Low Dose Risk Estimation: The Changing Face of Radiation Risk Assessment?

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Radiation Risk Assessment

Risk assessments for radiation-induced cancer and non-cancer endpoints following radiation exposure have relied almost exclusively on the available human data, both from atomic bomb survivors and from medical and occupational exposures.

Advantages and Disadvantages for Radiation Risk Assessment

Advantages:

1. Human Data
2. Available for a broad range of doses
3. Available for relatively low doses

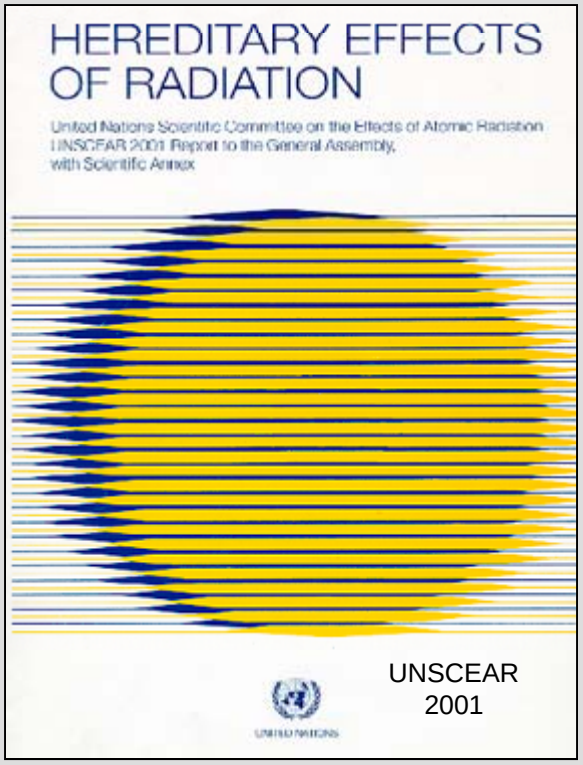
Disadvantages:

1. Obviates the need for use of mechanistic data
2. Does not take account of an understanding of the disease process used for the risk assessment

Epidemiology has not revealed heritable effects in humans – and so mouse experiments are relied upon

In years past, radiation protection centered on the possibility of hereditable effects passed on to future generations.

With continued study of the children of the atomic bomb survivors and of the children of cancer survivors, genetic effects have not been detected and the major concern is somatic effects on the individuals exposed.



Epidemiologic Studies of Exposed Human Populations

JAPANESE ATOMIC BOMB SURVIVORS

RADIOTHERAPY - CANCER

- Cervical
- Endometrial
- Childhood
- Breast
- Hodgkin Lymphoma

RADIOTHERAPY - NON-MALIGNANT

Spondylitis	Mastitis
Thymus	Infertility
Tonsils	Otitis Media
Menstrual Disorders	Ulcer
Scalp Ringworm	Hemangioma

DIAGNOSTIC

TB – Fluoroscopy	Scoliosis
Pelvimetry	General

RADIONUCLIDES

Thorotrast	P - 32
I – 131	Ra - 224
Uranium	Plutonium

OCCUPATION

- Ra Dial Painters
- Miners (Radon)
- Radiologists
- Technologists
- Nuclear Workers
- Atomic Veterans

