EIGHTH ANNUAL BEEBE SYMPOSIUM 2009

Factors Influencing Risk

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Factors Influencing Risk.

- Genetic considerations.
- Age at Exposure.
- Gender.
- Fractionation and protraction of exposure.

Factors Influencing Risk.

- **Genetic considerations.**
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Genetic Factors.

- There are now two clear instances from human epidemiological studies which imply the existence of a radiosensitive sub-population.

Scoliosis, Multiple Diagnostic X-rays and Breast cancer.

- Mean Age at Diagnosis…..11yr (0-19)
- Mean No. of radiographs 26.8 (0-332)
- 3000 women diagnosed with scoliosis .
- Mean # Years Exposed …6.1 (0-55)
- Mean Total Breast Dose (cGy)… 12.1 (0-111)
  - Ronckers et al Can. Epi Biomarkers Prev. 2008, 17(3), 605-613.

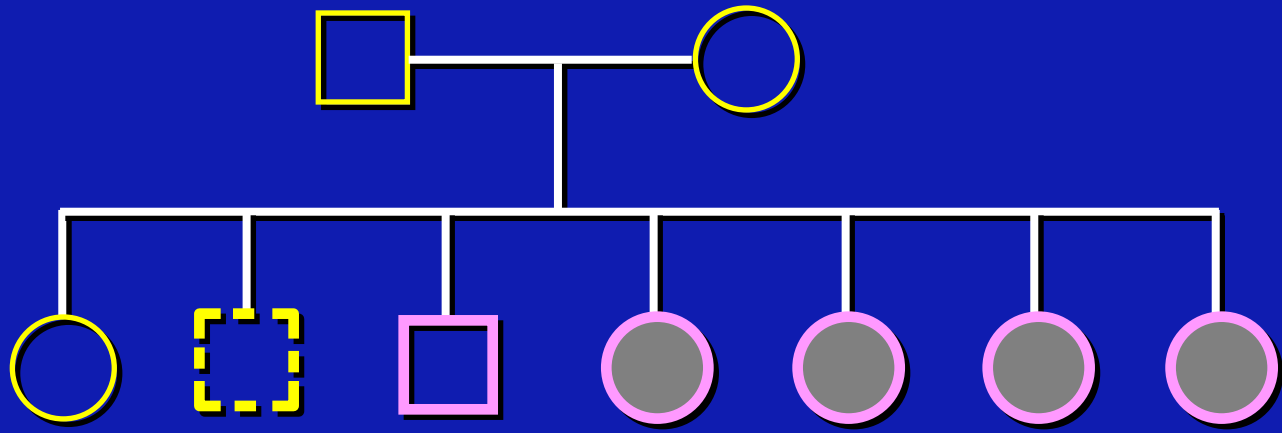
Scoliosis, Multiple Diagnostic X-rays and Breast cancer.

- Borderline significant radiation dose-response for breast cancer in the whole cohort (ERR/Gy=2.86).
- Dose-response much greater) for a sub-set of women with a family history of breast cancer in first or second degree relatives. (ERR/Gy=8.37
- Ronckers et al Can. Epi Biomarkers Prev. 2008, 17(3), 605-613.

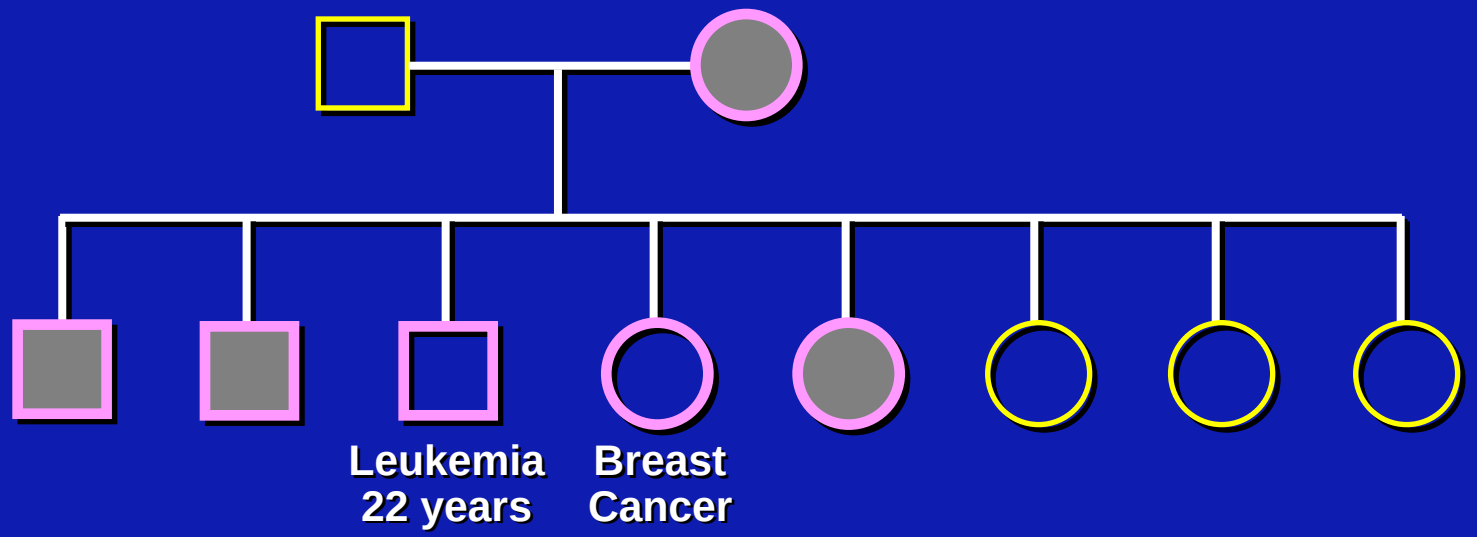
Israeli study of Children Epilated for the Treatment of Tinea Capitis

- More than 20,000 children involved.
- A sub-set included 525 large families, with 5 or more children.
- Overall, about 1% of those irradiated developed meningioma, but it was not random..
- Marked clustering in some families, with multiple children developing the malignancy..
  - Sadetsky et al. The Lancet Oncology, 2007

Family #1
(Origin: Morocco)



Family #2
(Origin: Morocco)



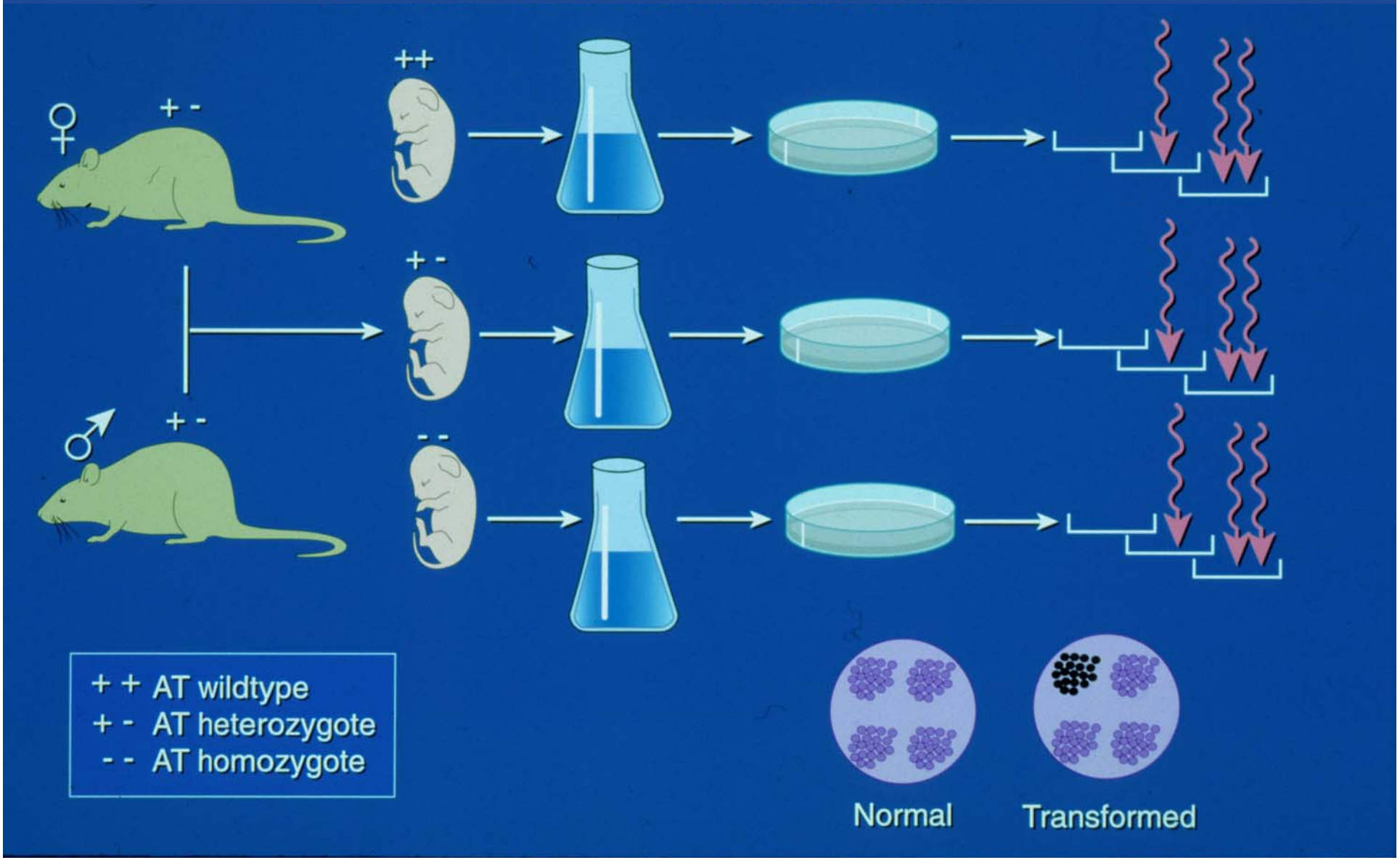
Conclusion.

