutations having PBSO have occult cancers
- Most commonly in the fallopian tube
- Some only Tubal In-situ Carcinoma (TIC)
- Variation probably due to the extent with which the tubes are sampled
- The frequency contrasts dramatically with accepted incidence of ovarian: tubal cancers(50:1)

The Fimbria as the preferred site for early serous cancer

- Less commonly recognized as not the typical presentation of a tubal cancer
- Spread rapidly to other sites and/ become complexed with the ovary
- Unique region-large surface area and exposed to biological events that also impact on the ovarian surface
(Genotoxic effect of ovulation)



TIC-arising in the fimbria of BRCA + and merging with invasion



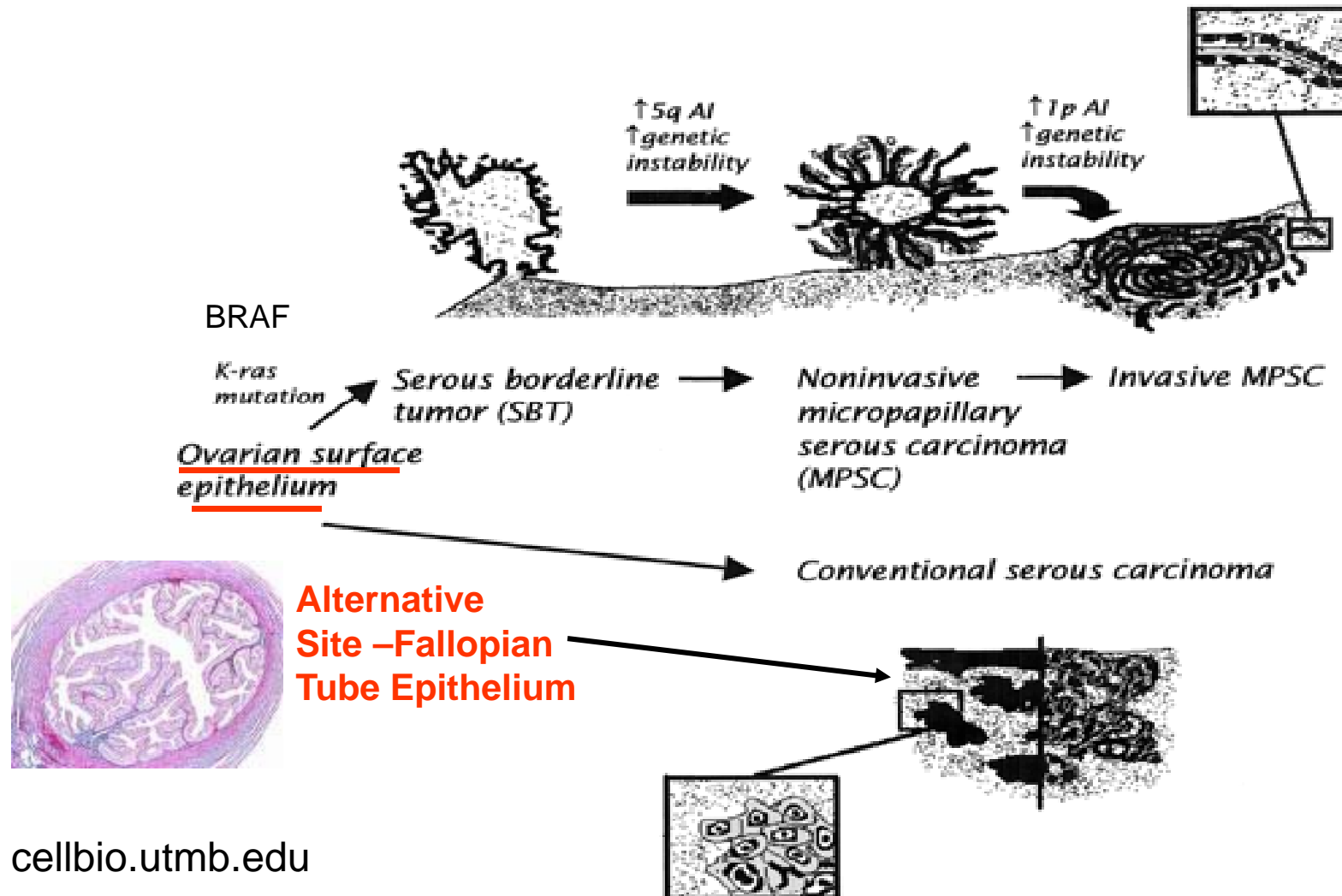
Origin of “Ovarian” Cancer

2 distinct pathways and possible origins

1. **OSE-mullerian inclusion-** endosalpingiosis/invagination of OSE during repair following ovulation/implantation of cells from endometrium /fallopian tube - typically multi-step pathway and account for many early stage cancers- **slow process**
2. **Rapid development** –P53 mutations- express a phenotype that closely resembles fallopian tube mucosa- **BRCA related**