ENVIRONMENT

- Chernobyl
- Weapons Fallout
- Natl Background
- Techa River

From: John Boice

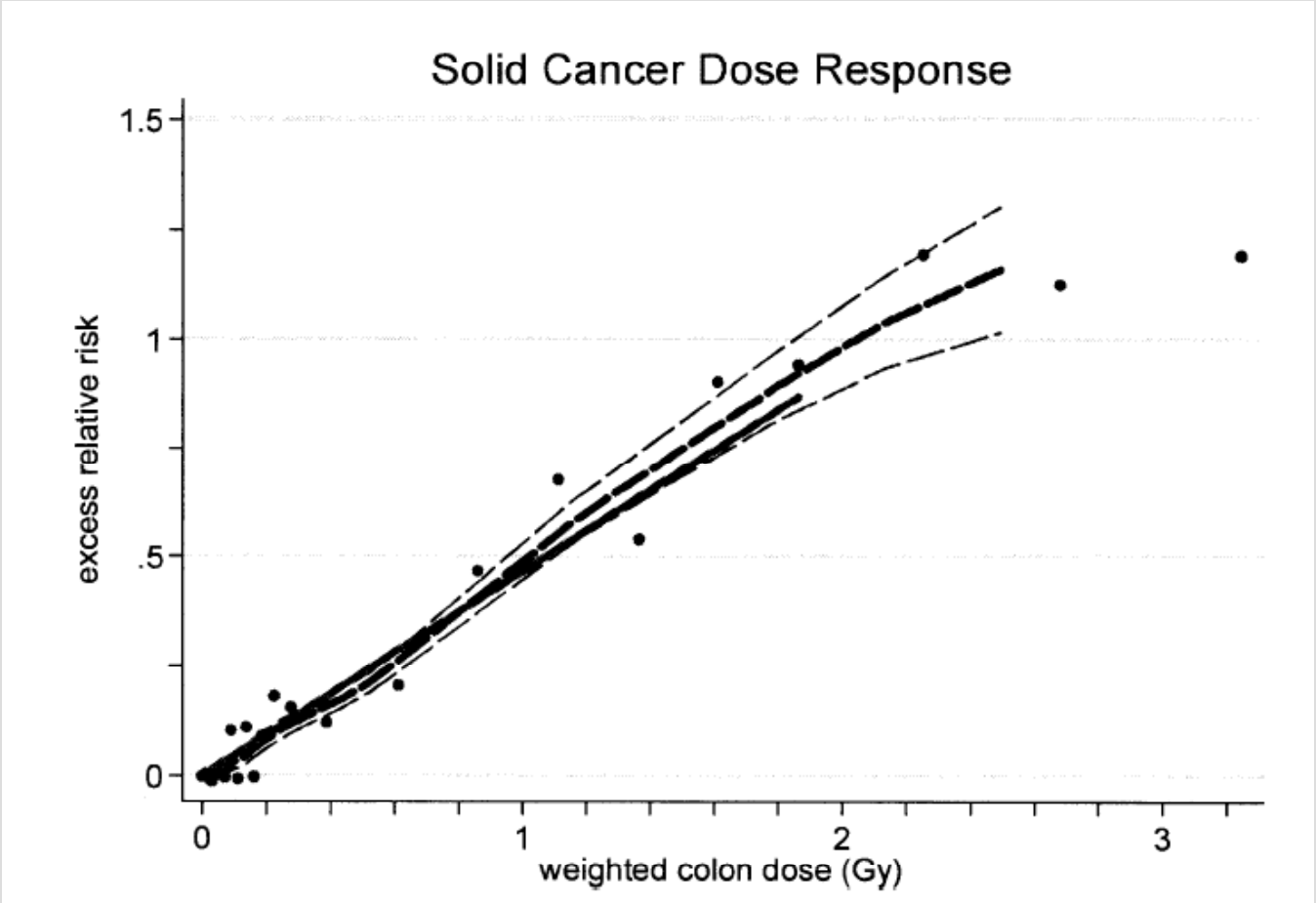
Epidemiological associations have been reported for exposures > 100-150 mSv

Radiation epidemiology has demonstrated excess cancers for exposures over 100-150 mSv and many data are consistent with a linear relationship between dose and effect up to about 2 Sv.

For radiation protection, a linear non-threshold model is used to interpolate risks from higher doses to the low dose domain where epidemiology is incapable of distinguishing effects.