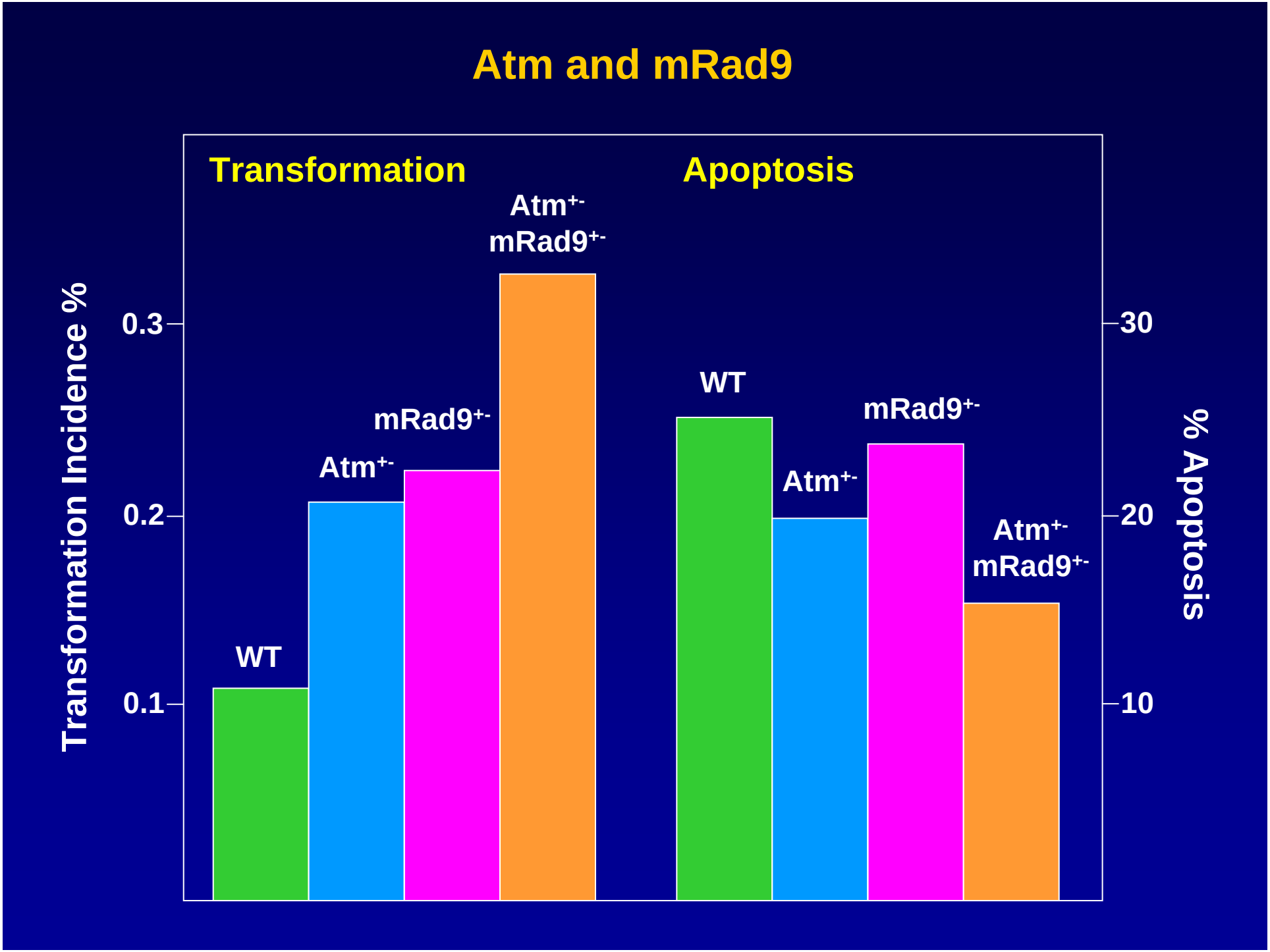
- While there are instances from human epidemiological studies which imply the existence of a radiosensitive sub-population
- The genes involved have not been identified.
- This is worth studying.

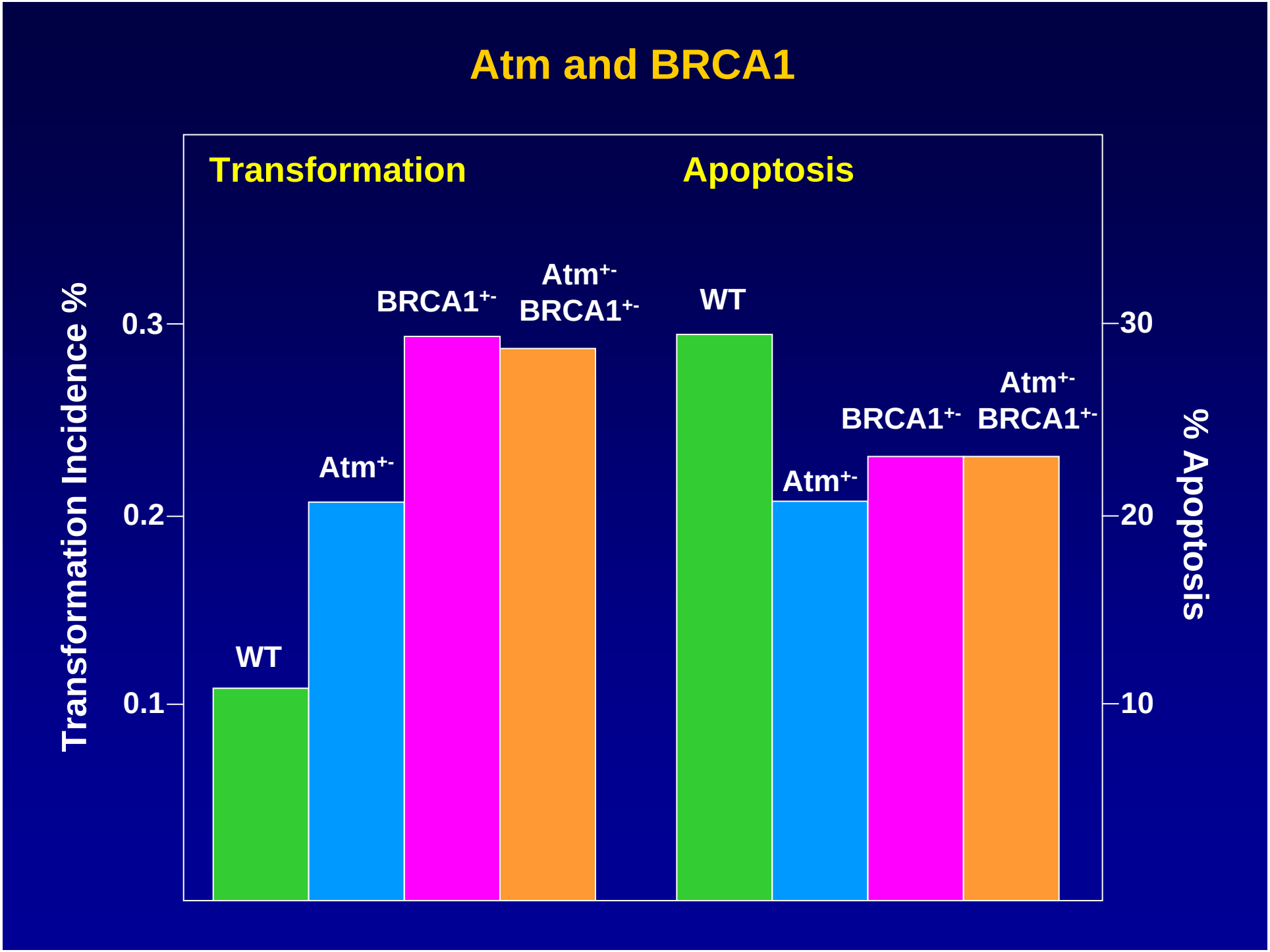
The Plan: Use Mice Heterozygous for Various Candidate Genes and Score:-