Dualistic Model- for Serous Cancer

Singer et al





Ovarian Cancer Screening Guidelines V1. 2008

“Recommend concurrent TVUS and CA12-5 every 6 months starting at age 35

or 5-10 years earlier than earliest age of first diagnosis of ovarian cancer in the family”

What is this advice based on ?

Where is the evidence?

Summary of Published Studies up to 2004

TOTAL 7600 “women at increased risk” screened

46 invasive cancers diagnosed-

? **15 stage 1-2** invasive EOC

31 advanced/peritoneal

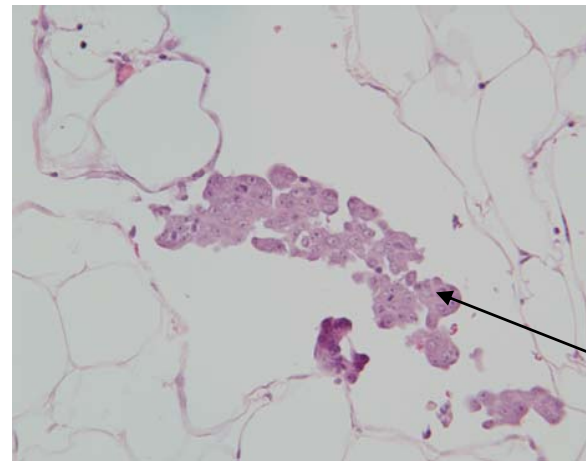
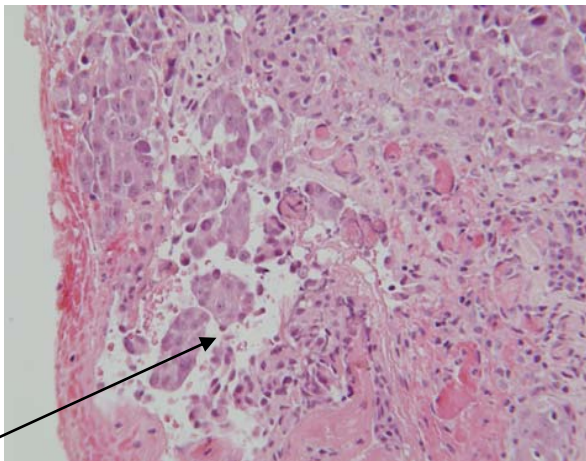
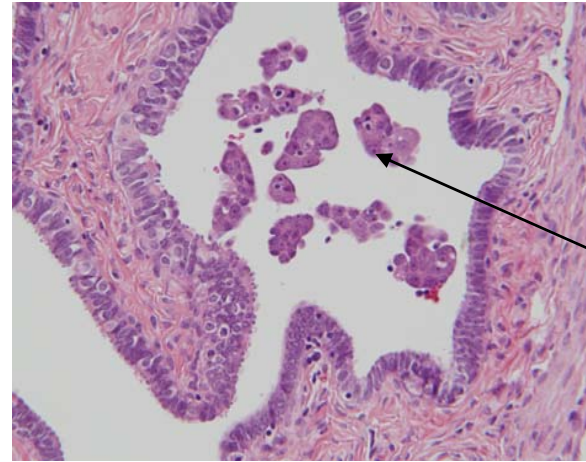
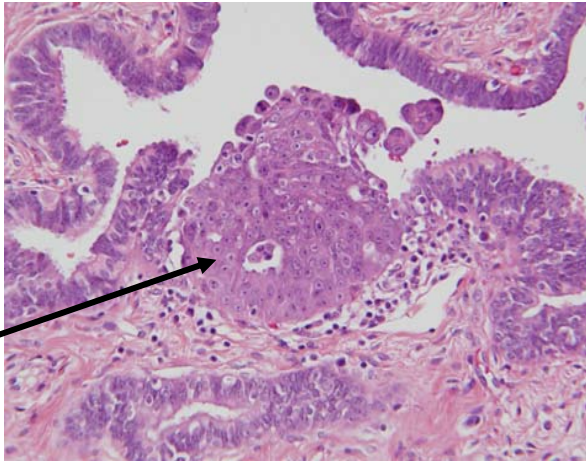
15 Borderline stage 1

1 Granulosa stage 1

21 interval cancers- 19 advanced stage

3 subsequent studies in high risk population confirm low yield of screening
Annual surveillance with TVUS and CA125 appears ineffective

Early detection of minimal volume vs. early stage
Is this a valid endpoint for screening?