Japanese Atomic Bomb Survivors

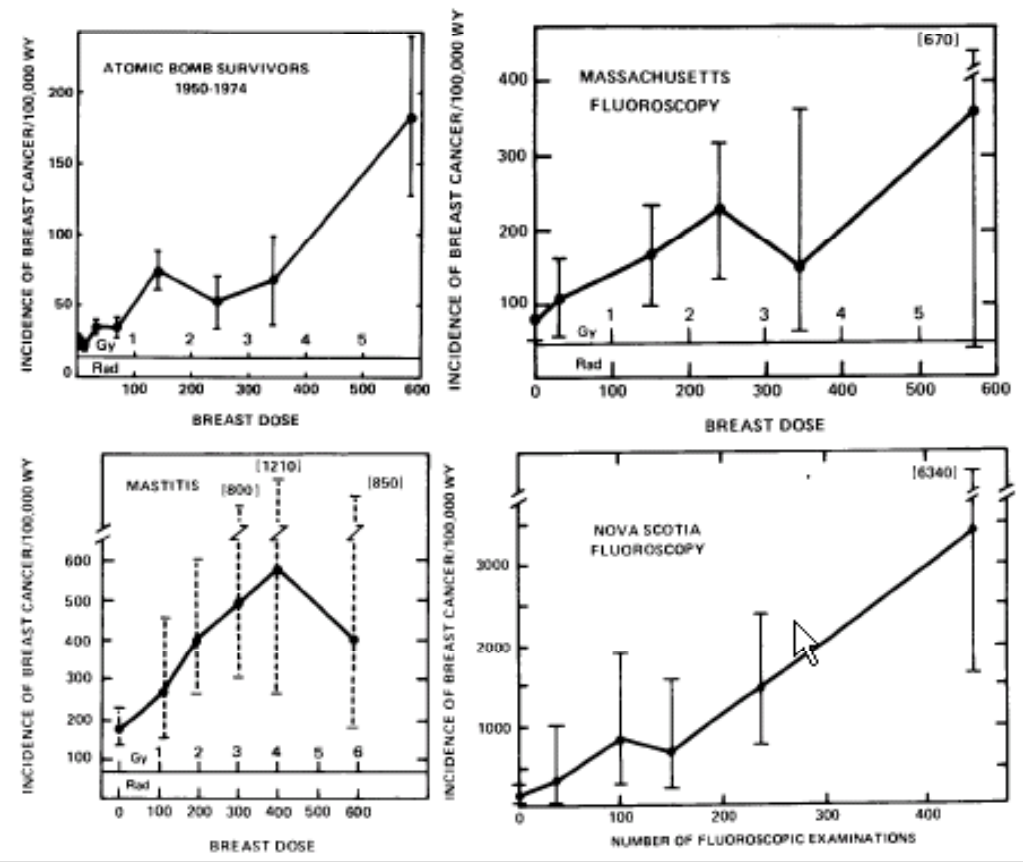
Cancer Incidence, 1958-98



Preston, *Rad Res* 168:1, 2007

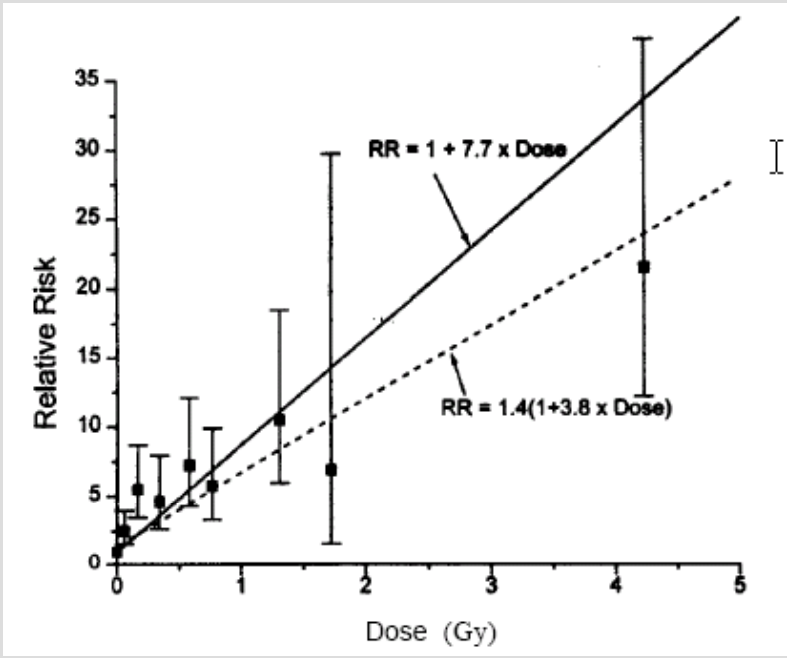
Medically Exposed Populations – Pooled Analysis of Multiple Studies

Breast



Boice, *Radiology* 131:589, 1979

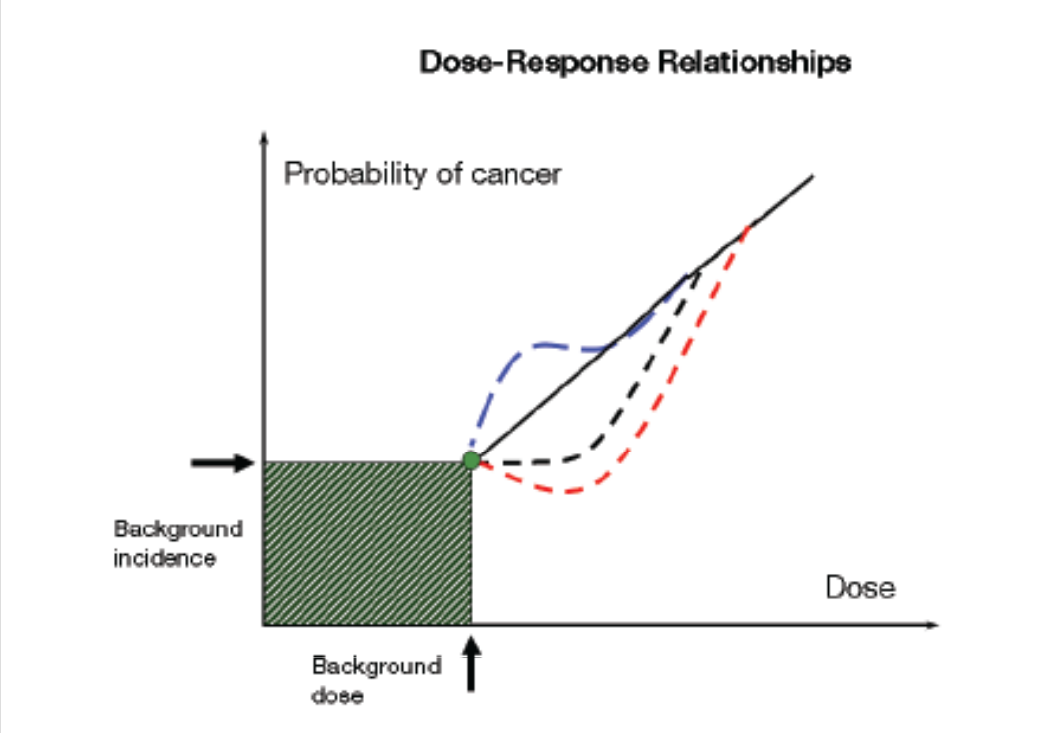
Thyroid



Ron, *Rad Res* 141:259, 1995

Risk Below 100 mSv - Judgment

In the case of cancer, epidemiological and experimental studies provide evidence of radiation risk albeit with uncertainties at doses about 100 mSv or less