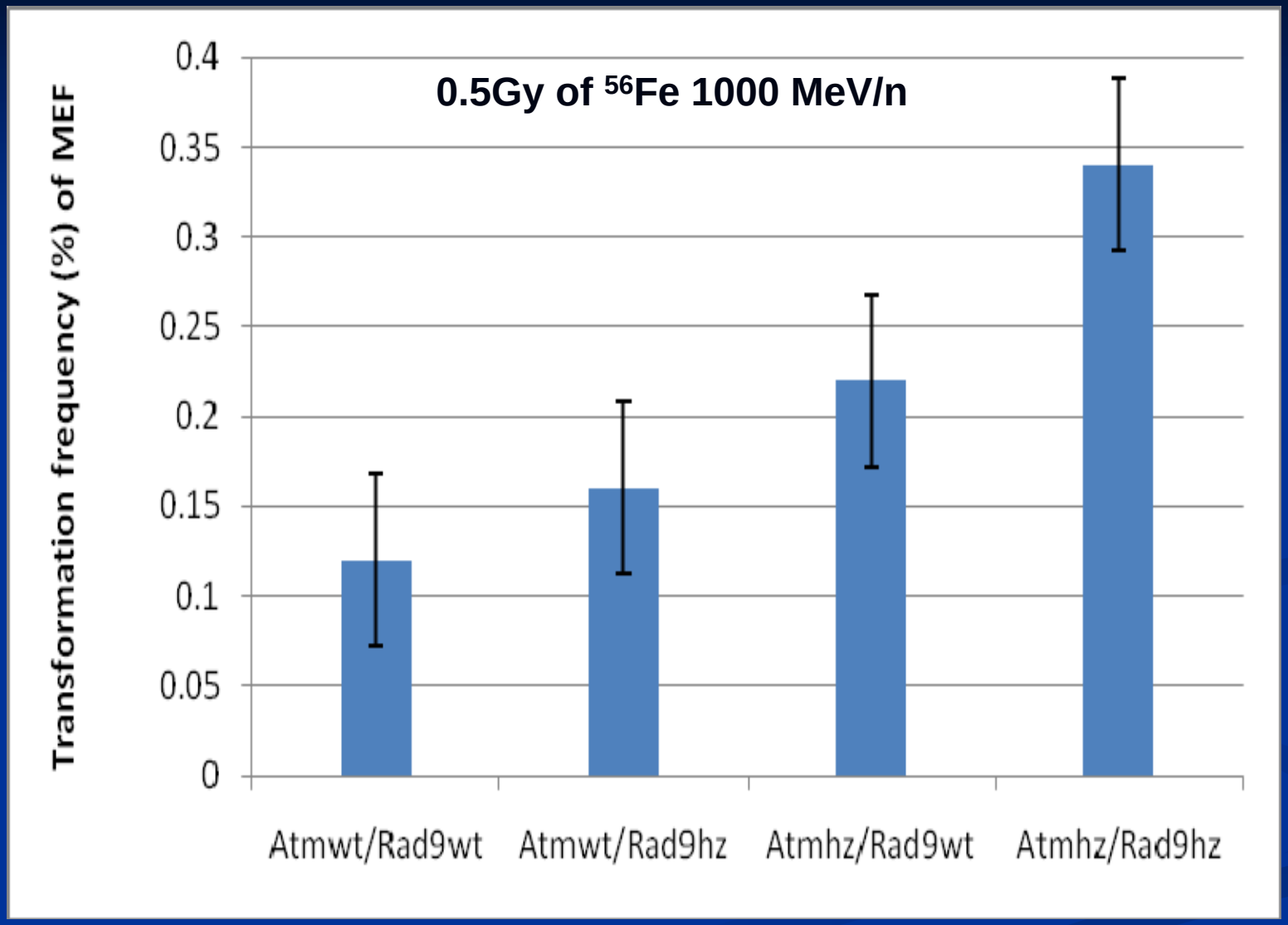
- Oncogenic Transformation in embryo fibroblasts as a surrogate for carcinogenesis.
- Ocular cataracts, as an in vivo endpoint relevant to NASA.

