



# Oral antioxidants for radioprotection in medical imaging scans

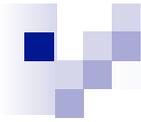
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# Overview of Presentation

- 1) Trends in Diagnostic Imaging Use
- 2) Theory of radiation injury
- 3) Pharmacologic approaches to radioprotection
- 4) Validation through previous research
- 5) Future directions



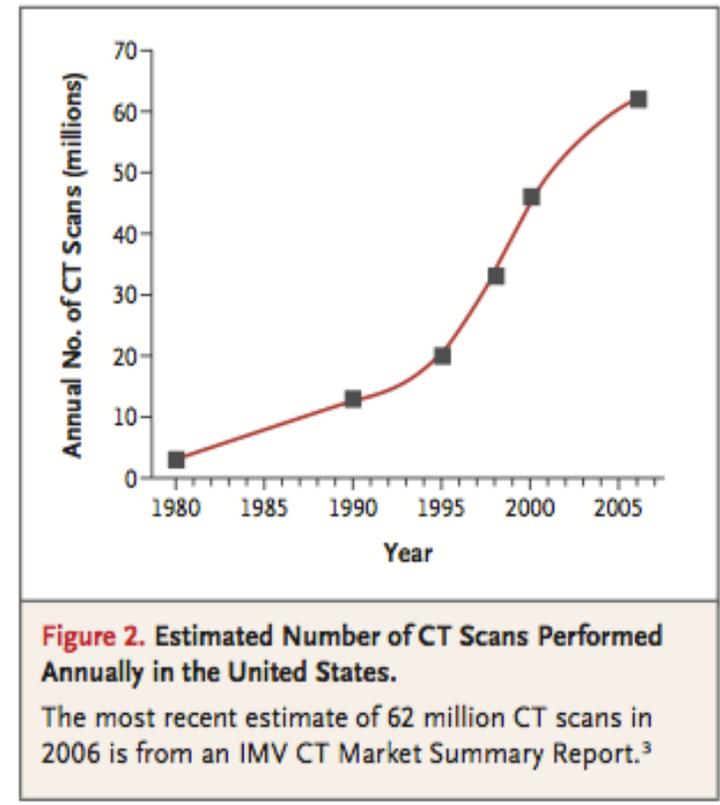
# Trends in Diagnostic Imaging Usage

# Some North American statistics

- ~70 million CT exams per year in the USA
- ~40 million mammograms per year in the USA
- ~20 million nuclear medicine studies per year in the USA

“In 2006, medical exposure **constituted nearly half of the total radiation exposure of the U.S. population** from all sources.” (*National Council on Radiation Protection & Measurements*)

“Medical imaging has become essential to medical care and treatment in Canada. **In 2012, Canadians underwent...4.4 million computed tomography (CT) exams. This represents nearly double the number of such exams performed in 2003.**” (*Canadian Institute for Health Information*)

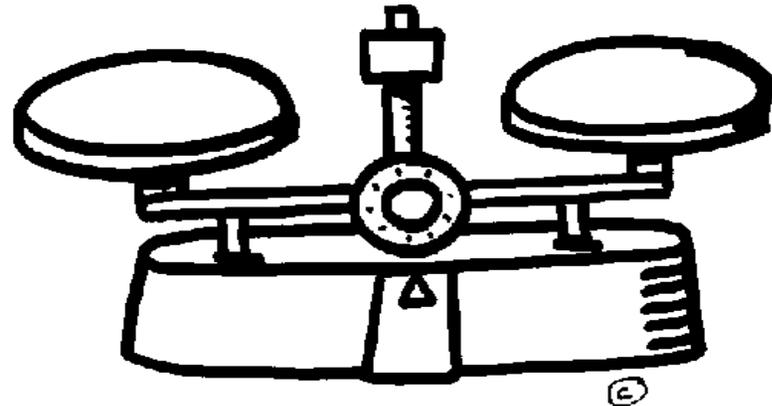


*Brenner (2007) New England Journal of Medicine*

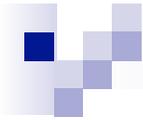
# Does more radiation mean better medicine?

With more radiation we can...