Limits of Epidemiology at Doses Below 100 mSv

- **The effect to be detected at low doses is, not surprisingly, very low and the statistical power of epidemiology is insufficient to demonstrate excesses**
- **Bias is more important**
- **Confounding becomes more influential**
- **Adjustments for “uncertainty” can have more influence than the data**
- **Model used can have more influence than the data**

Major Conclusions for Cancer from Radiation Epidemiology

The major conclusions from radiation epidemiology studies are:

- **a single exposure can increase your cancer risk for life**
- **the young are more susceptible than the old**
- **in-utero susceptibility is no greater than early childhood**
- **females are more susceptible than males.**
- **risks differ by organ or tissue and**
- **some sites have not been convincingly demonstrated to be increased after exposure.**

Noncancer Disease Risk

- **Whilst recognizing the potential importance of the observations on noncancer diseases, the Commission judges that the data available do not allow for their inclusion in the estimation of detriment following low radiation doses, less than about 100 mSv. This agrees with the conclusion of UNSCEAR (2008), which found little evidence of any excess risk below 1 Gy. (ICRP Report 103, 2007)**

- **A Draft ICRP Report provides an update on radiation-induced tissue reactions (non-cancer effects) with particular emphasis on lens of the eye and cardiovascular disease that indicates a lowering of the nominal threshold dose for these endpoints**

What Epidemiology Tells Us

- **Epidemiologic data are the basis for cancer risk estimates and for noncancer effects**
- **LNT is used for predicting solid cancer risks at low doses for radiation protection purposes**
- **Human evidence below 100 mSv is inconclusive and will remain so**
- **Thus, continued judgment and radiation biology principles will remain as being paramount in estimating risks at low doses.**

Advances in Radiation Biology and Their Role in Risk Estimation at Low Doses

Recent advances in radiation biology with experimental animals and cellular systems have required reconsideration of possible adverse outcomes at low doses.

Knowledge of the roles of induced genomic instability, bystander cell signaling and adaptive response in the genesis of radiation-induced health effects is insufficiently well developed for radiological protection purposes; in many circumstances these cellular processes will be incorporated in epidemiological measures of risk. (ICRP 103, p 143)

New technologies for developing a molecular understanding of adverse health outcomes and for defining cellular, tissue and organ responses to low doses of radiation have not been exploited in the risk assessment process

Is There a Solution ?

The solution would seem to lie in using a combination of epidemiology, laboratory animal studies and cellular and molecular biology research to reduce the reliance on extrapolations from the available data to the levels of interest, for the populations of interest and for the exposure characteristics of interest. Use of a biologically-based risk assessment process is indicated.

Key Events Framework

- **The US EPA's Guidelines for Carcinogen Risk Assessment define a framework for incorporating mechanistic data into cancer risk assessment for predicting tumor response at low environmental exposures**
- **The framework is defined by mode of action and key events together with a human relevance framework**
- **A similar approach can be used for non-cancer endpoints**

Mode of Action

The term "mode of action" is defined as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation.

A "key event" is an empirically observable precursor step that is itself a necessary element of the mode of action or is a biologically based marker for such an element

Key Events for Tumor Development: DNA-reactive MoA (e.g., Ionizing Radiation)

- Exposure of target cells to ultimate DNA-reactive and mutagenic entity
- Reaction with DNA in target cells to produce DNA damage
- Replication or repair errors from damaged template
- Mutations in critical genes in target cell
- Enhanced cell proliferation
- Additional mutations induced from DNA damage and repair/replication
- Clonal expansion of mutant cells
- Preneoplastic lesions and neoplasms develop
- Malignant behavior

