Petition on Cancer, Epidemiology and Overview of Mechanisms of Carcinogenesis

Elizabeth Ward, PhD

Request from Dr. Howard

"I request that the STAC review the available information on cancer outcomes associated with exposures resulting from the September 11, 2001 terrorist attacks, and provide advice on whether to add cancer, or a certain type of cancer, to the List (of WTC related health conditions) specified in the Zadroga Act."

It is _____ that exposure to WTC dust may cause cancer

a) unlikely
b) possible
c) biologically plausible
d) probable
e) proven

What is the scientific rationale?

Scientific rationale

- What we know
- What don’t we know
- What we believe

Review of Data

(1) Epidemiologic studies

(2) Potential carcinogens present in WTC dust

(3) Mechanisms of carcinogenesis

Epidemiologic Cohorts

(adopted from Perlman et al., 2011)

Name or sponsor	Groups Studied	Size (12/31/2010)	Notes
Fire Department of New York	Firefighters and EMS Workers	15,415	Employer-based medical program
NY & NJ WTC Clinical Consortium	Law enforcement & other responders, sanitation & construction workers, volunteers	29,572	Provides screening, monitoring and treatment
WTC Environmental Health Center	Area workers, residents, students	5,130	Monitors & treats, includes children
WTC Health Registry	Rescue & recovery workers, area workers, residents, students	71,437	30% recruited from employers & govt. agencies, others self-enrolled

FDNY Study

- 9,853 firefighters employed on 1/1/1996; 8,927 WTC-exposed starting on 9/11/2001
- Standardized incidence ratio for all cancers among WTC-exposed firefighters of 1.10 based on general population rates and 1.19–1.32 based on unexposed firefighters
- Elevated or borderline excesses for stomach, colon, melanoma, prostate, thyroid, NHL compared to general population rates

Other epidemiologic findings related to cancer

- No excess of all cancers combined or 8 major organ systems in first follow-up of WTC Health Registry Cohort
- Case reports suggesting possible excess of multiple myeloma

Limitations of Epidemiologic Evidence

- Misclassification → difficult to accurately estimate exposure → reduced strength of association → lack of clear "exposure-response" trend
- Complex and multiple exposures → difficult to attribute causality → lack of consistency in findings among exposed populations & studies
- Population sizes → insufficient to rule out small risks and risks for rarer cancers

Limitations of Epidemiologic Evidence, cont.

Cancer's latent period → cancer risk may not appear until 20 or more years after first exposure.

Latent period is most relevant in epidemiologic studies when results are negative and follow-up period may be too short to observe an effect.

If epidemiologic data are not definitive, what can we learn from exposure data?

- Interpreting air sampling data from WTC site is difficult and controversial; no data in the critical first week after the building collapse
- (Belief) Relatively low air levels measured in some early studies at the WTC site inconsistent with observed high rates of respiratory symptoms
- One approach to evaluating potential cancer hazard is to examine composition of the initial dust/smoke (as reflected in the dust samples collected)

Who could have been or could be exposed to the materials present in the *initial* dust/smoke?*

Initial collapse of the WTC

- Local and downwind residents
- Rescue workers
- Commuters
- Shop/business owners, operators & customers

Re-suspension of the dust/smoke during the following week

- Professional & volunteer rescue workers
- Outdoor & indoor cleanup workers
- Residents & workers in Wall Street area downwind

Re-suspension of dust/smoke during the next weeks/months

- Workers not wearing respiratory protection at WTC site
- Indoor cleanup workers not wearing respiratory protection
- Residents & workers returning to poorly cleaned buildings

*Although not measured, gases would be associated with many of these exposures

Adapted from Lioy, 2006

What materials were present in the initial dust/smoke?

- Gypsum (major component of drywall)
- Concrete dust (cement dust, crystalline silica)
- Glass fragments and man-made vitreous fibers
- Asbestos
- Polycyclic aromatic hydrocarbons (PAH's)
- Metals (hexavalent chromium, nickel, arsenic)
- Volatile organic compounds (benzene)

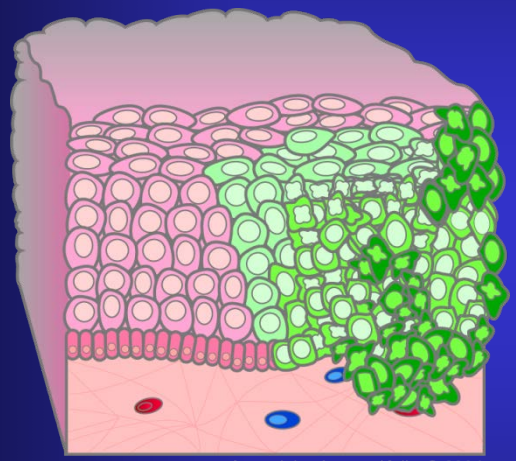
Which materials appear to be of most concern for cancer?

- Gypsum (major component of drywall)
- Concrete dust (cement dust, crystalline silica)
- Glass fragments and man-made vitreous fibers
- Asbestos
- Polycyclic aromatic hydrocarbons (some PAH's)
- Metals (hexavalent chromium, nickel, arsenic)
- Volatile organic compounds (benzene)

RED = IARC Group 1, NTP human carcinogen

Understanding Cancer and Related Topics

Understanding Cancer



Artwork by Jeanne Kelly. © 2004.

Developed by:
Lewis J. Kleinsmith, Ph.D.
Donna Kerrigan, M.S.
Jeanne Kelly
Brian Hollen

Discusses and illustrates what cancer is, explains the link between genes and cancer, and discusses what is known about the causes, detection, and diagnosis of the disease.