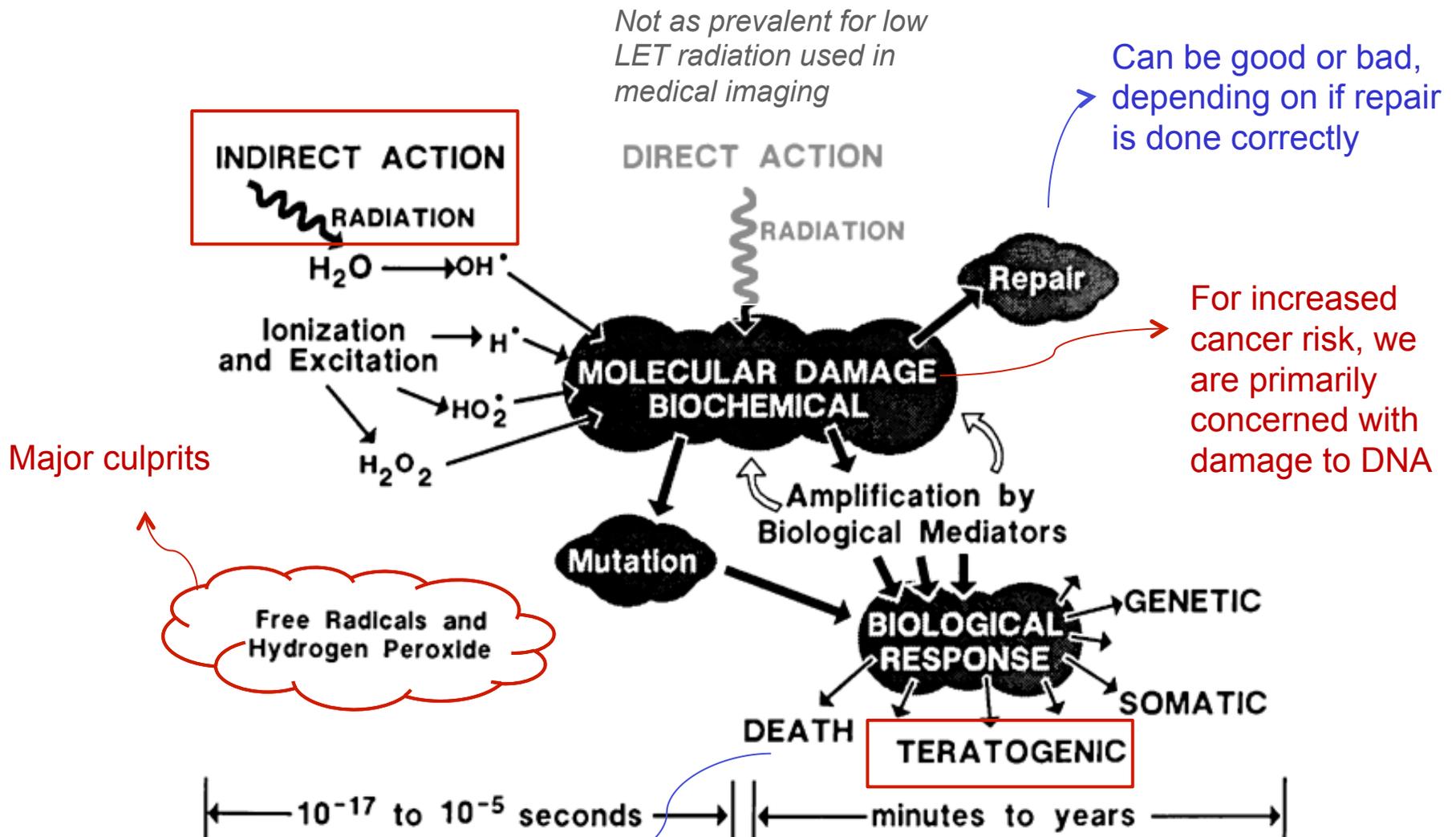
- Do angioplasty on coronary arteries
- Coil or stent aneurysms
- Perform whole-heart and whole-brain perfusion CT
- Radiate tumours
- Perform a wide variety of body interventions
- Study cardiac function (nuclear stress tests)



***But ionizing radiation is not completely safe...***



# Theory of Radiation Injury



Not as prevalent for low LET radiation used in medical imaging

Can be good or bad, depending on if repair is done correctly

For increased cancer risk, we are primarily concerned with damage to DNA

Major culprits

Free Radicals and Hydrogen Peroxide

Textbook of Military Medicine, Part 1 Volume II, 1989

Includes apoptosis to prevent proliferation of fatally injured or mutated cells

“1.5 – 2.0% of all cancers in the US may be attributable to irradiation from CT scanning”  
– Brenner (2007) *New England Journal of Medicine*