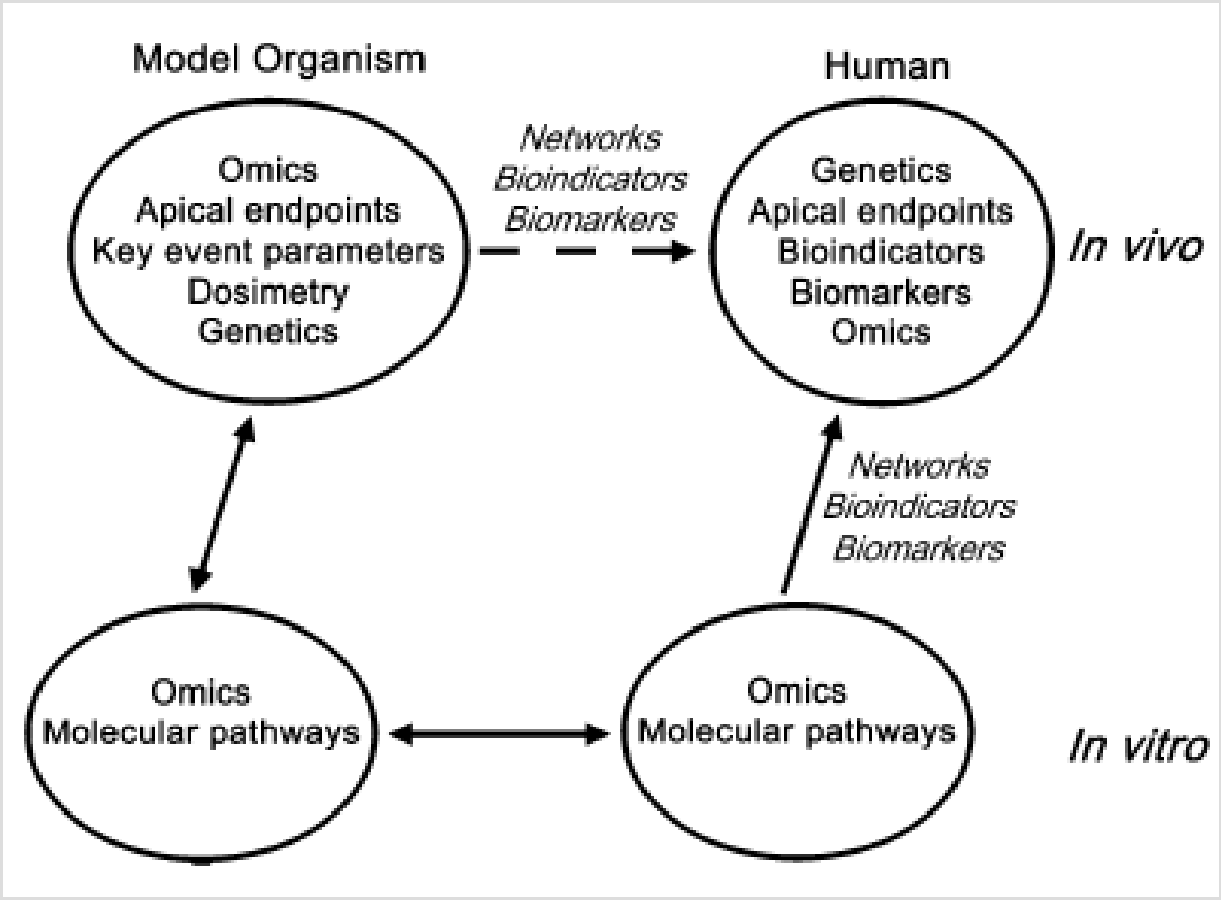
Adapted from Preston and Williams, 2006

Key Events and Bioindicators

The identification of specific key events in tumor formation can be used for the