Kurman et al Am J Obst Gyn 2008

Prevention of BRCA related ovarian cancer

- OCP ↓ risk by 50%
- BSO reduces ovarian cancer risk in *BRCA1/2* mutation carriers by 96% and breast cancer risk by 53%. (Rebbeck et al N Engl J Med 346:1616-1622, 2002 Kauff ND, et al: N Engl J Med 346:1609-1615, 2002)
- BSO does not eliminate the risk of ovarian cancer entirely - 1% to 2% of women may develop peritoneal carcinoma.
- Age late 30's -40's A1 50's A2
- Adverse effects include loss of fertility and immediate onset of menopause with vasomotor symptoms and possible sexual dysfunction as well as potential late effects

Risk Reducing Surgery

- 13-53% of high risk women opt for RRSO

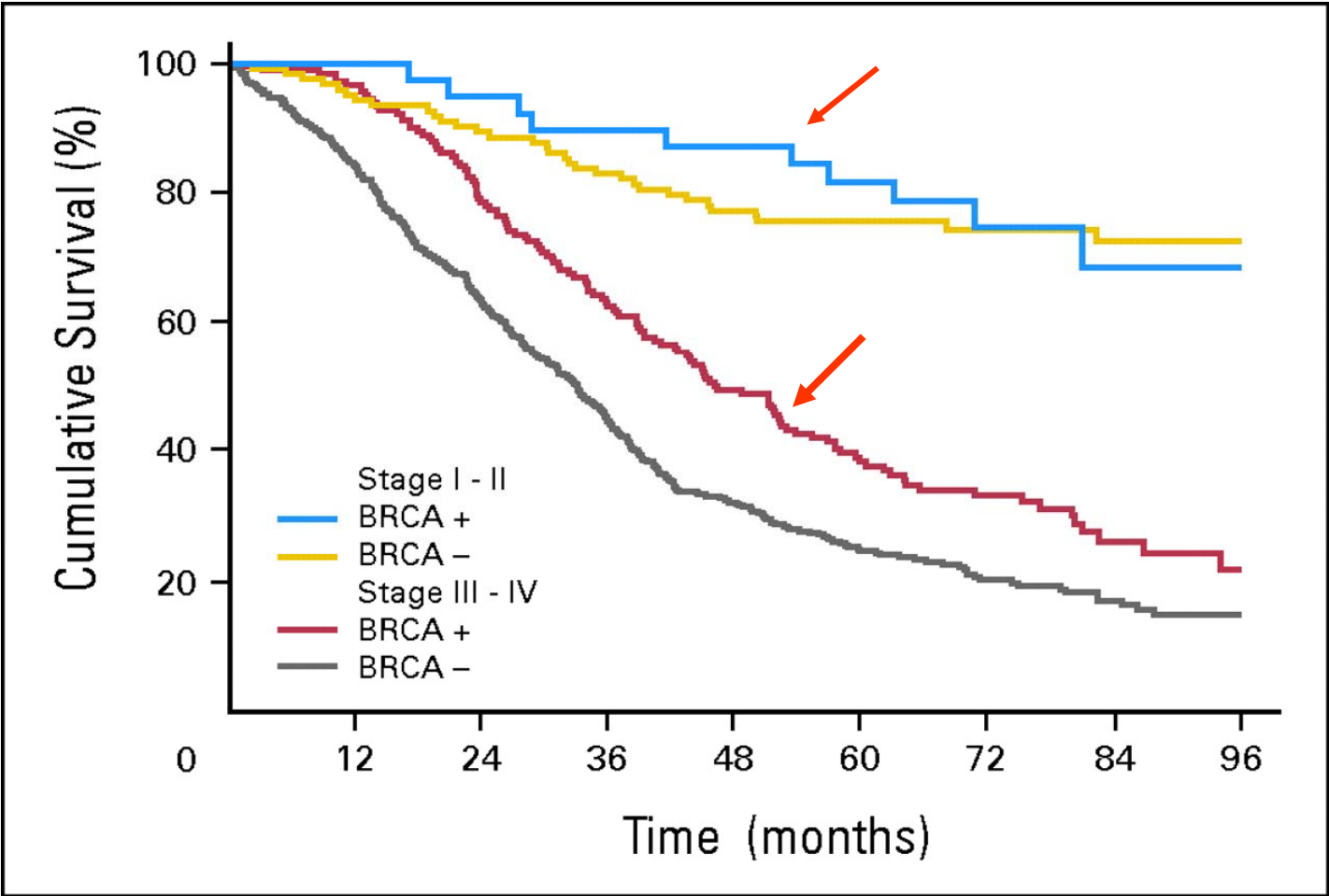
Wainberg and Husted-Cancer Epidem.Biomarker Prev. 2004;12,1989
Literature review- 7 studies- 5 USA and 2 Europe