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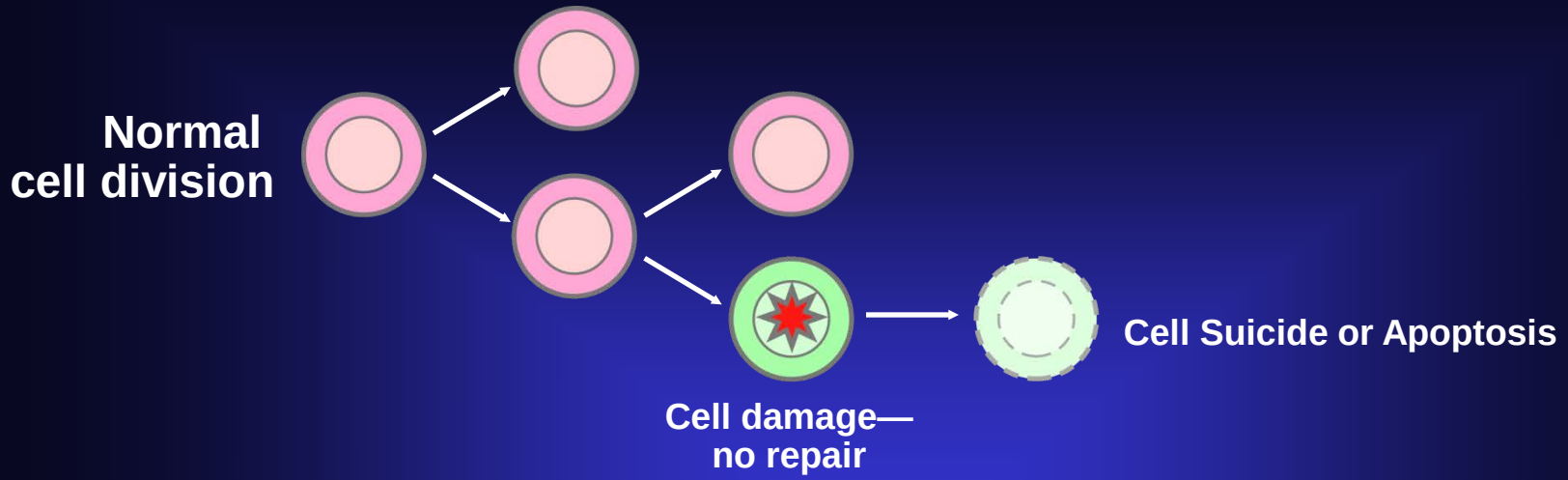
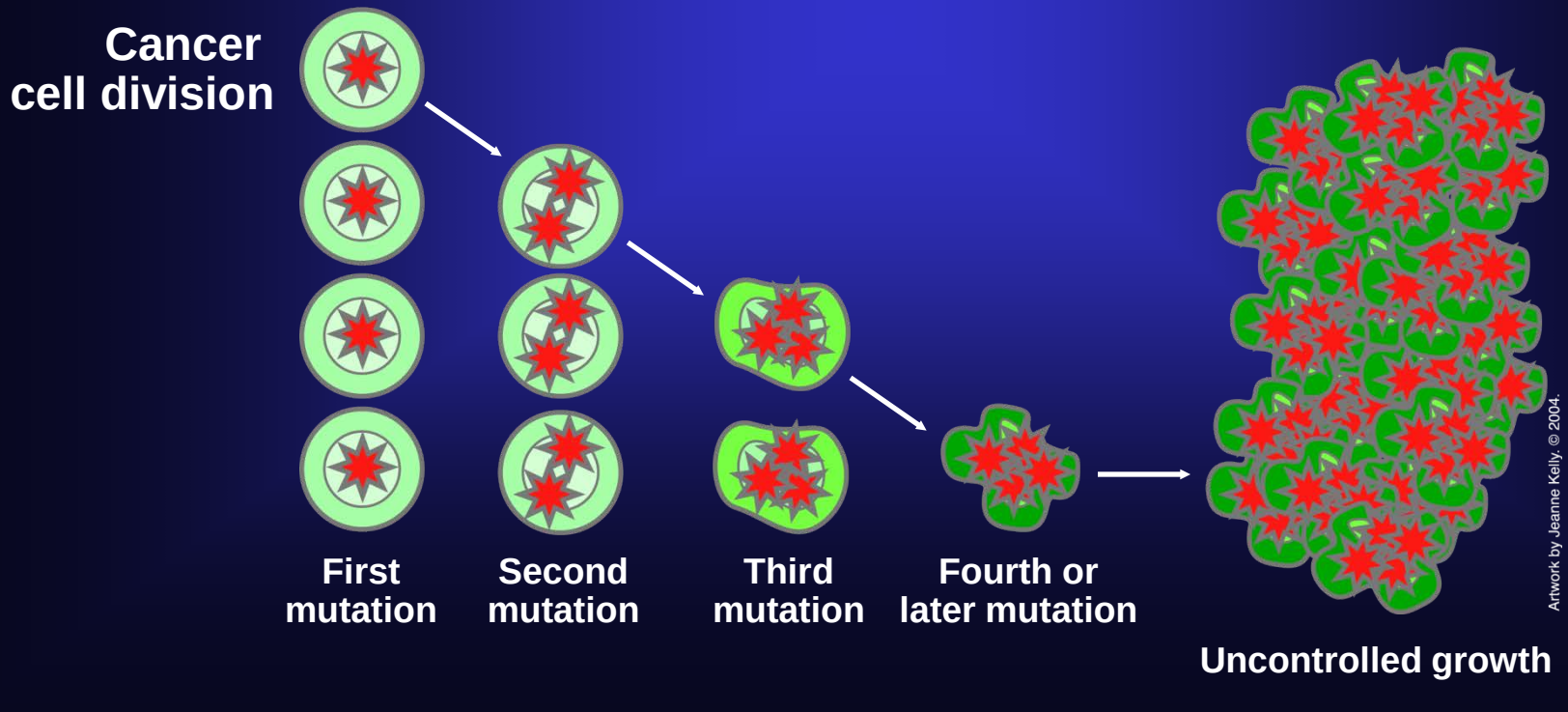
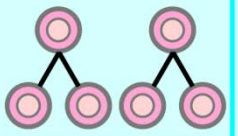
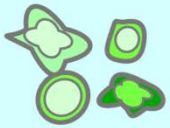
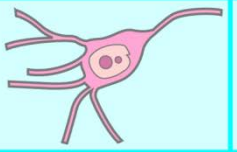
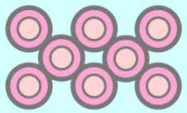
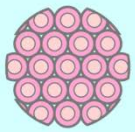
Loss of Normal Growth Control





Microscopic Appearance of Cancer Cells

Normal	Cancer	
		Large number of irregularly shaped dividing cells
		Large, variably shaped nuclei
		Small cytoplasmic volume relative to nuclei
		Variation in cell size and shape
		Loss of normal specialized cell features
		Disorganized arrangement of cells
		Poorly defined tumor boundary

Artwork by Jeanne Kelly. © 2004.