selection of informative bioindicators of response – either preneoplastic lesions or tumors

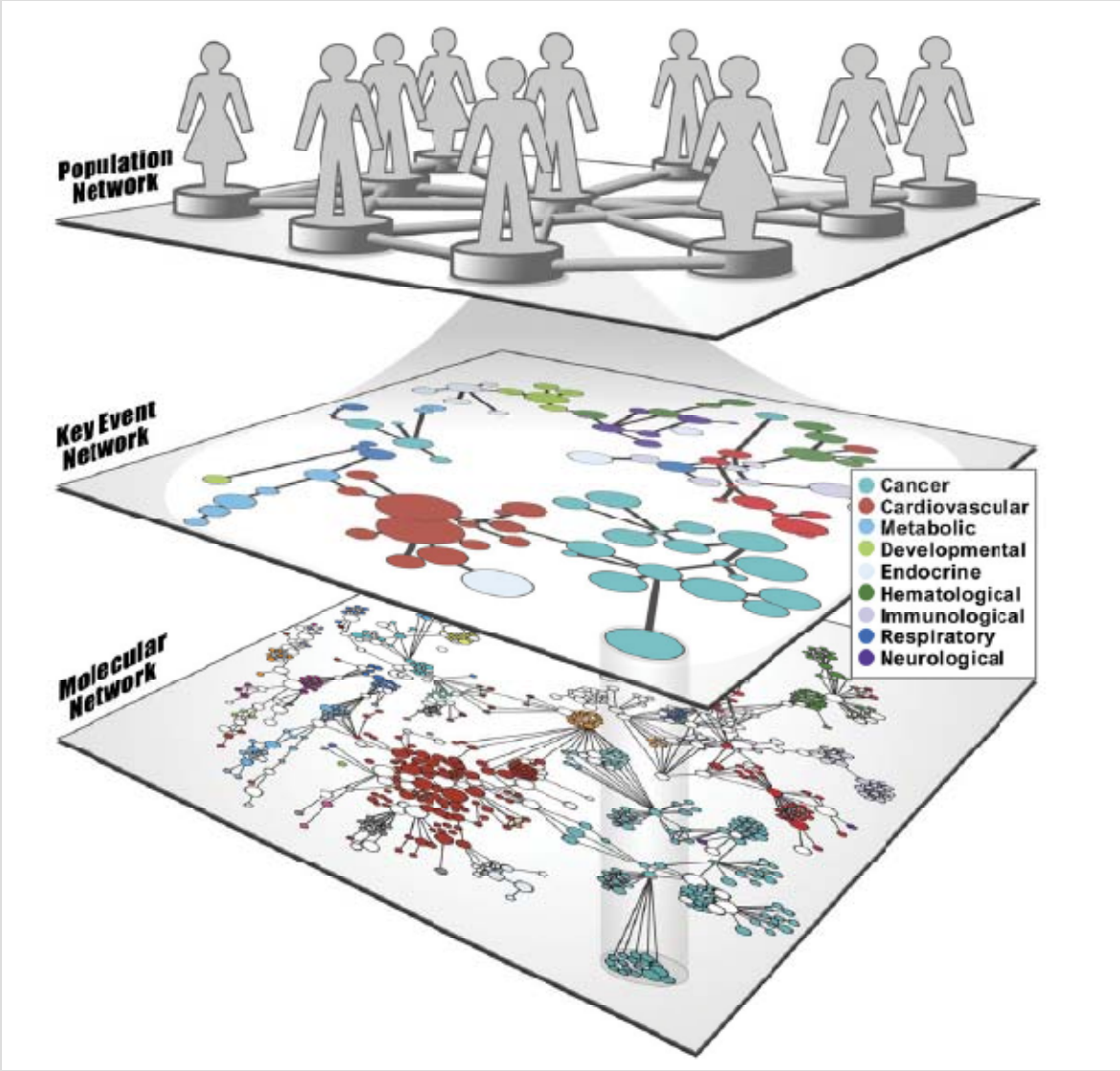
Bioindicators of Tumors – Qualitative and Quantitative