Reflects

prevailing values and belief of clinicians
population characteristics
overconfidence in screening
health care costs

**?? Bilateral Salpingectomy after childbearing and bilateral oophorectomy
in late 40's or after menopause**

BRCA as a prognostic factor



**Median
Survival
56 vs. 38 m**

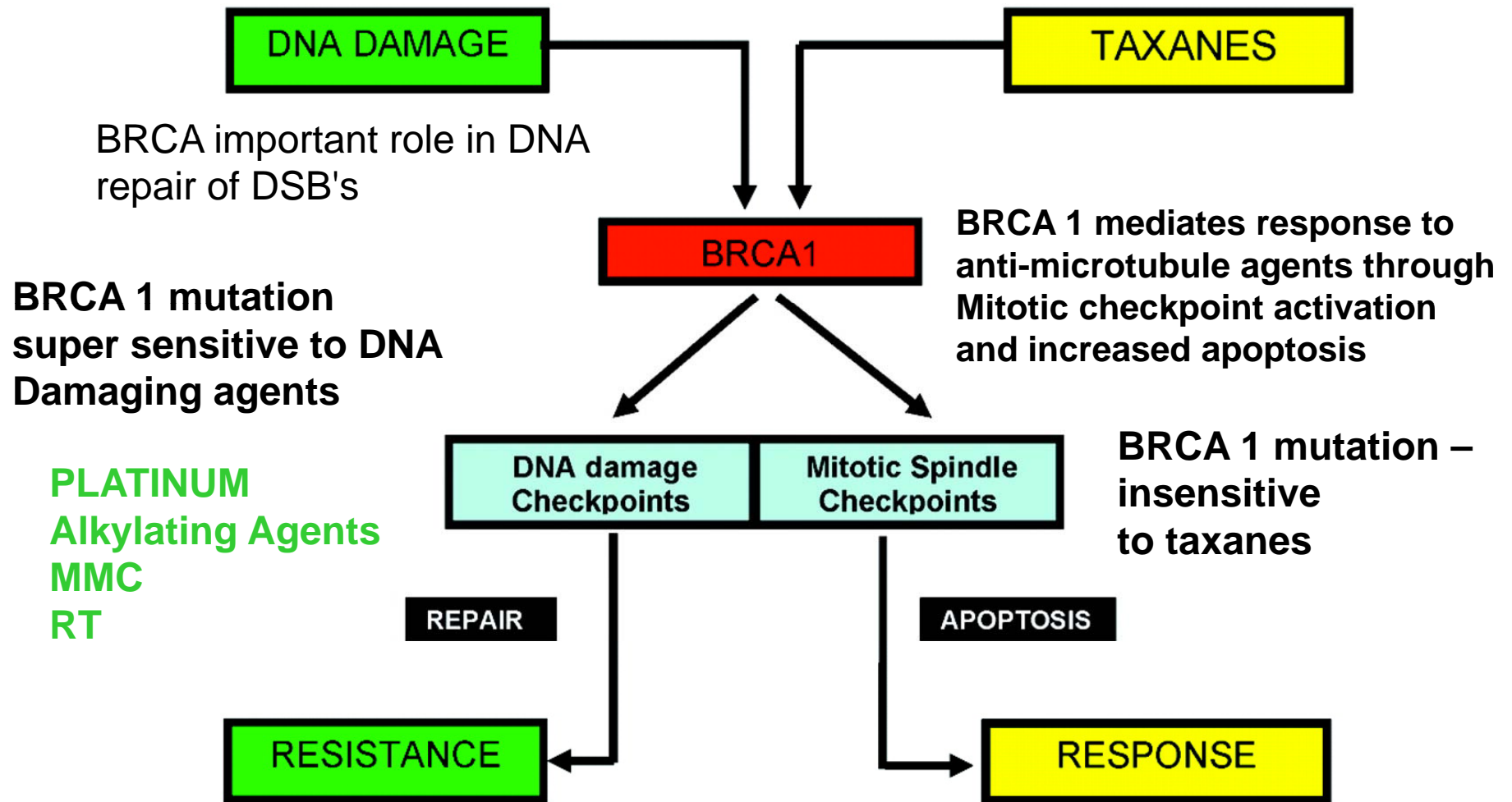
Chetrit, A. et al. J Clin Oncol; 26:20-25 2008