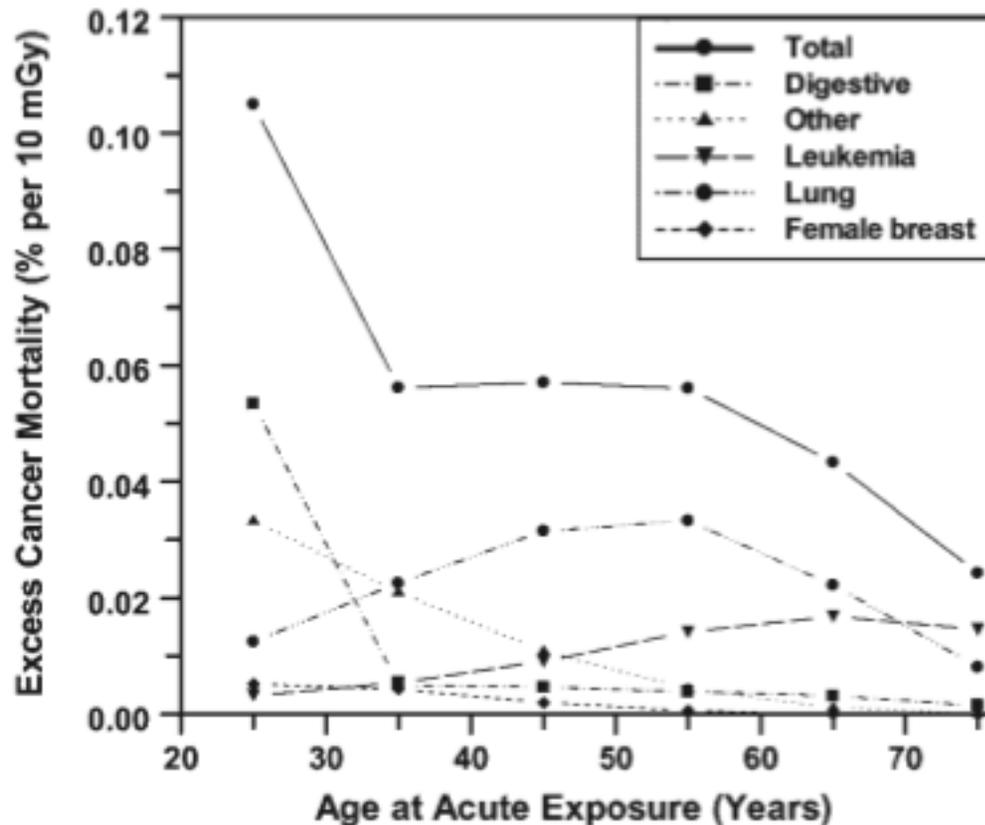


Figure 2. Graph shows estimated excess cancer mortality risk according to age at time of exposure in a stationary population, with U.S. mortality risk rates, that is exposed to a radiation dose of 10 mSv (14). Data are averages between the sexes.

**Consider the following scenario:** a 27 year old woman presents to ER after a 7 hour flight back from vacation in Europe complaining of chest pain.

- Hearing the story, the emergency physicians requests a CT to rule out pulmonary embolus.

- The resident on call is paged and accepts the order. The CT is performed an hour later and reported as normal.

**No effort was made to premedicate or protect the patient in any way.**



## Notes on risk populations:

- Some patients have genetically defective BRCA (a tumour suppressor gene), hence are more prone to breast and ovarian cancer
  - These patients require frequent screening, but are also at most risk of radiation induced malignancy
  - A patient with a BRCA mutation who gets CXR or CT at age < 30 years has 1.5-4x higher probability of developing breast cancer than the rest of the BRCA population, depending on the dose received (Pijpe et al, 2012, BMJ).
- Children are also highly radiosensitive compared to adults, due to the abundance of rapidly dividing cells in their bodies
  - Cumulative CT doses of 50-60 mGy in children may triple the risk of leukemia and brain cancer (Pearce et al., 2012, Lancet)



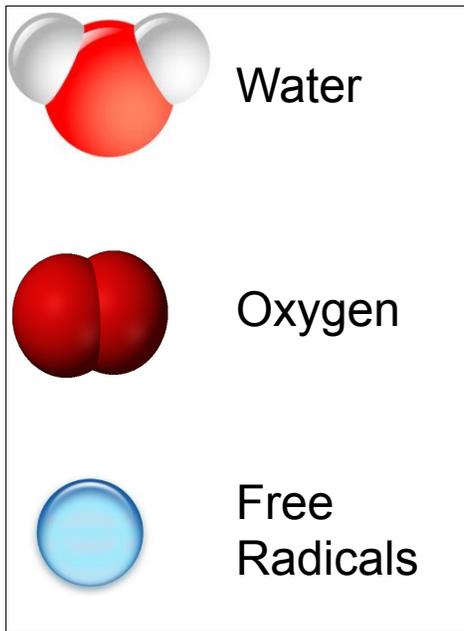
# Mitigating injury during medical imaging