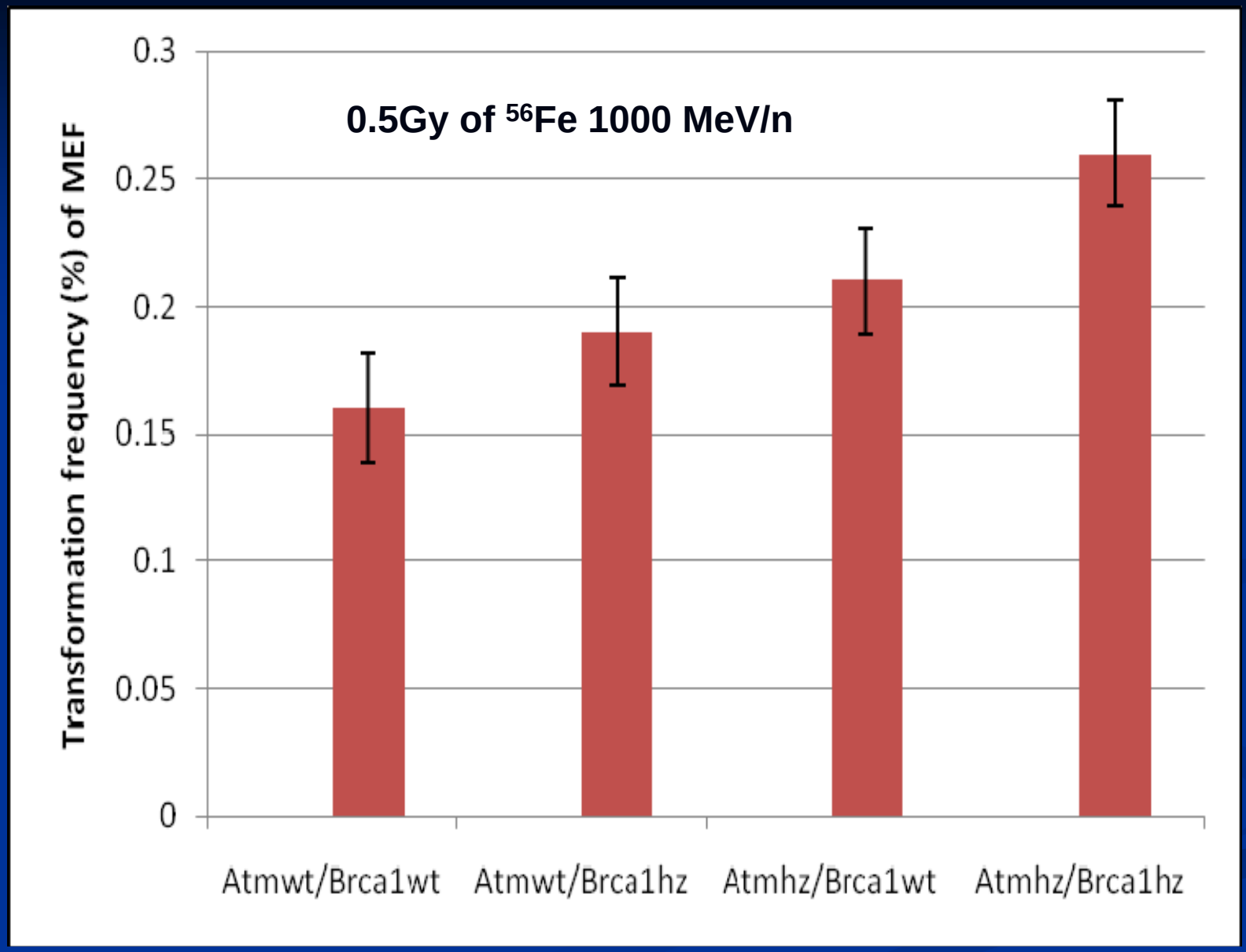
In Vitro Cell Transformation

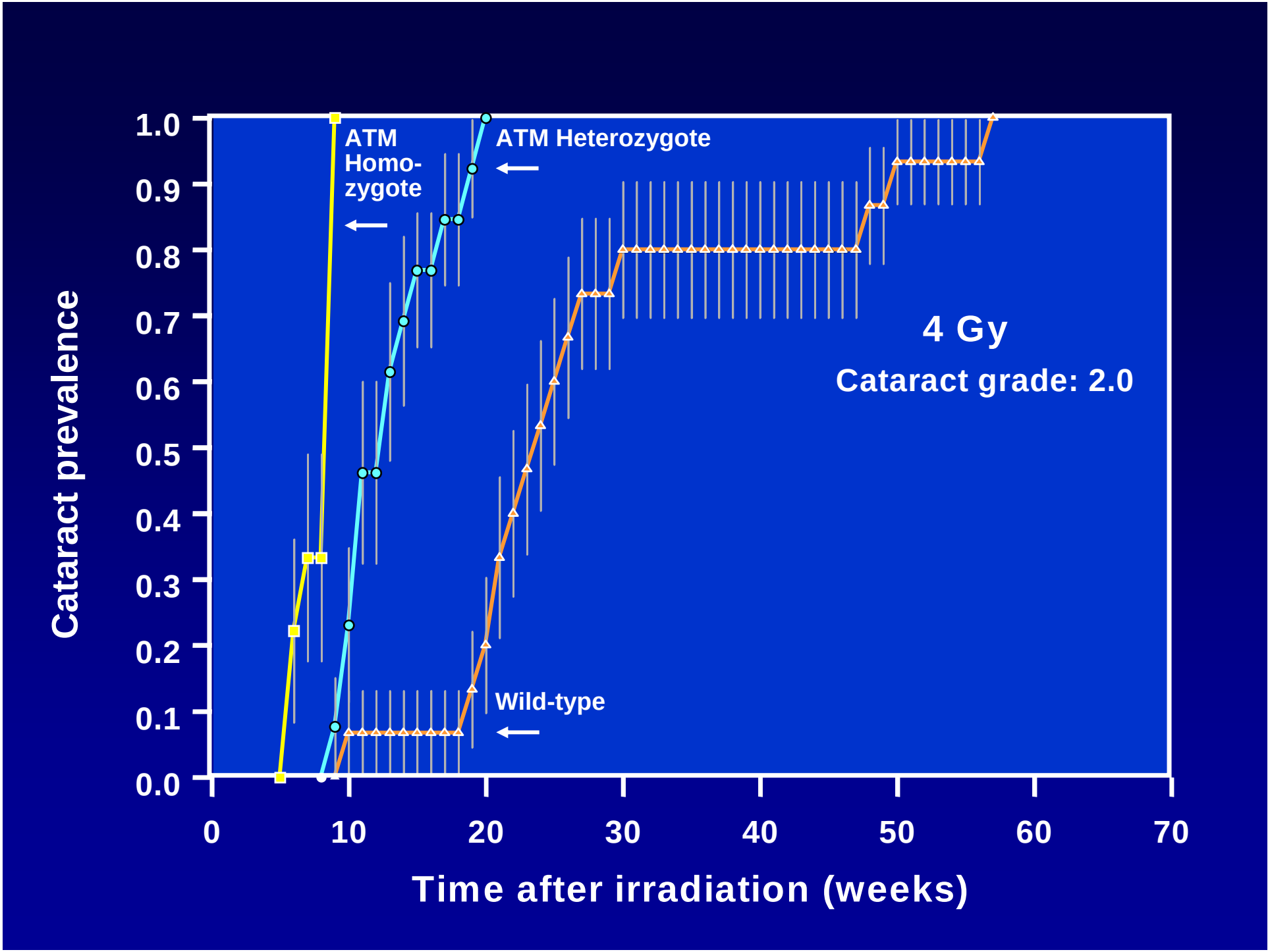


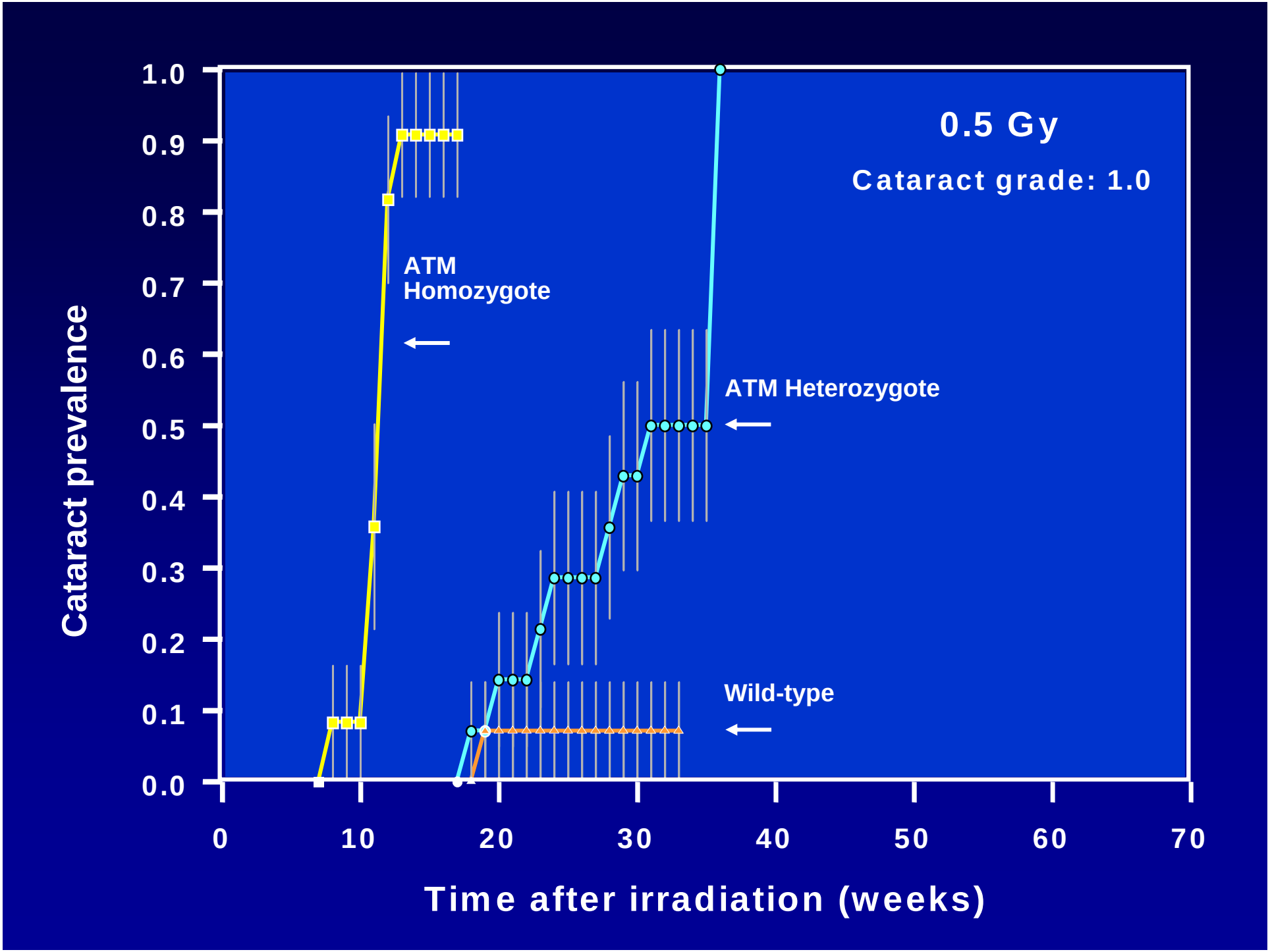

Atm and mRad9
Transformation
Apoptosis
Transformation Incidence %
% Apoptosis
0.3
0.2
0.1
30
20
10
WT
Atm+-
mRad9+-
Atm+- mRad9+-
WT
mRad9+-
Atm+-
Atm+- mRad9+-


Atm and BRCA1
Transformation
Apoptosis
Transformation Incidence %
% Apoptosis
0.3
0.2
0.1
30
20
10
WT
Atm+-
BRCA1+-
Atm+-
BRCA1+-
WT
Atm+-
BRCA1+-
Atm+-
BRCA1+-


0.5Gy of 56Fe 1000 MeV/n
Transformation frequency (%) of MEF
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
Atmwt/Rad9wt
Atmwt/Rad9hz
Atmhz/Rad9wt
Atmhz/Rad9hz


0.5Gy of 56Fe 1000 MeV/n
Transformation frequency (%) of MEF
0.3
0.25
0.2
0.15
0.1
0.05
0
Atmwt/Brca1wt
Atmwt/Brca1hz
Atmhz/Brca1wt
Atmhz/Brca1hz


Cataract prevalence
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
10
20
30
40
50
60
70
Time after irradiation (weeks)
ATM Homo-zygote
ATM Heterozygote
Wild-type
4 Gy
Cataract grade: 2.0


0.5 Gy
Cataract grade: 1.0
ATM
Homozygote
ATM Heterozygote
Wild-type
Cataract prevalence
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
10
20
30
40
50
60
70
Time after irradiation (weeks)

Genes Identified

- **ATM** 66 exons 150 kb
- **BRCA1** 24 exons 5.6 kb

- **Rad9** 9 exons 10.0 kb

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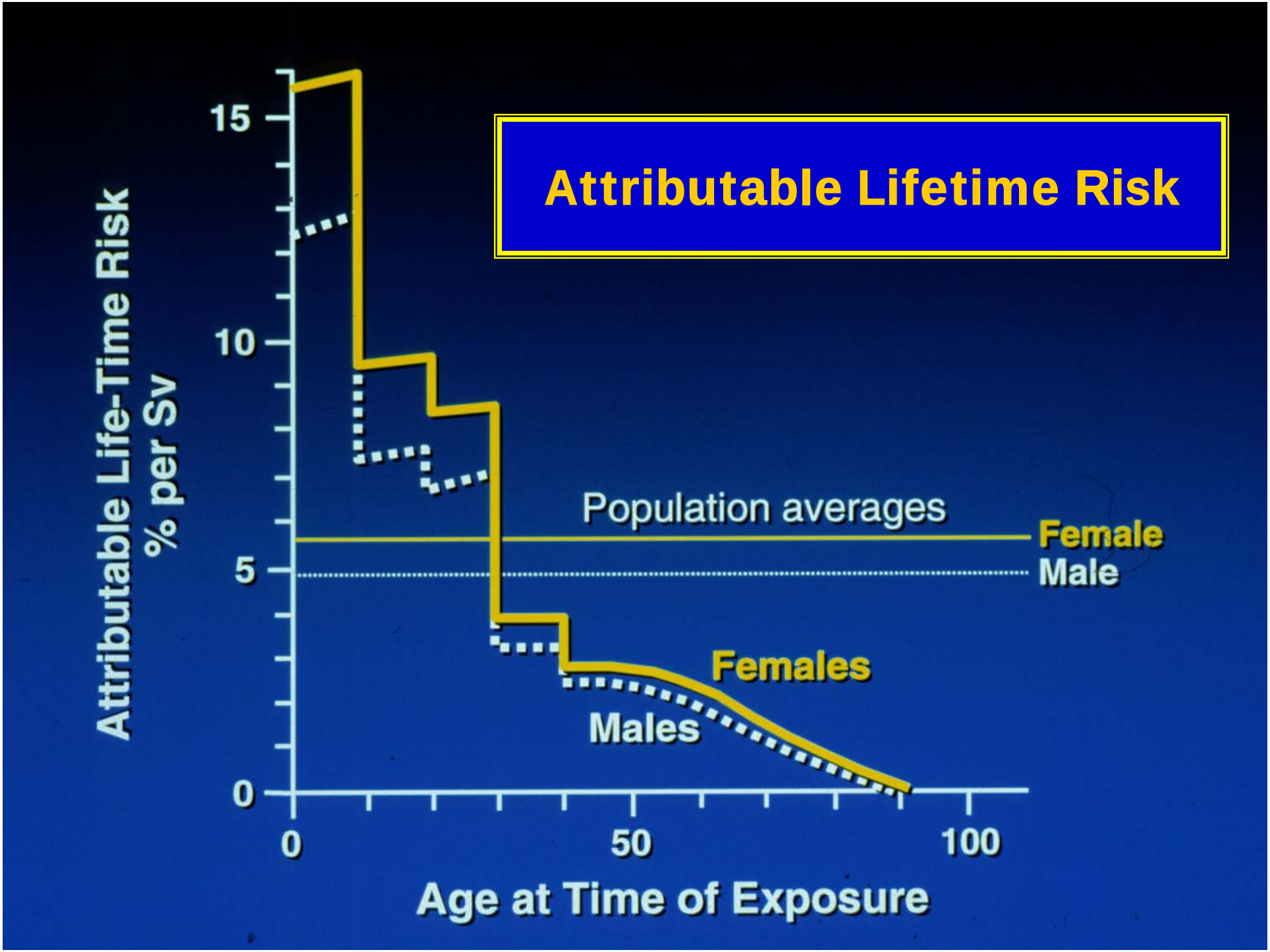
- Fractionation and protraction of exposure.