- **Some bioindicators can be used to establish the shape of a tumor dose-response at levels below those at which any increase in tumors from exposure can be identified – qualitative**
- **Other bioindicators can possibly be used to estimate the frequency of tumors at low levels of exposure - quantitative**



Schematic illustration of how systems approaches fit into the traditional parallelogram for risk assessment.

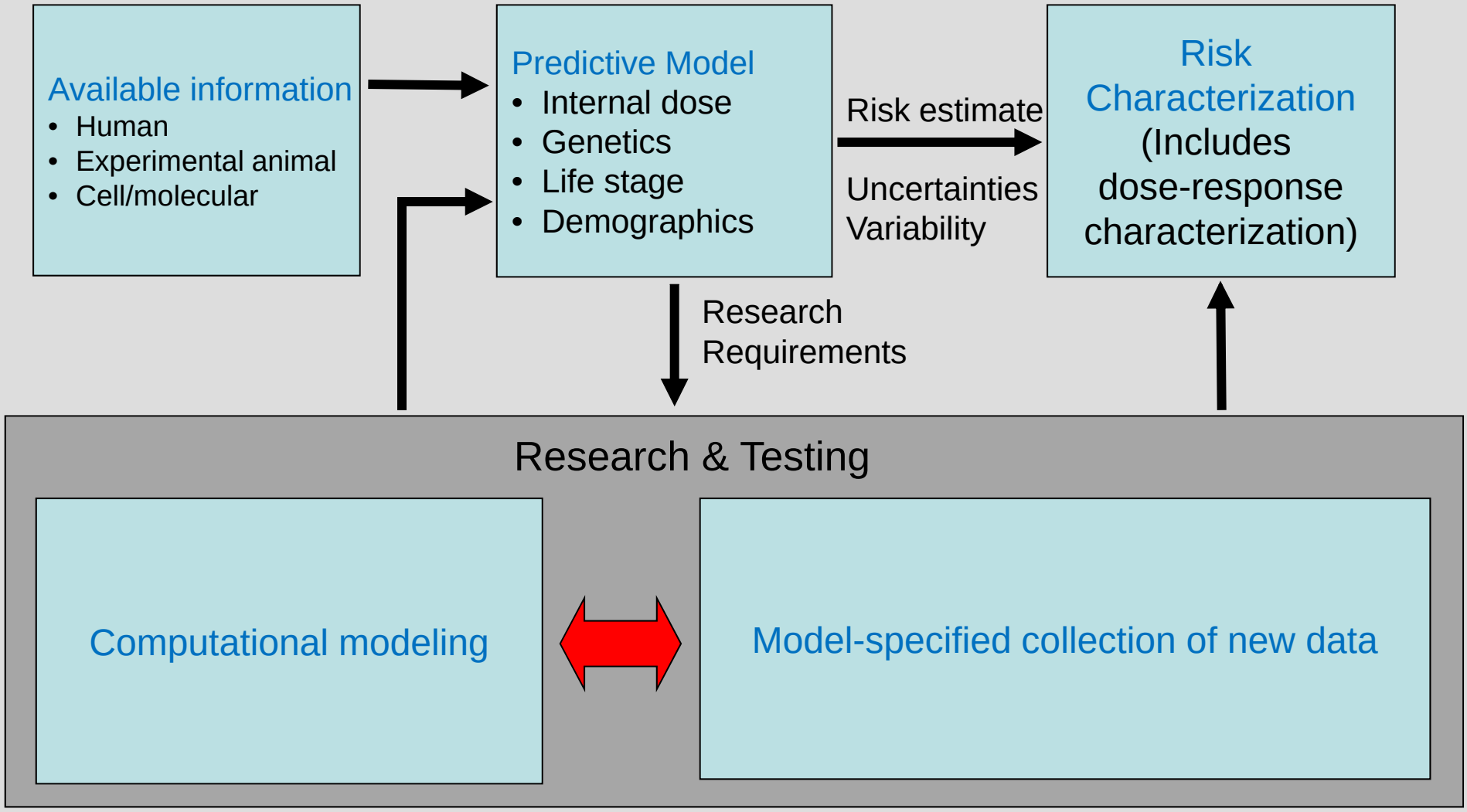
Edwards and Preston, 2008



Networks at different levels of abstraction can be used to merge molecular level changes with measured events at the individual or population level. Molecular networks, driven mainly by data from genome-wide assays, are related to key events in disease processes.

Edwards and Preston, 2008

In an ideal world…



From Stephen Edwards

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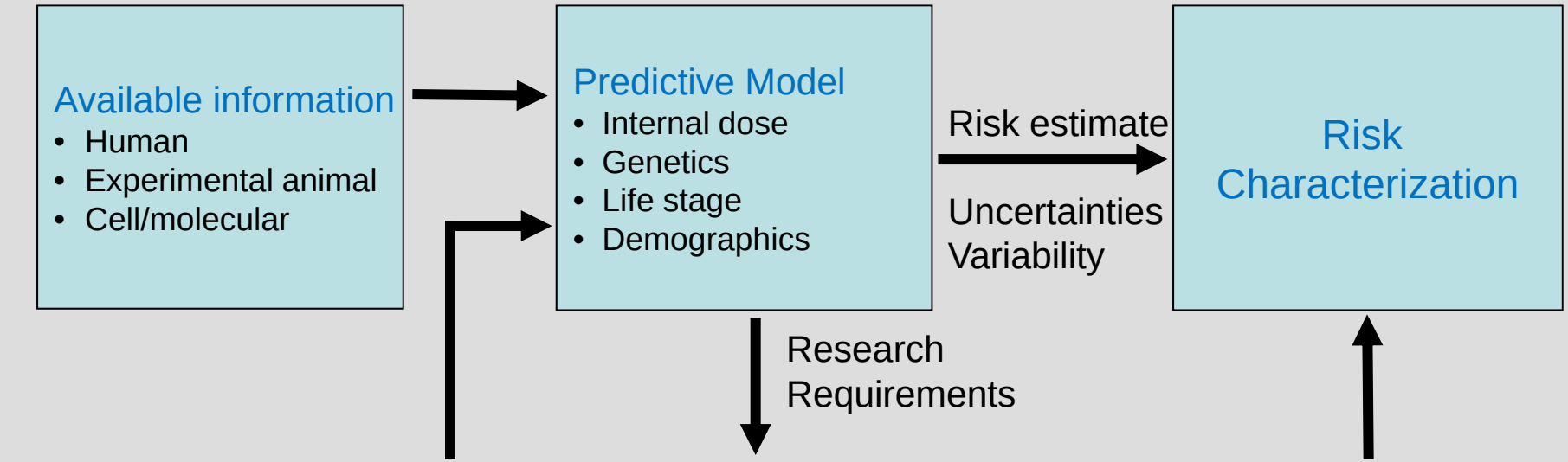