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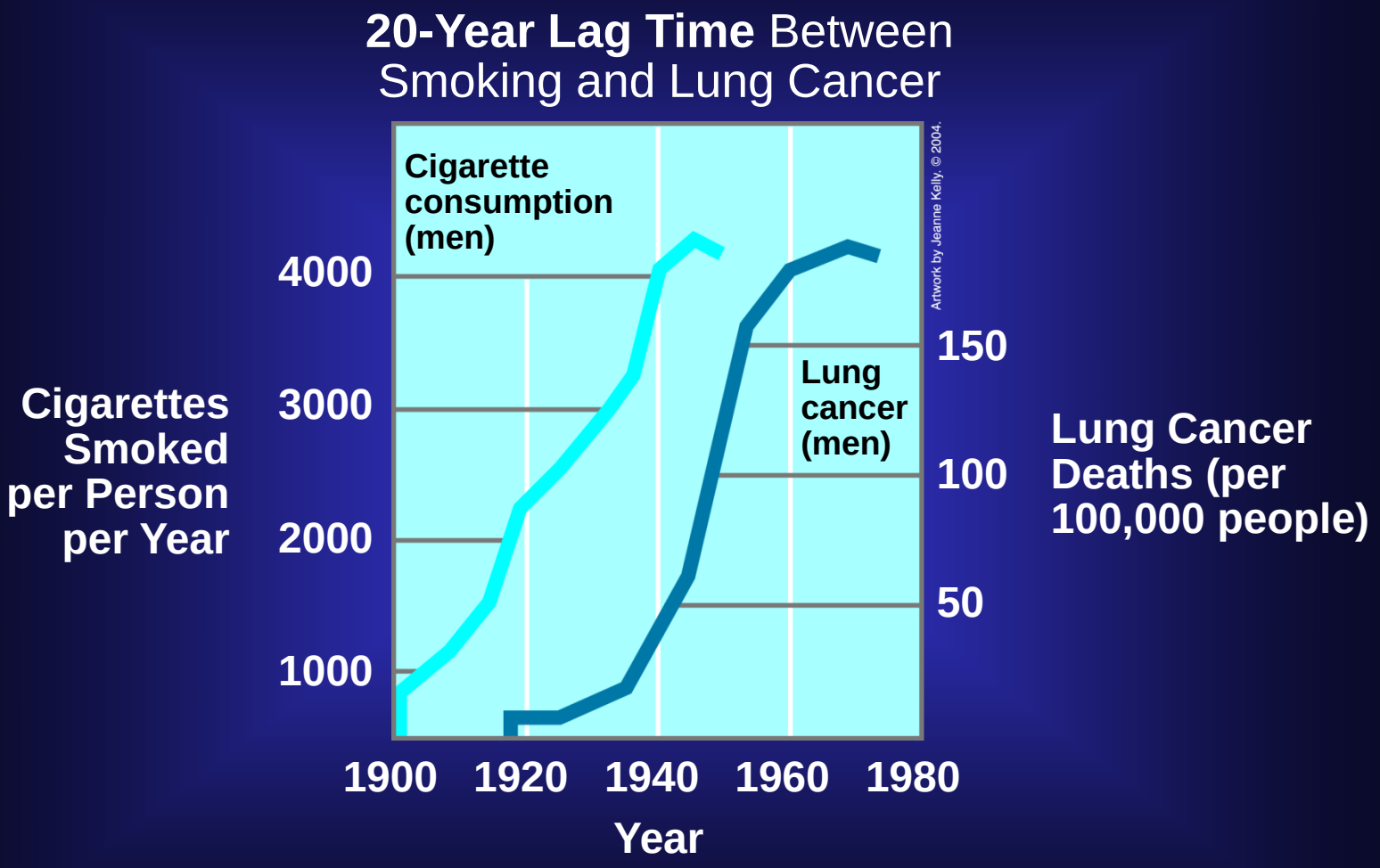