Attributable Lifetime Risk

Attributable Life-Time Risk
% per Sv

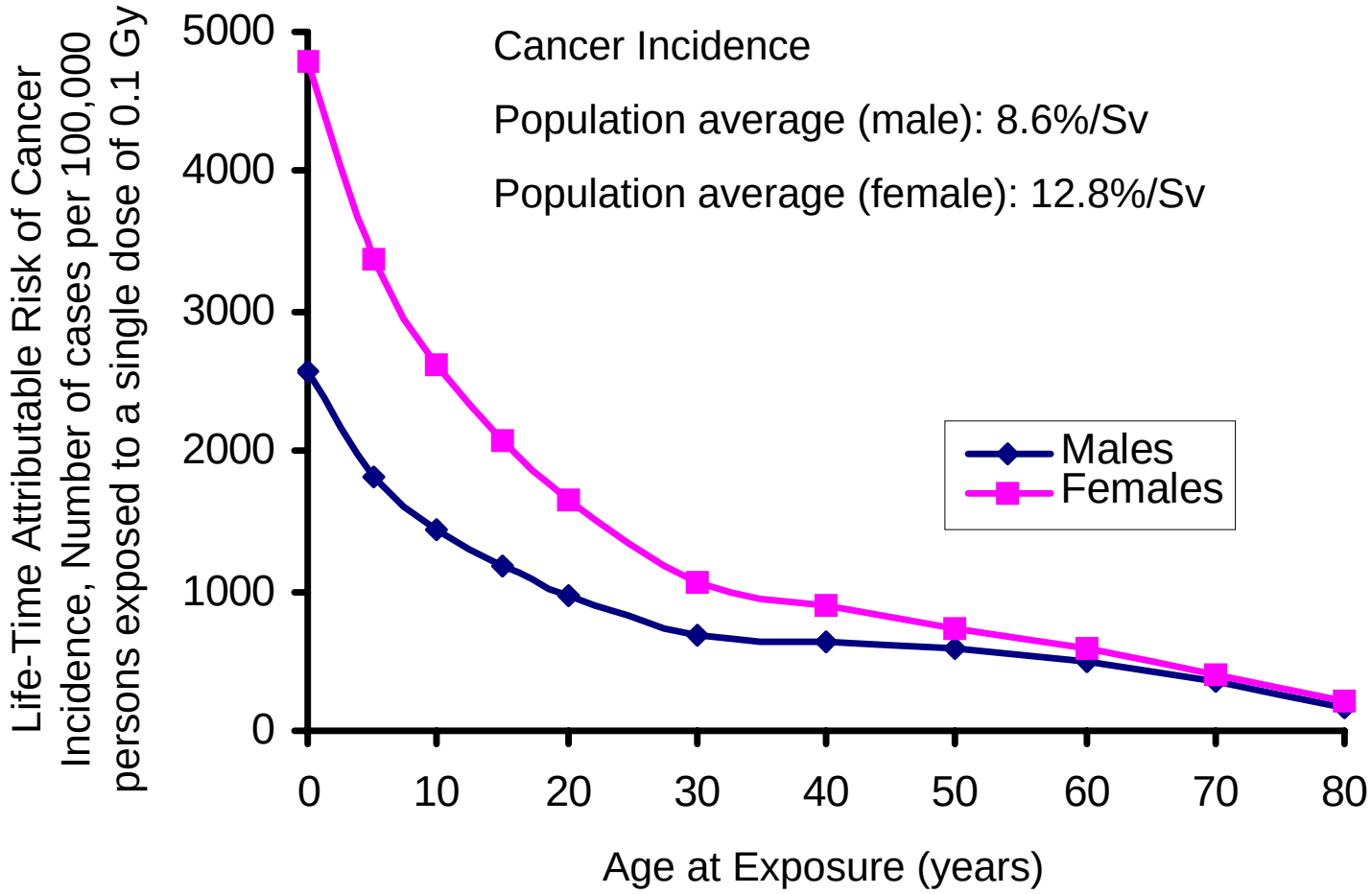
15
10
5
0

Population averages
Female
Male

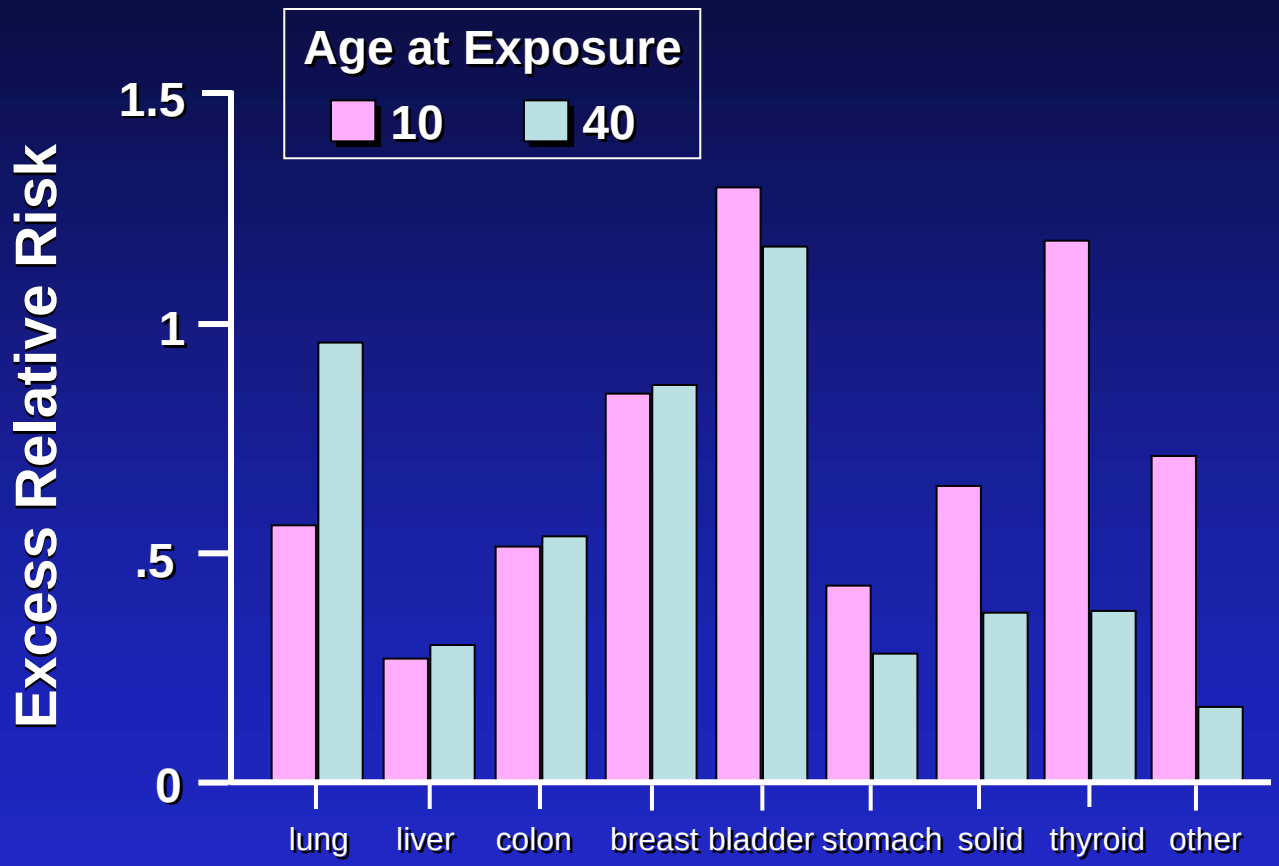
Females
Males

0
50
100

Age at Time of Exposure


Life-Time Attributable Risk of Cancer Incidence, Number of cases per 100,000 persons exposed to a single dose of 0.1 Gy
5000
4000
3000
2000
1000
0
0
10
20
30
40
50
60
70
80
Age at Exposure (years)
Cancer Incidence
Population average (male): 8.6%/Sv
Population average (female): 12.8%/Sv
Males
Females