BRCA related Ovarian Cancer

Implications for treatment

- **18%** high grade serous cancers BRCA +
- **15%** Ovarian Cancers down regulation of BRCA 1 due to hypermethylation of BRCA 1 promoter
- LOH at BRCA 1 or 2 locus in 30-70%
- Low BRCA 1 mRNA levels in sporadic OC
- **BRCA important determinant of response to chemotherapy**

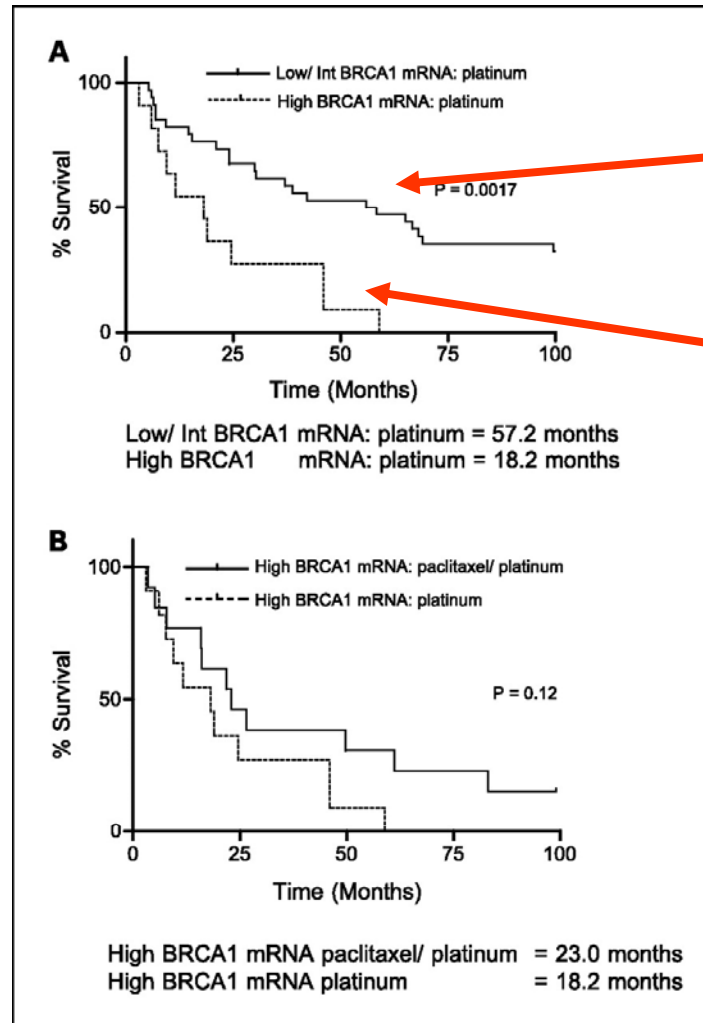
BRCA1 and response to DNA- and microtubule-damaging chemotherapy



James, C. R. et al. Oncologist 2007;12:142-150

Implications for Treatment

Sporadic Ovarian Cancer



Low BRCA 1 m RNA
Platinum only 57 m

High m RNA levels
Platinum only 18m

?Taxanes better for high
BRCA 1 mRNA

Quinn, J. E. et al. Clin Cancer Res 2007;13:7413-7420

BRCA1 or 2 Carrier

Tumour

- No "normal" *BRCA1/2*
- *BRCA1/2* function - DS DNA repair by HR
- Abnormal DNA repair- Mutant cells rely on SS repair mechanisms