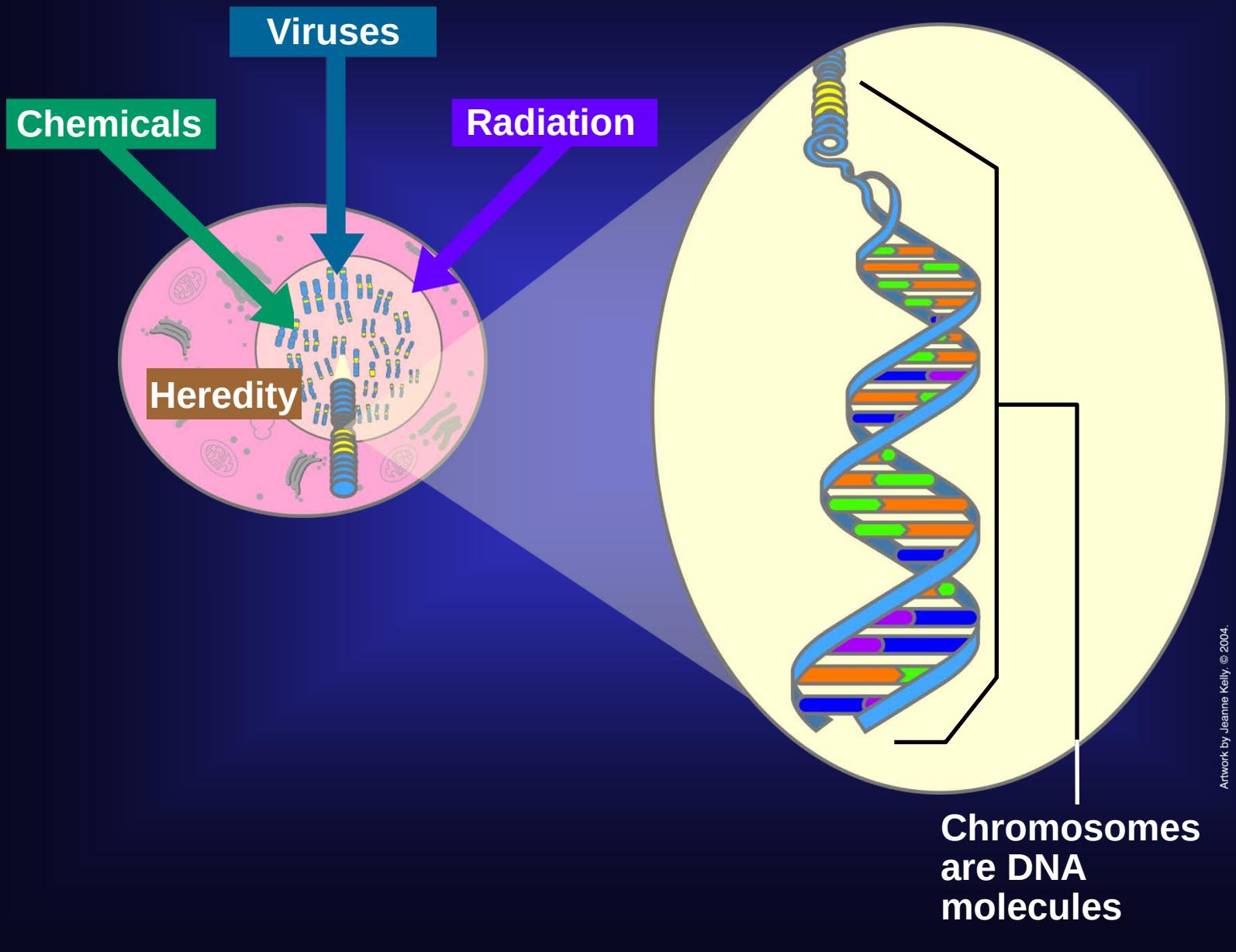
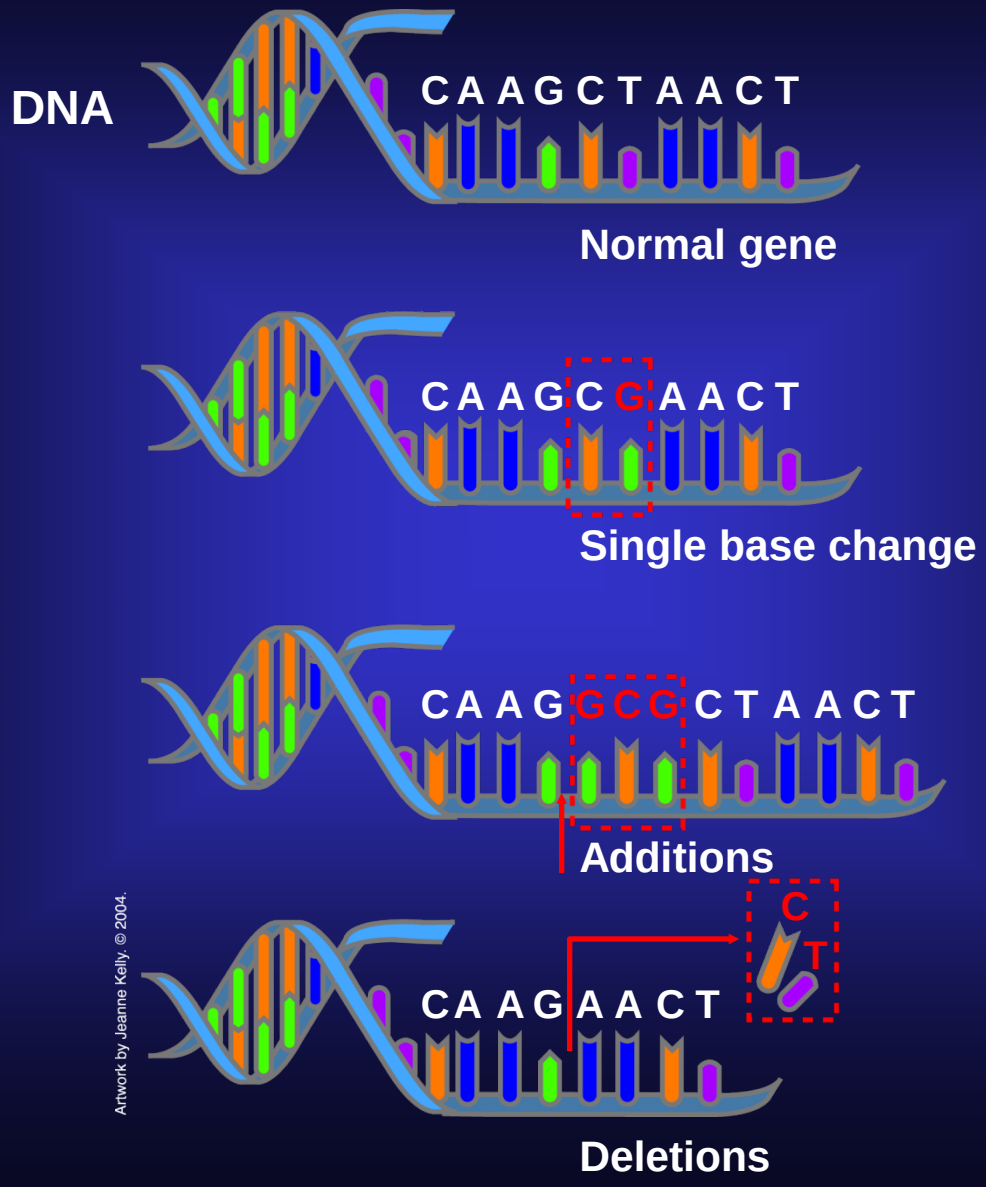
Lag Time