BEIR VII

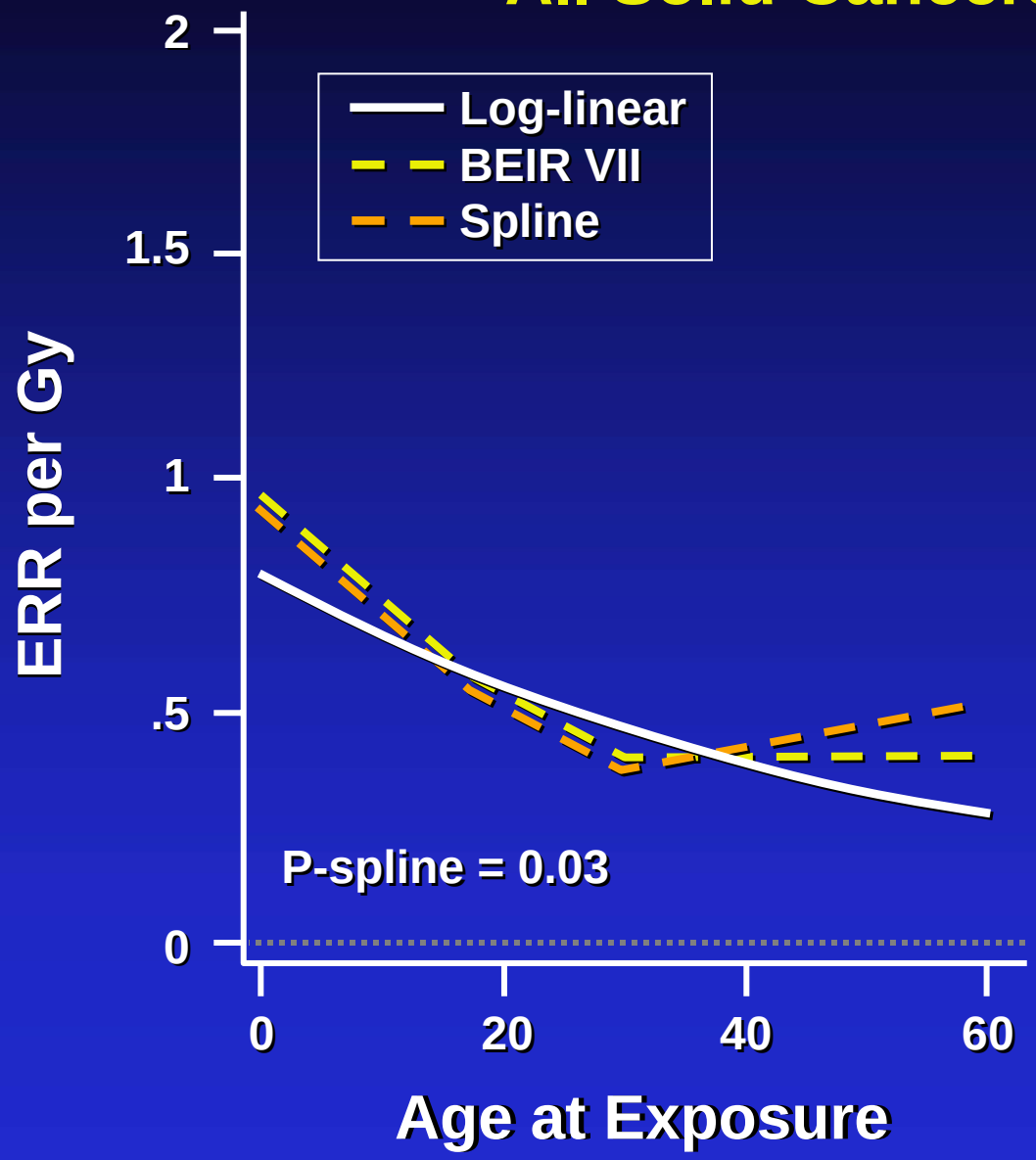


Gender averaged ERR's at age 70 for exposure at age 10 or 40
Preston et al, 2007.

All Solid Cancers. Variation with Age at Exposure.

- **BEIR VII;** Log-Linear trend to decrease for 0-30yrs, no further change after age at exposure 30yr.
- **Preston et al (2007)** Excess risks declined with age at exposure less than 40 years, but increased with age at exposure late in life.
- Lung cancer is the only one to consistently increase with age

All Solid Cancers



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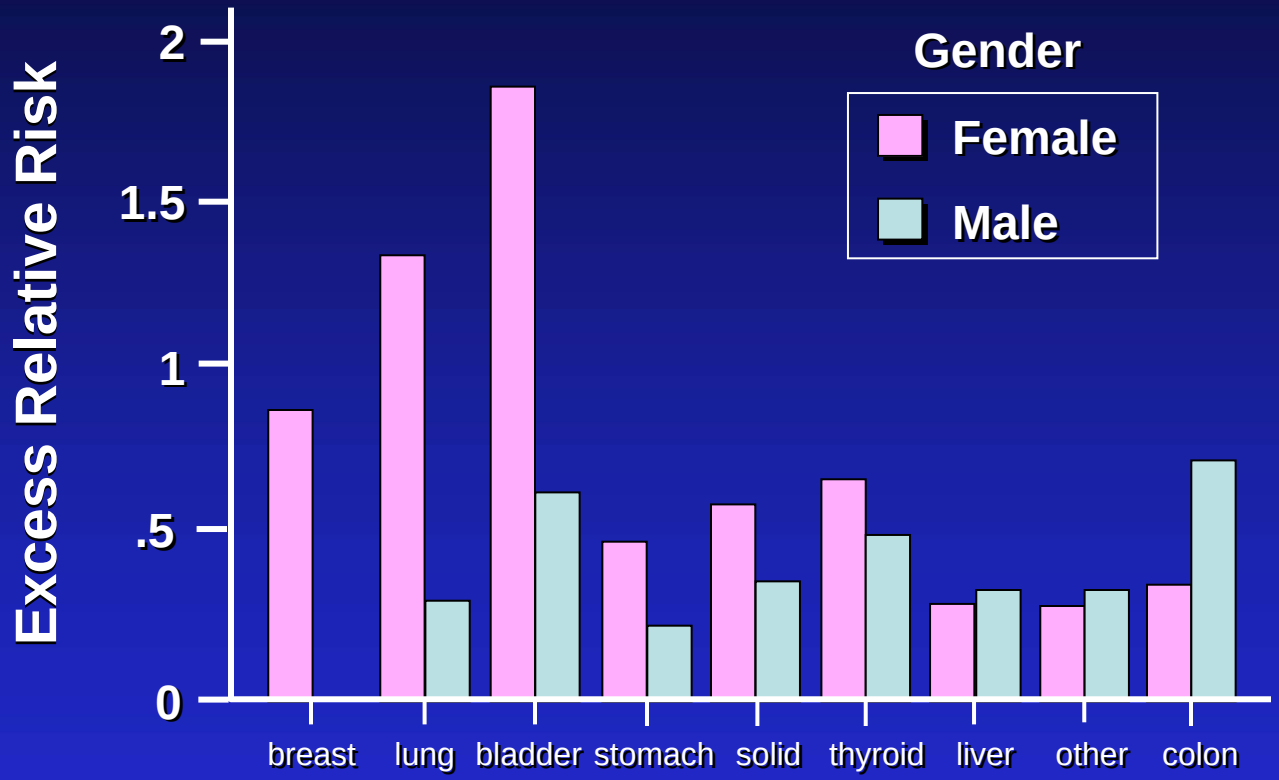

Gender specific ERR's at age 70 for exposure at age 30
Preston et al, 2007.

Effect of Gender on Risk.

- Overall, women have higher ERR's than men.
- The largest gender effects on ERR's are for lung & bladder; base-line rates affected by smoking.
- When gender-specific cancers are excluded, excess absolute risks are essentially equal.

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DDREF

- NCRP (1978) 2 to 10 (animal studies)
- BEIR III (1980) 2.25 (α/β ratio)
- BEIR V (1990) 2 to 10 (best estimate 4)
- UNSCEAR (1977) 2.5 (leukemia at high & low doses)
- UNSCEAR (1986) 2 to 10
- ICRP (1990) 2
- BEIR V11 (2006) 1.5 (α/β ratio)

The Effect of Dose Protraction.