Normal tissues

- 1 normal copy *BRCA1/2*
- *BRCA1/2* function retained
- Normal DNA repair

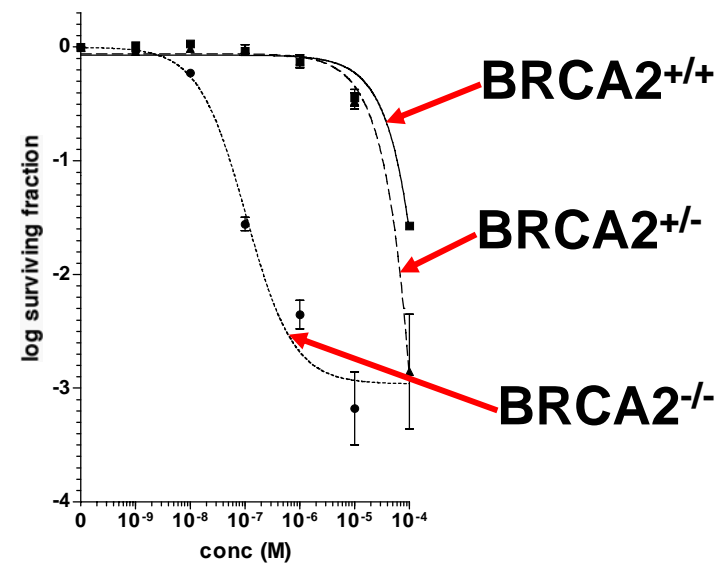
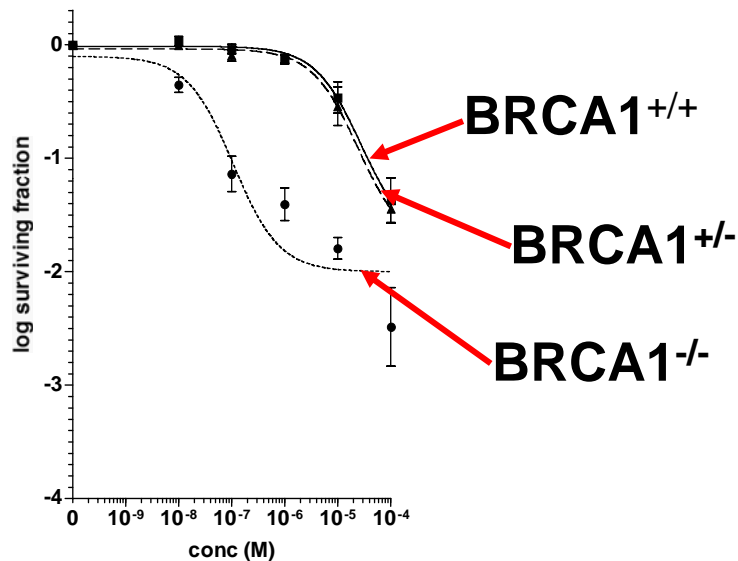
PARP- enzyme involved in base excision repair- key pathway in repair of DNA SS breaks

Hypothesis- inhibition of PARP in BRCA- cells could result in chromosome instability and selective cell death

Farmer et al Nature april 2005

BRCA1^{-/-} and BRCA2^{-/-} cells are extremely sensitive to PARP inhibition

Up to 1000 FOLD ENHANCED SENSITIVITY



No difference in sensitivity between heterozygous and wild-type BRCA cells

Targeted inhibition → selective and less toxic therapy

Response to AZD 2281

by platinum free interval

	Total	Platinum Sensitive	Platinum Resistant	Platinum Refractory
number	46	10	25	11
RECIST response	28%	50%	32%	0%
CA125 response	39%	80%	32%	18%
Either RECIST/CA125	46%	80%	44%	18%

Questions to be answered

- What about patients with reduced BRCA function due to hypermethylation
- In vitro and in vivo evidence of potentiation of alkylating agents
- When to use- first line in combination
-maintenance
- Are there long term risks of inhibiting DNA repair?

New Insights into PARPi and Platinum resistance

“From therapeutic target to therapeutic shield”

- Secondary or counter mutations in BRCA 1 and 2 restore the reading frame of protein and leads to detectable levels of BRCA 1 and 2 protein
- Resistance to platinum and PARPi –(*but ? more sensitive to taxanes*)

The Future and The Possibilities

- Argues for identification of mutation carriers-
new therapeutic options
- BRCA as a prognostic marker
- Chemo-prevention in high risk patients
- Type of BRCA mutation and response
- Tumour biopsy – resistance markers RAD51
- Prophylactic Salpingectomy → BO (later) ??

BRCA Ovarian Cancer

Conclusions

- Enormous progress since started testing for BRCA mutations
- Insights into the pathogenesis of “ ovarian cancer”
- Insights into the unique biological behaviour
- Mechanisms of drug sensitivity
- New targets New Drugs