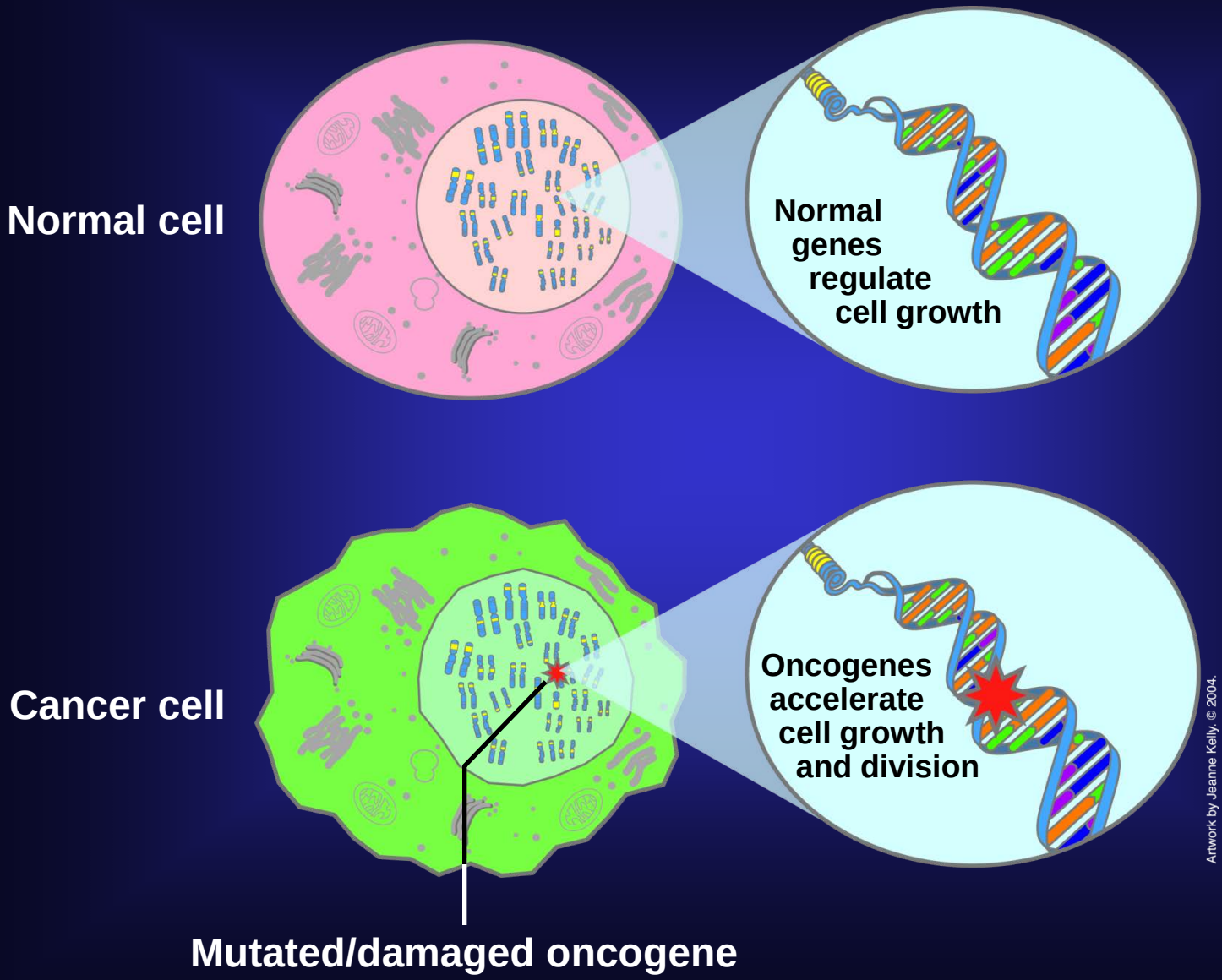
Genes and Cancer



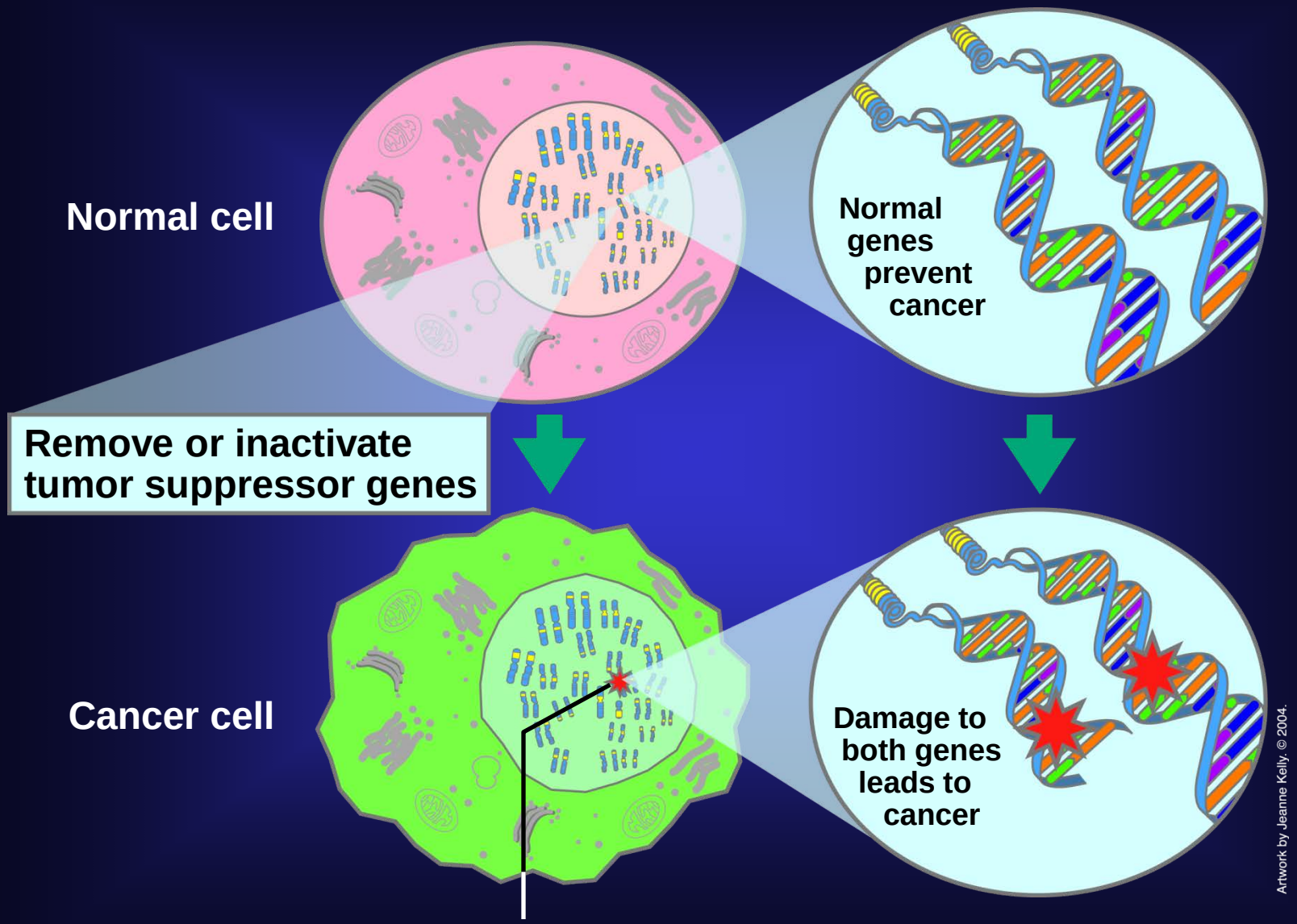
DNA Mutation



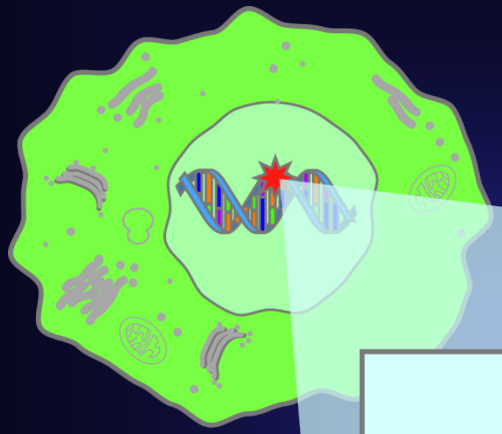
Oncogenes

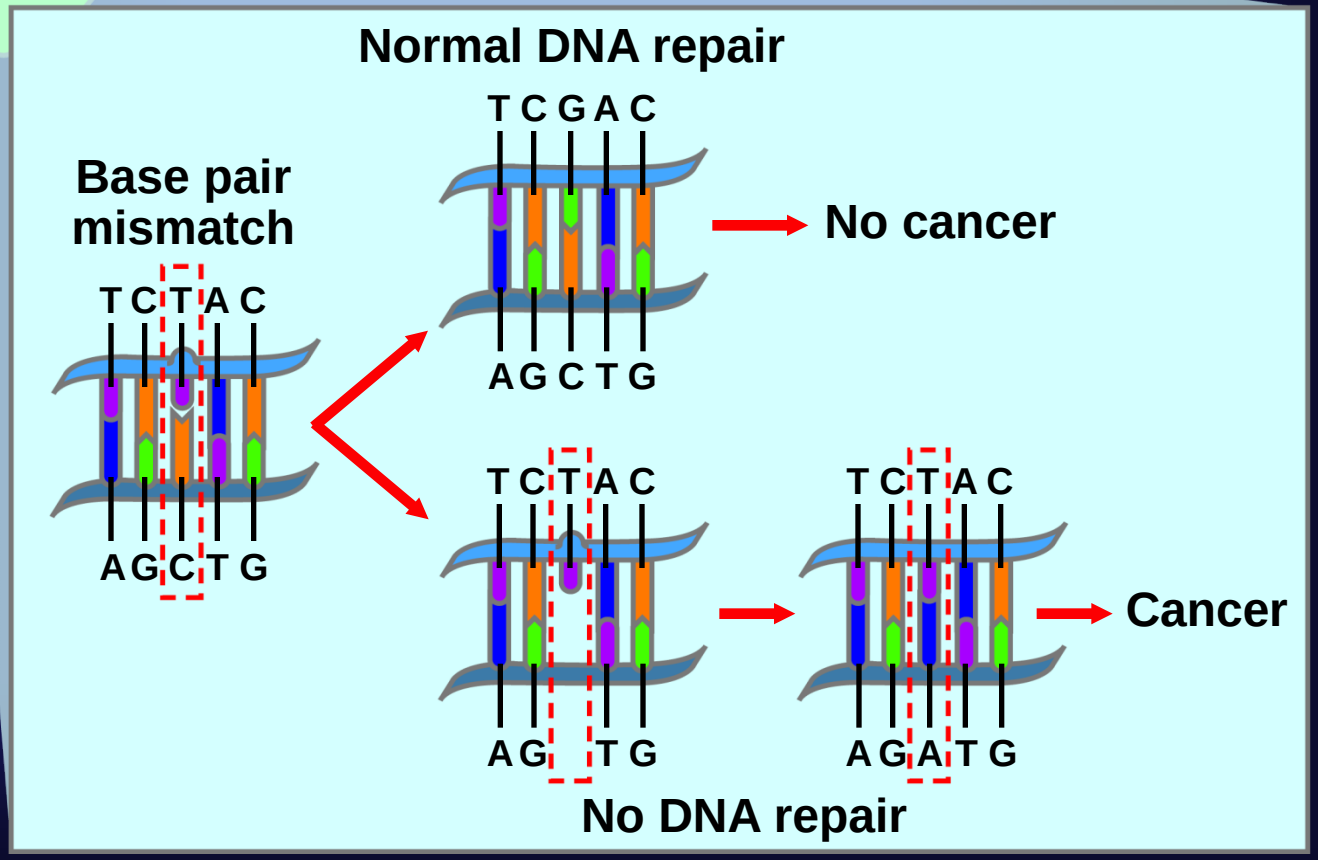


Tumor Suppressor Genes



DNA Repair Genes

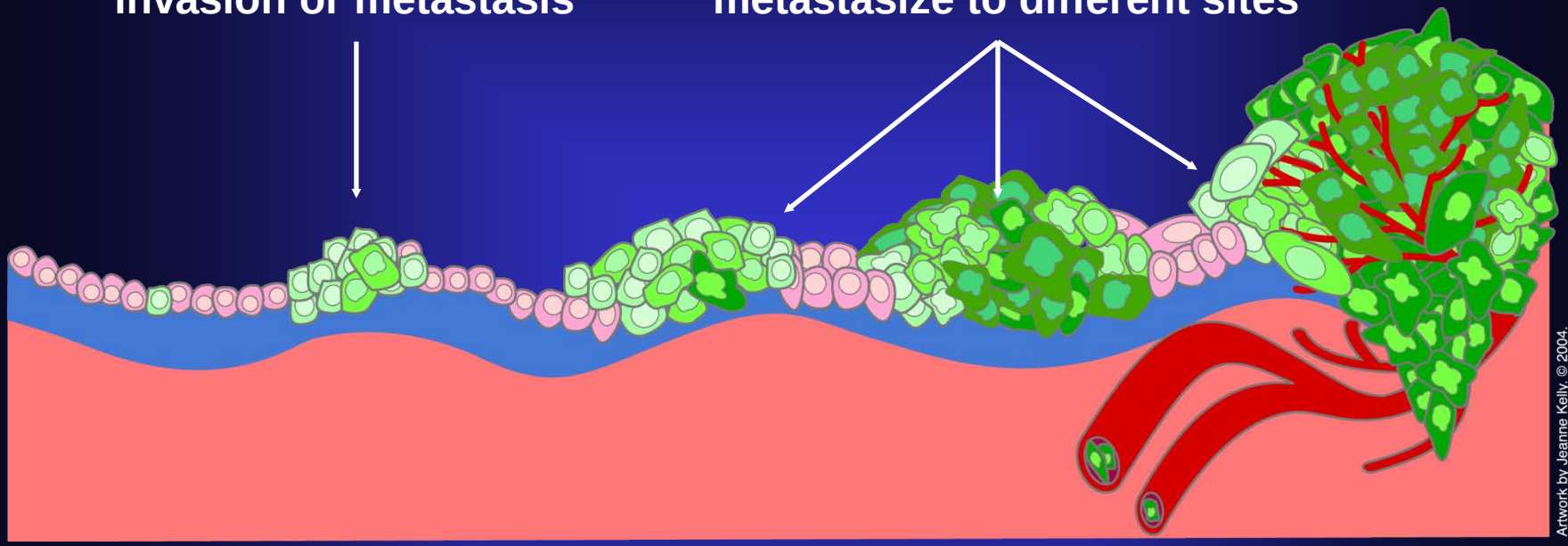




Cancer Tends to Involve Multiple Mutations

Benign tumor cells grow only locally and cannot spread by invasion or metastasis

Malignant cells invade neighboring tissues, enter blood vessels, and metastasize to different sites



Time

Mutation inactivates suppressor gene

Cells proliferate

Mutations inactivate DNA repair genes

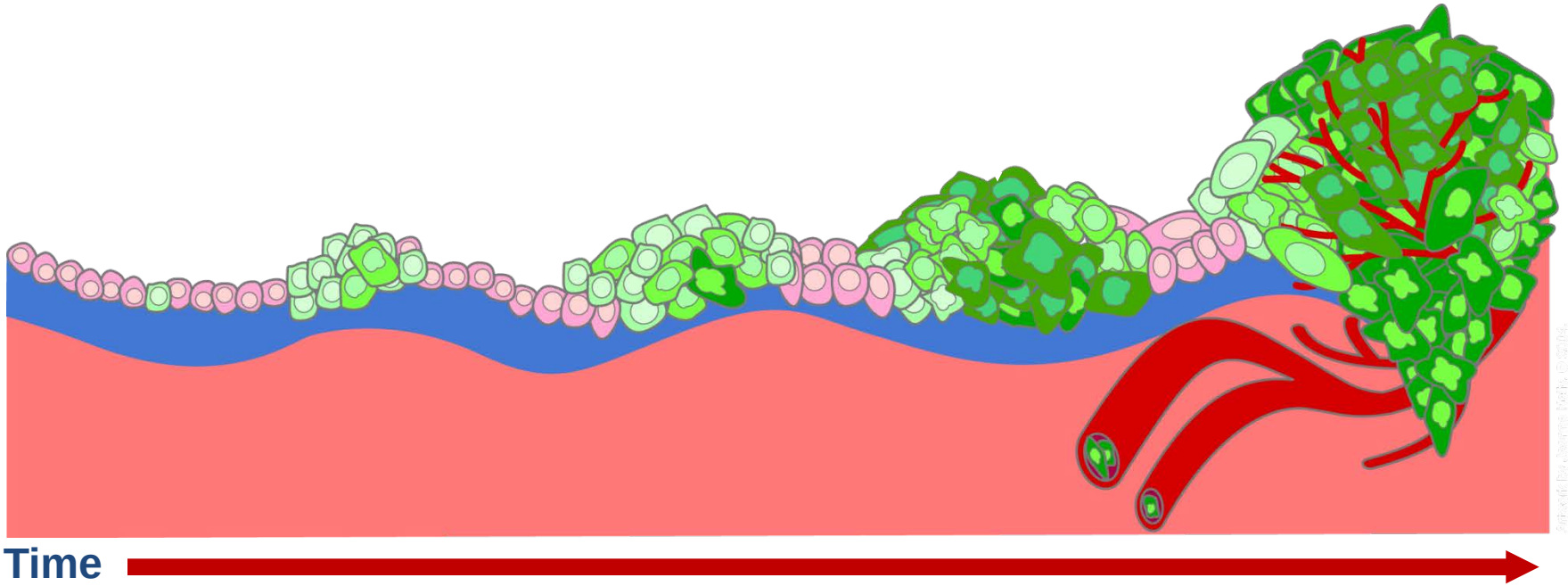
Proto-oncogenes mutate to oncogenes

More mutations, more genetic instability, metastatic disease

Process of Carcinogenesis

Many cancers take a long time to develop

Most tumors evolve through a number of stages



Time

Initiation **Promotion** **Malignant transformation** **Progression, invasion and metastasis**

Inflammation and Cancer

- Inflammation is a normal response to tissue damage resulting from infection, chemical irritation and/or wounding. When it becomes chronic, it can damage the body and lead to illness.

- Inflammatory diseases associated with cancer include certain immunologic disorders, infections and chronic chemical and mechanical irritation.