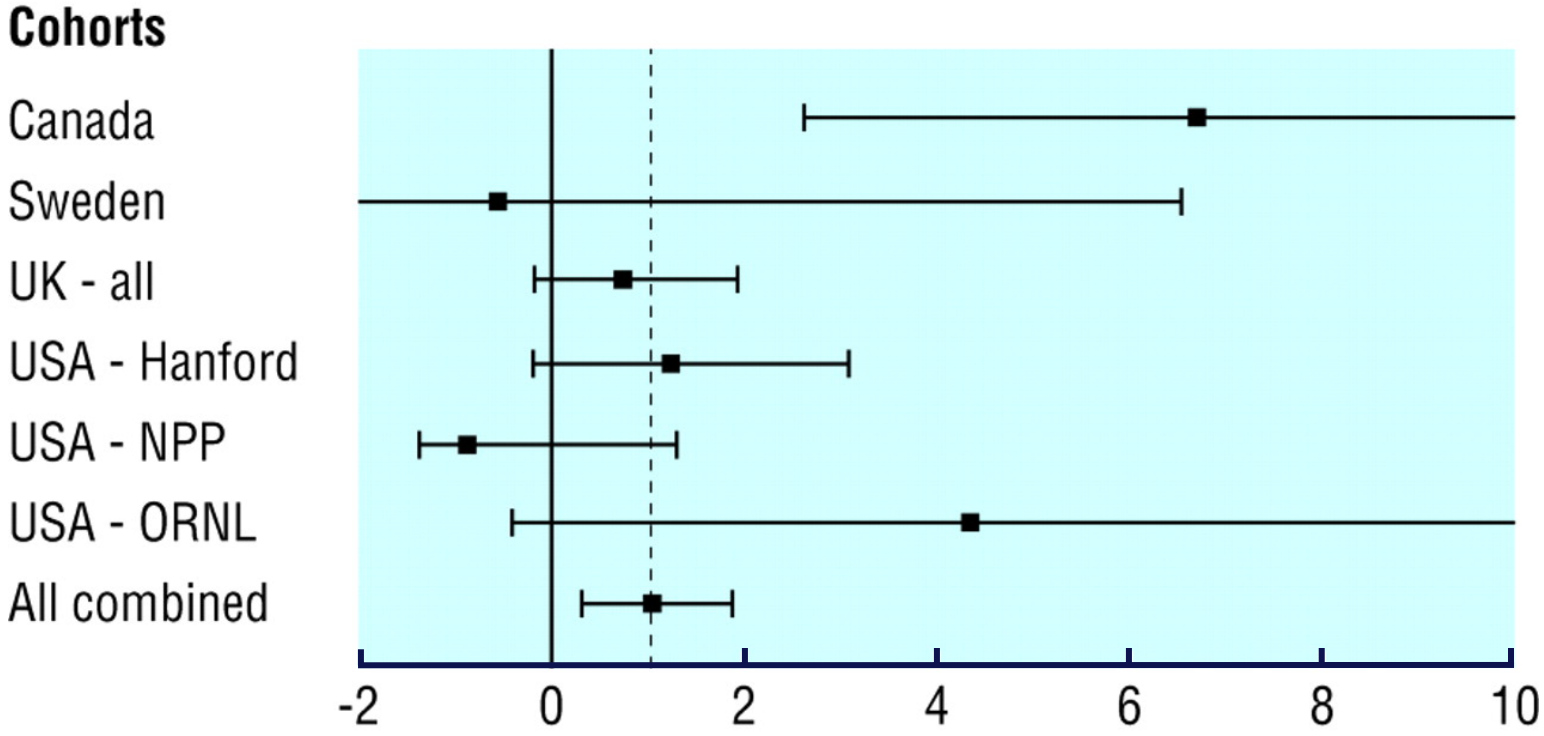
- We now have cancer risk estimates from several nuclear worker studies involving protracted exposures over many years to compare with the acute exposure of the A-bomb survivors.
- The 15-nation study (Cardis et al 2005.)
- The NRRW study from the UK. (Muirhead et al 2009)

IARC 15 Country Study (Cardis et al. 2005)

- 600,000 nuclear workers
- Average cumulative dose = 19.4 mSv
- All cancers (except leukemia) ERR

  = 0.97 (0.14 to 1.97)/Sv
- Leukemia ERR = 1.93/Sv (NS)

IARC 15 Country Study (Cardis et al. 2005)



NPP=Nuclear Power Plants
ORNL=Oak Ridge National Laboratory

Cardis, E et al. BMJ 2005;331:77

IARC 15 Country Study Criticised for two reasons.

- Result driven by the Canadian contribution. (Few workers, many cancers!)
- The predominance of lung cancers suggest a confounding effect of smoking .
- For both of the above reasons, the ERR/Sv may be exaggerated.

UK National Registry of Radiation Workers

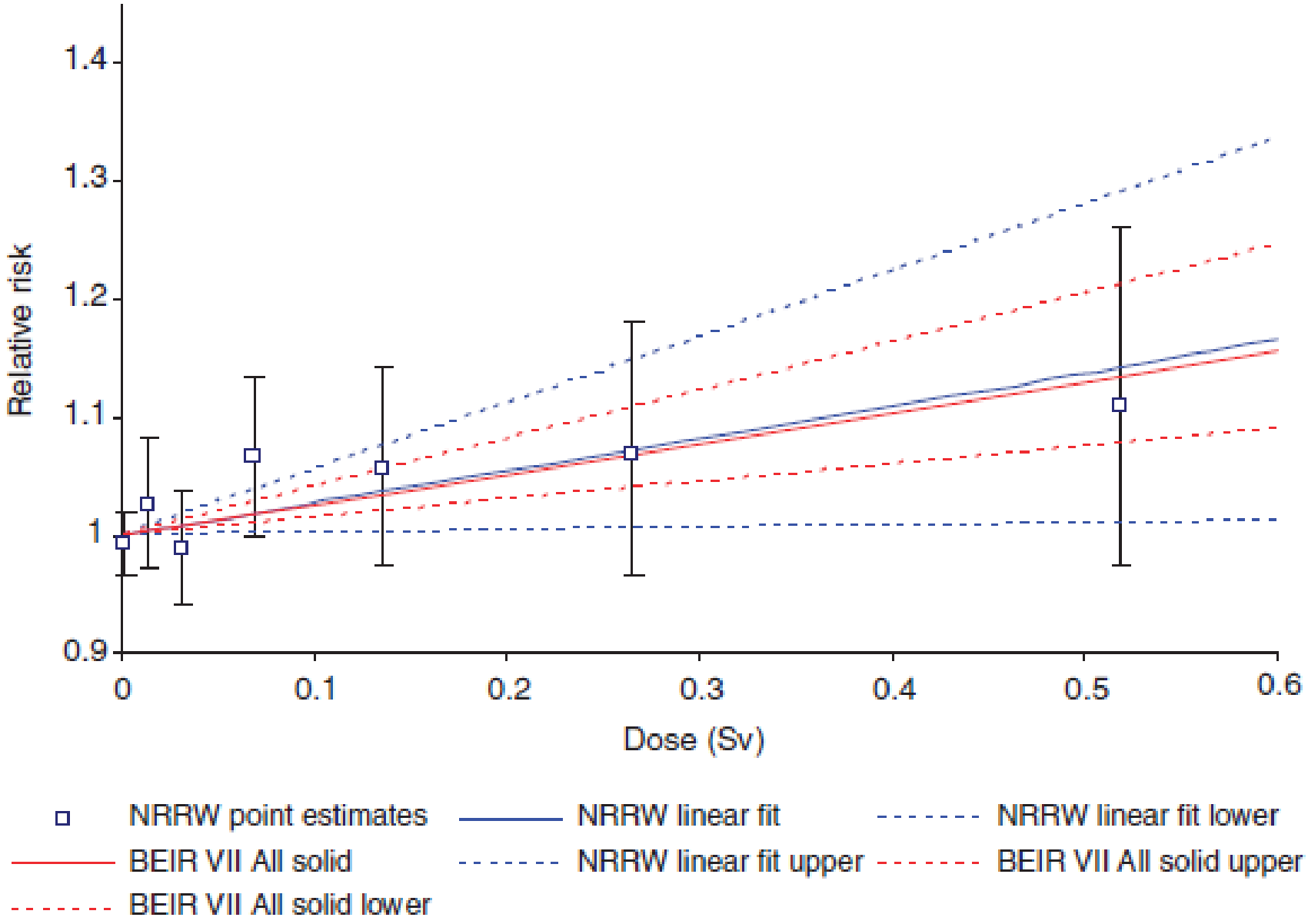
- 175,000 workers: long follow-up
- Healthy worker effect – i.e. all causes of death lower than general population
- ERR / Sv for solid cancer mortality similar to A-bomb survivors (0.275)
- Cancer risk increased with cumulative dose; Mean dose 24.9 mSv

Muirhead et al
BJC 2009

ERR/Sv for Cancer Mortality

	Leukemia excluding CLL	Solid cancers
A – bomb survivors	**1.4**	**0.26**
15 – nation study	**1.93***	**0.97**
UK – NRRW analysis	**1.7***	**0.275**

A - bomb survivors, BEIR VII Report
15 nation study, Cardis et al. 2005
UK – NRRW analysis, Muirhead et al., 2009
* Not Statistically Significant



Muirhead et al 2009

The Effect of Dose Protraction.

- Comparing nuclear worker studies with the A-bomb data lead us to conclude that the reduction of cancer risks by dose protraction is surprisingly small.
- However, the confidence intervals are so wide that they easily accommodate a DDREF of 1.0, 1.5, 2.0, or even larger (or 0.5 for that matter!!)

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I
NY®

A Recent History of Radiation Protection in the United States.