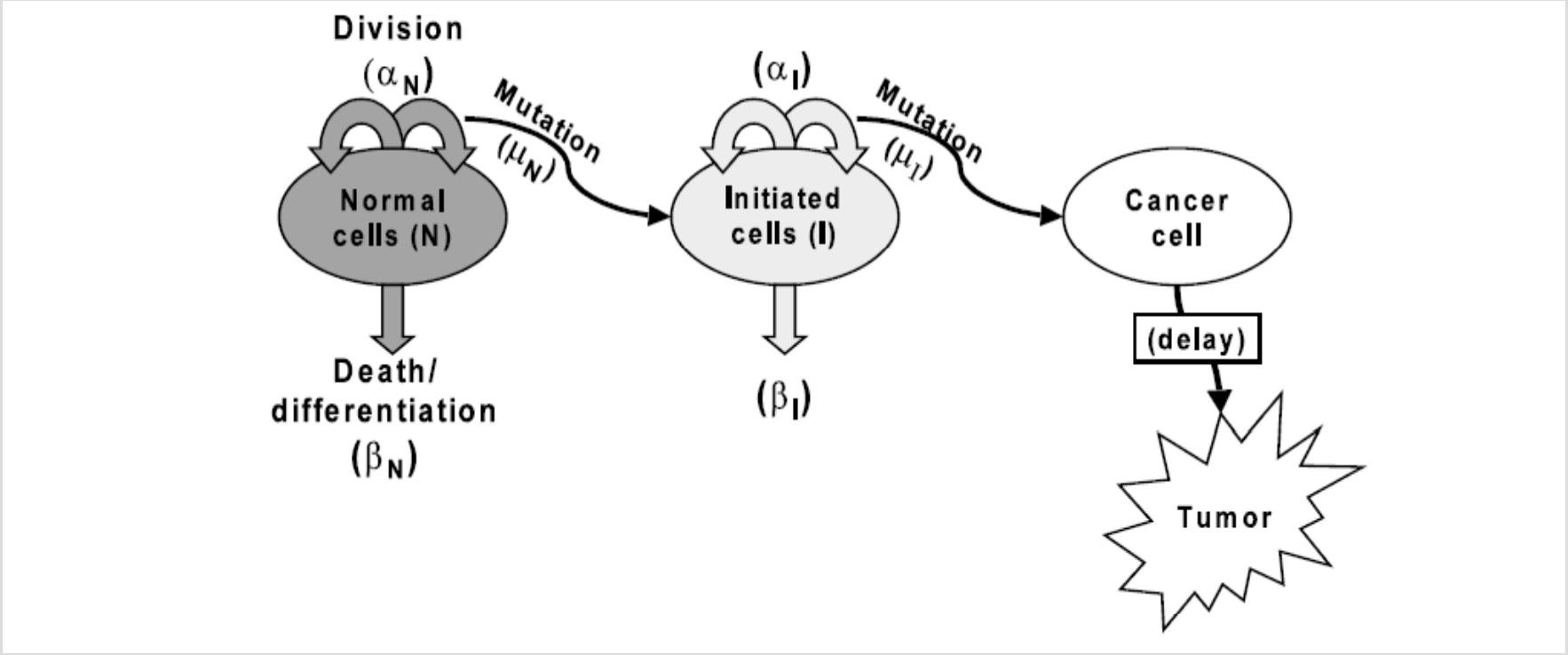
Research & Testing

Computational modeling
- Define conceptual model
- Identification of data gaps
- Estimate model parameters
- Estimate population variability
- Estimate model uncertainty

Model-specified collection of new data
- Exposure, biomonitoring data
- Animal toxicology, in vitro & in vivo
- Clinical studies
- Epidemiology

From Stephen Edwards

Two Stage Clonal Growth Model



From Conolly, Toxicology 181-182 (2002)

Example of Biologically-Based Model of Cancer Risks

Cancer Risks After Radiation Exposure in Middle Age

Igor Shuryak, Rainer K. Sachs, David J. Brenner

J Natl Cancer Inst 2010;0:1–9

Methods We analyzed observed cancer risk patterns as a function of age at exposure in Japanese atomic bomb survivors by using a biologically based quantitative model of radiation carcinogenesis that incorporates both radiation induction of premalignant cells (initiation) and radiation-induced promotion of premalignant damage. This approach emphasizes the kinetics of radiation-induced initiation and promotion, and tracks the yields of premalignant cells before, during, shortly after, and long after radiation exposure.

Models, Models Everywhere—Is There a Fit for Lifetime Risks?

John D. Boice Jr

New Technologies That Can Help

Ultra-High Throughout Sequencing

Tremendous amount of sequence data can be obtained at an astounding pace that allows for assessment of whole genome effects. Applications include:

Genome sequencing/resequencing
Small RNA discovery
Deep SNP discovery
Chromatin immunoprecipitation (ChIP)
RNA immunoprecipitation plus sequencing
Transcriptome analysis plus annotation
Alternate splicing discovery and characterization
Gene Expression Profiling

Genome-Wide Tiling Arrays

- **Tiling Arrays** are a subtype of microarray chips. They function on a similar principle to traditional microarrays in that labeled target molecules are hybridized to unlabeled probes fixed on to a solid surface. Tiling arrays differ in the nature of the probes. Short fragments are designed to cover the entire genome or contigs of the genome. Depending on the probe lengths and spacing, different degrees of resolution can be achieved. The number of features on a single array can range from 10,000 to greater than 6,000,000, with each feature containing millions of copies of one probe. Tiling arrays are quickly becoming one of the most powerful tools in genome-wide investigations.

Epidemiology and Molecular Epidemiology Studies

- **Enhance informative data by assessment of specific set of bioindicators in available biological samples. Develop linkage between measures of these and adverse health outcome in a target organ. Use bioindicator data to enhance tumor dose-response at low exposure levels.**

Conclusions

- **Large scale epidemiology studies for low chronic exposures (occupational) are still required**
- **Epidemiology has to be supported by experimental animal and cellular data to enhance low dose risk estimation and for addressing uncertainty**
- **New technologies and experimental models have made such low dose cellular and molecular studies feasible**
- **Just do it!**

Additional Slide If Needed

Genome-Wide Tiling Array Approaches