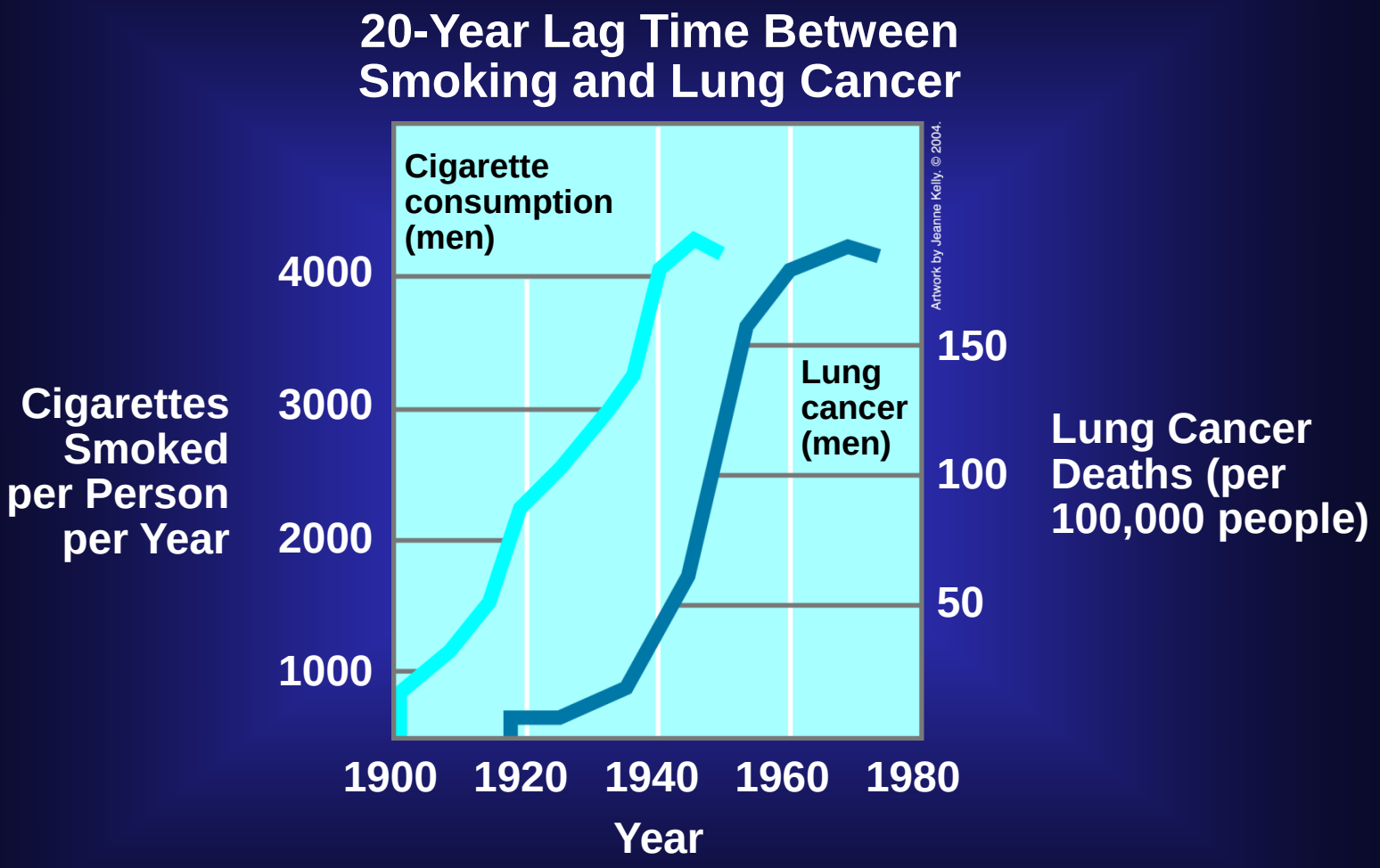
- Inflammation can lead to cancer through a variety of mechanisms: increased cell proliferation, generating mutagens from releasing reactive oxygen and nitrogen species, and producing biologically active chemicals that influence the cellular/tissue microenvironment.

Other considerations

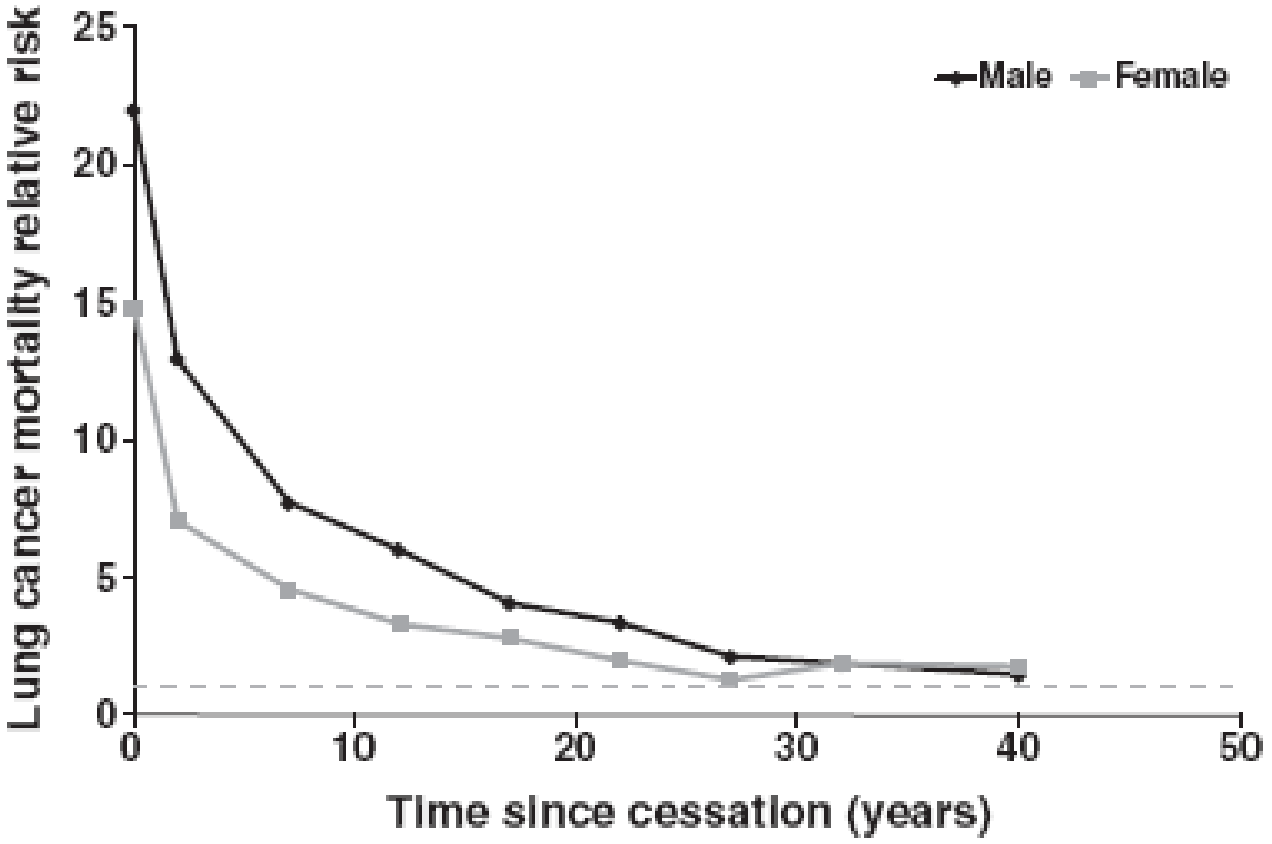
- **Duration of exposure**: Since inhaled fibers and dusts may remain in the body for a long time, a short-term environmental exposure can lead to a long-term biological exposure

- **Latent period:** Although on average it takes 20 or more years for a solid tumor to develop after, most carcinogens can act at during multiple stages of the carcinogenic process, and can impact cancer risk in a shorter time frame; this is most evident when an exposure is withdrawn.