Dose Limits, 1950's ICRP

Based on genetic effects

1956; Dose limit for radiation workers

reduced to 0.1R/week (5R/Yr)

1/10 for the general public

Dose Limits, 1950's ICRP

Based on genetic (heritable) effects:

1956; Dose limit for radiation workers

reduced to 0.1R/week (5R/Yr)

1/10 for the general public

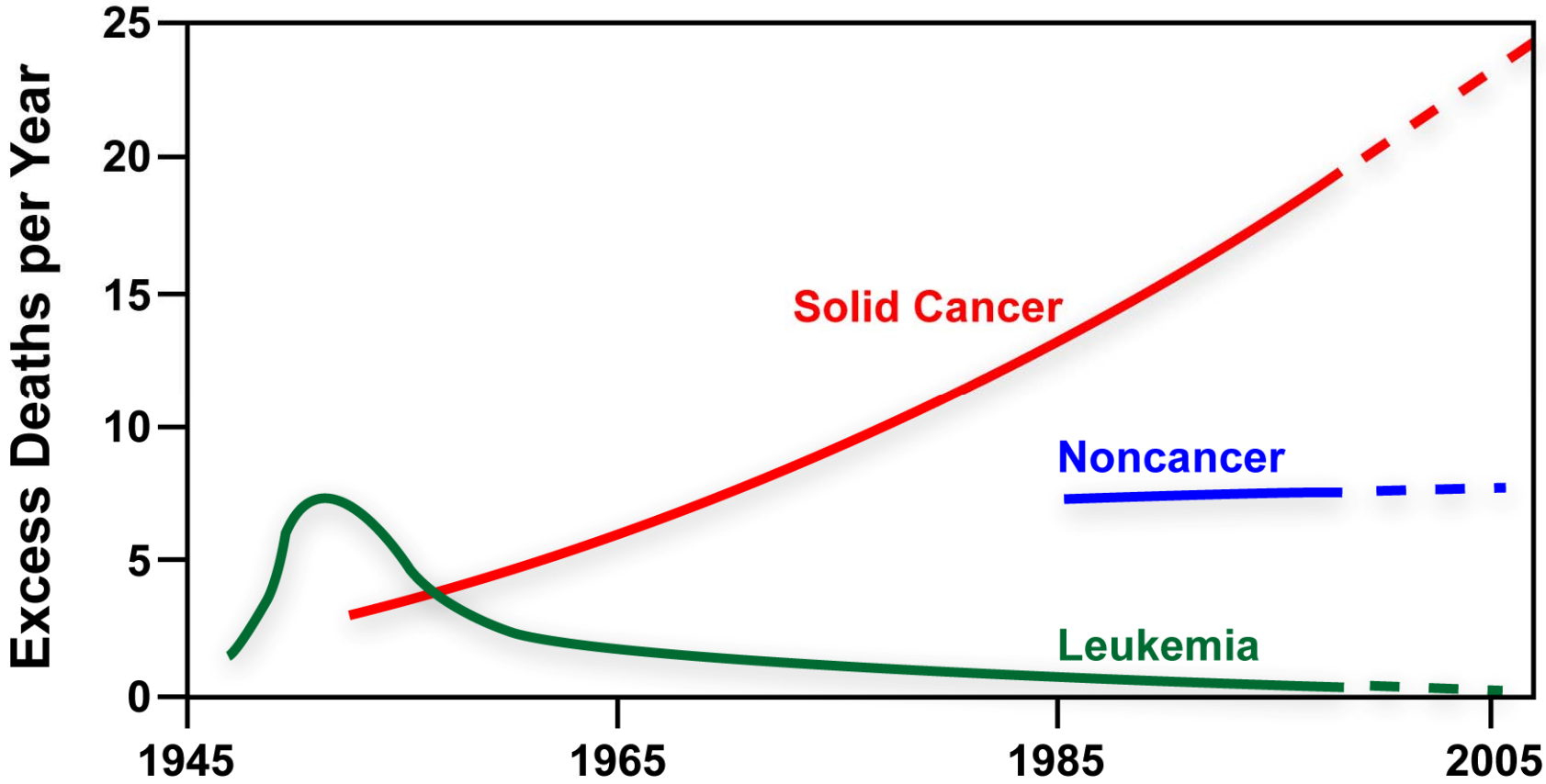
This is essentially unchanged to this day

(Except it is now called 50mSv!)

1950's ; Genetic Effects in Drosophila (Muller)

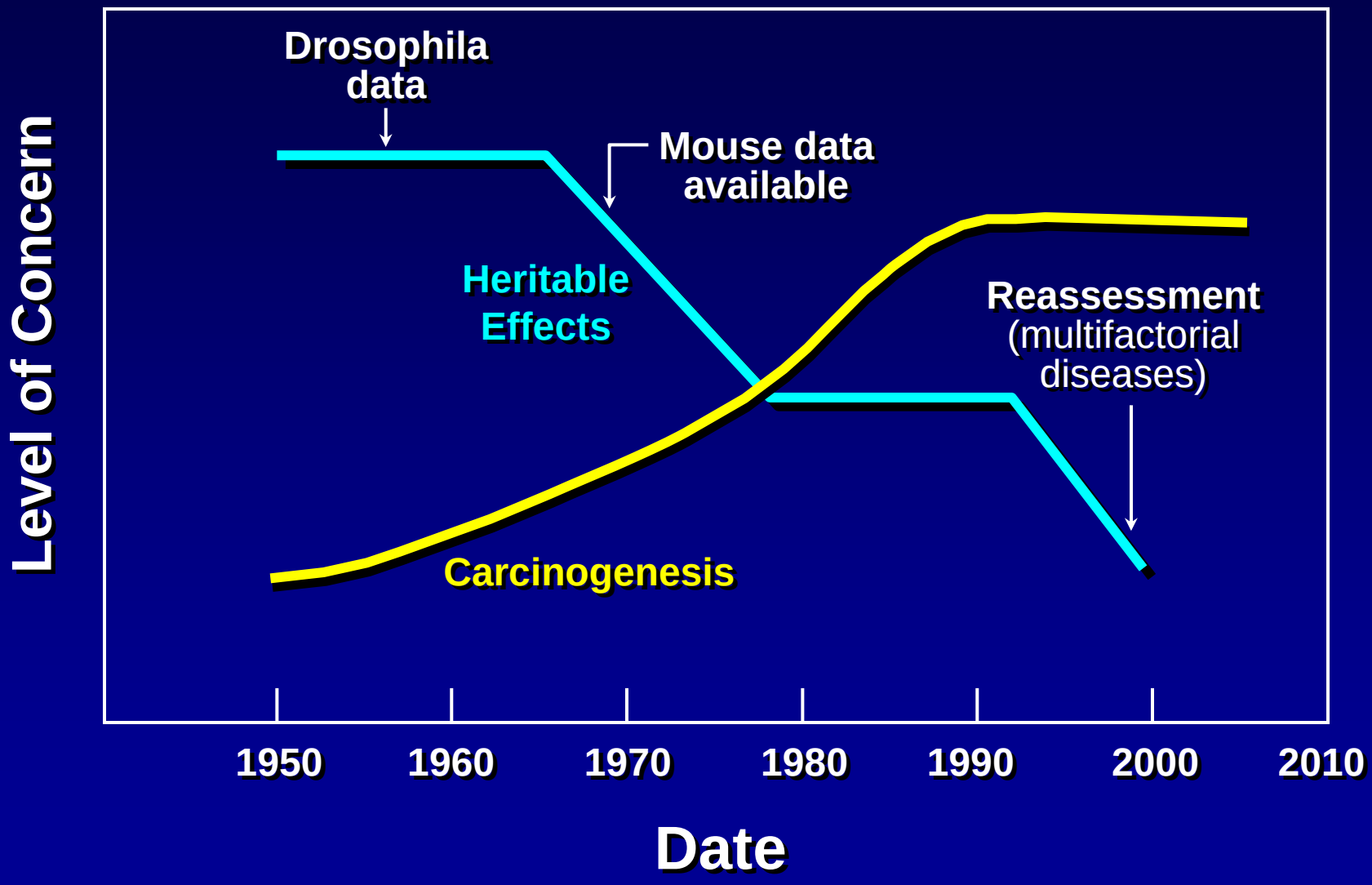
- Mutations, spontaneous or induced, are usually harmful **WRONG ASSUMPTION**
- Any dose entails some risk. (i.e. no threshold)
- Number of mutations is proportional to dose; a linear extrapolation from high doses provides a valid estimate of low dose effects. **LNT**
- The effect is independent of the rate at which the radiation is delivered or the spacing between exposures. **OK FOR DROSOPHILA NOT FOR MICE**

Radiation-Associated Deaths in the Life-Span Study



Because of the increasing number of solid cancers in the A-bomb survivors :

- ICRP (1991) added the requirement that occupational exposure averaged over 5 years should not exceed 20mSv/year.
- NCRP (1993) added the cumulative limit of 10mSv x age.
- Both retained the 50mSv in one year.


Level of Concern
Drosophila data
Mouse data available
Heritable Effects
Reassessment (multifactorial diseases)
Carcinogenesis
1950
1960
1970
1980
1990
2000
2010
Date

% of Detriment due to genetic component (ICRP)

- 1955.....100%
- 1977.....25%
- 1991.....18%
- 2007.....4%

History of Radiation Protection in the U.S.

- NCRP “recommends”. NRC “regulates”
- NRC never adopted the cumulative limit (age x 10mSv)recommended by NCRP.
- The NRC limit is 50mSv per year, and every year! More than is allowed in any other Western country that follows ICRP.

Population Averaged Cancer Risk %/Sv

	Incidence	mortality
➢Male	8.6	4.6
➢Female	12.8	6.2
➢Combined	10.8	5.4

Calculated from BEIR V11 Data including a DDREF of 1.5

Cancer Risks for a Radiation Worker Receiving the Maximum Permissible Dose from age 18-65 years

Rule	Total Dose	Cancer Incidence	Cancer Mortality
NRC 50 mSv/yr	2.35 Sv	19.0	10.8
NCRP 50 mSv/yr + 10 mSv x age	0.65 Sv	6.1	3.3

Eighth Annual Beebe Symposium 2009

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