Lag Time

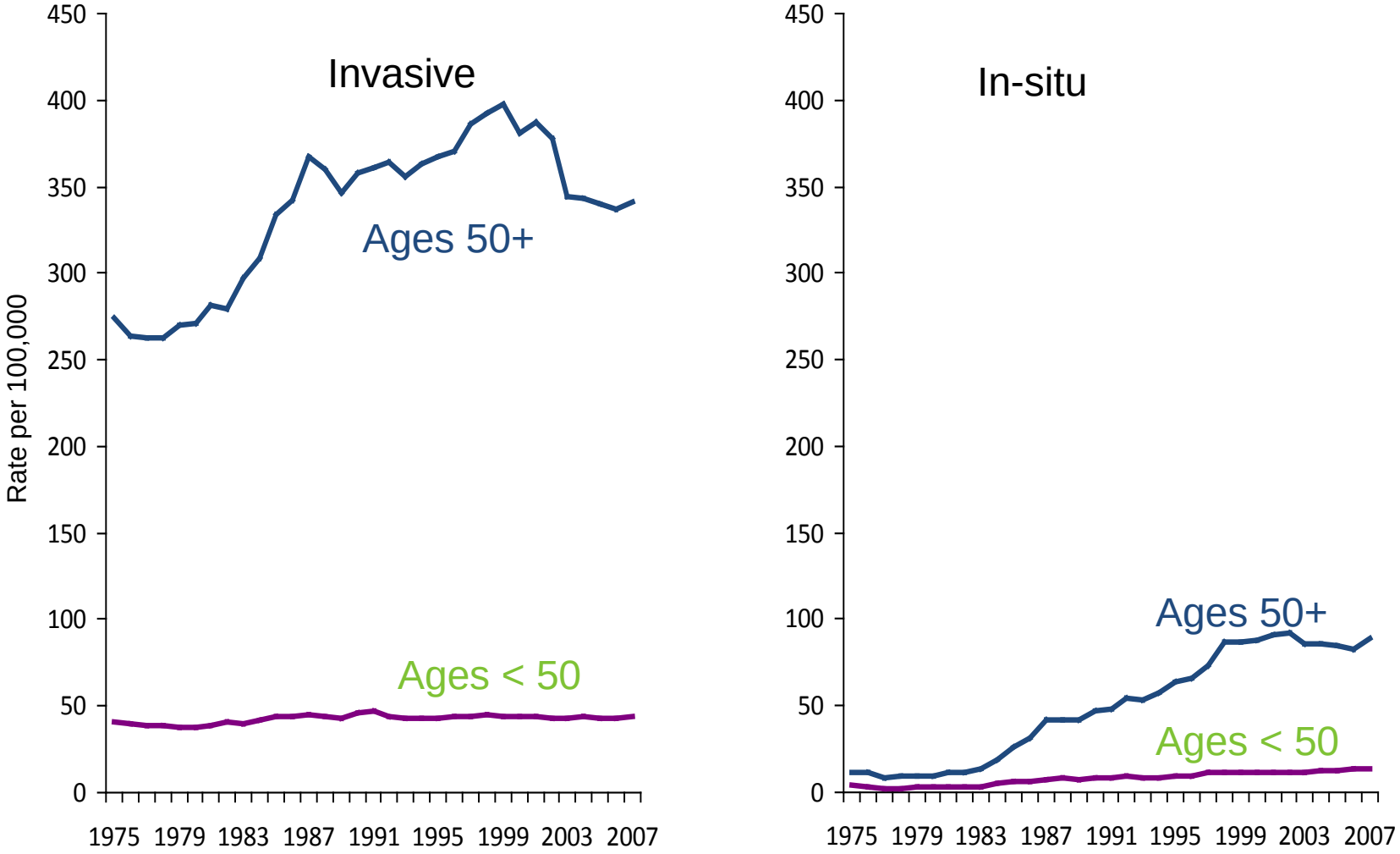


Relative risk of lung cancer falls rapidly after smoking cessation



Source: Oza S, et al. *Preventive Medicine* (2011).

Incidence rates* of invasive and in-situ female breast cancer by age, adjusted for delayed reporting, US, 1975–2007



*Rates are per 100,000, age-adjusted to the US standard population.
Data Source: Surveillance, Epidemiology, and End Results (SEER) Program, SEER 9 registries, National Cancer Institute.

Moving on

- Asbestos
- PAH’s
- Particulates
- Metals and VOC’s

Concrete dust

- Concrete is a mixture of Portland cement, sand, gravel and water

- Pulverized concrete contains crystalline silica and cement dust, including Portlandite ($Ca(OH)_2$) which is highly caustic

- Crystalline silica causes lung cancer in humans (IARC); most common health effect is lung disease (silicosis); also associated with renal disease, scleroderma, rheumatoid arthritis

Cement dust

- Most (but not all) studies of respiratory health among cement manufacturing workers have found *increased symptoms* (cough, phlegm and dyspnea) and *reduced lung function* (FEV_1,FVC and FEV_1/FVC ratio)

- One study found *increased prevalence* of ulcer-like and reflux-like dyspepsia among cement workers vs. unexposed controls and high- vs. low-exposed cement workers

- Cohort and case-control studies have *suggested associations* between cement-exposed occupations and cancer of the lung, stomach, colon and head & neck, including pharynx and larynx

Carcinogenicity of cement dust

- Has not been reviewed by IARC or NTP

- Although the UK Health and Safety Executive (2006) did not find that epidemiologic evidence was convincing of a causal association between cement dust exposure and cancer, they noted that:

"As a highly alkaline substance, cement can cause irritation at sites of contact, such as the mouth, throat and lungs. Persistent chronic irritation will cause repeated cycles of cell death, cell proliferation and other inflammatory responses. It is recognized that this process can be a step on the pathway to cancer. Thus it is biologically plausible that cement dust could have the potential to cause cancers at sites of contact."

Preview

- After the 4 presentations and discussion (before the public comment period that will begin at 3:45 pm) we will poll the committee

It is _____ that exposure to WTC dust may cause cancer.

a) unlikely

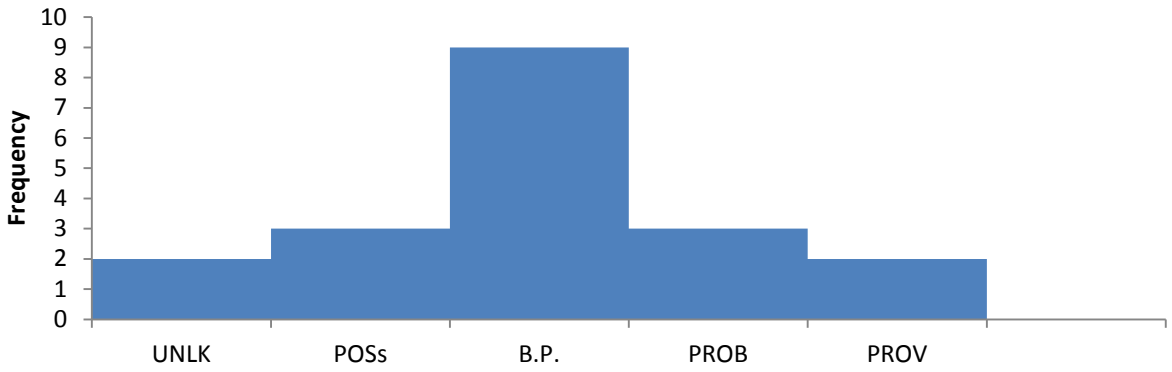
b) possible

c) biologically plausible

d) probable

e) proven

WTC STAC Committee



Range of Opinion

Framing tomorrow's discussion

- Identify critical evidence not presented
- Discussion of opposing positions…?
- Discussion of scientific rationale…?
- Discussion of cancer sites…

- Cautions and perspectives
- Draft letter of response