- Traditionally, radiologists have focused on external/radiation source factors:
  - Basic principles: time, distance, shielding
  - Reducing dose to “As Low As Reasonably Achievable” (ALARA)
  - Only scanning when necessary, and when clinical course can be affected by results of scan (CanMEDS principles)

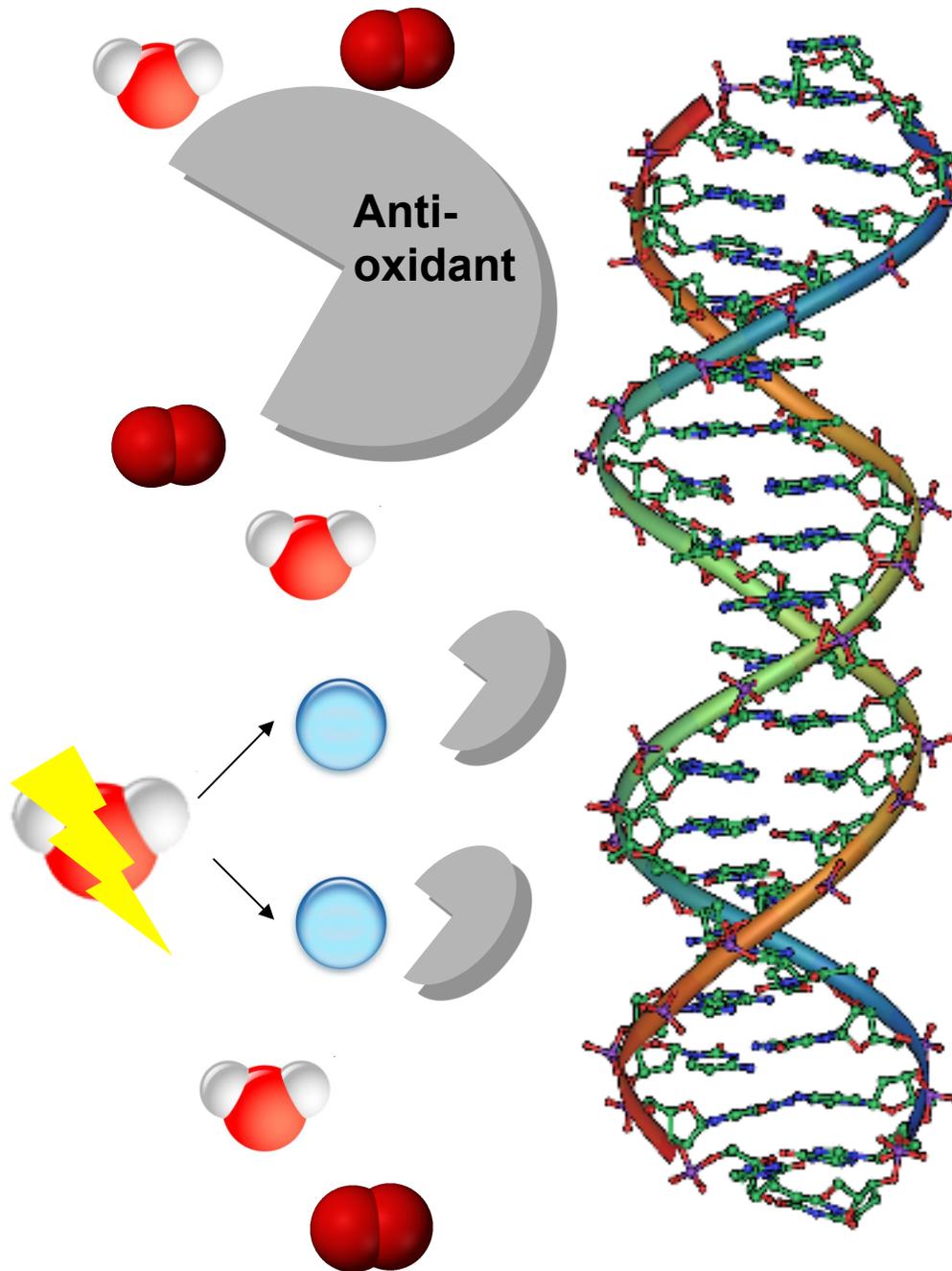


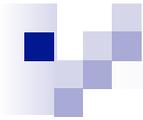
# What about the patient?

- Less attention has been given to increasing the patient's "radioprotective" capacity:
  - Upregulating repair proteins
  - Cell cycle inhibitors (i.e. give a cell more time to repair damaged DNA before replicating)
  - Genome stabilizing agents and epigenetics (too cutting edge to be implemented right now)
  - **Antioxidants to scavenge free radicals**



**Ionizing Radiation**





# Pharmacologic Approaches to Radioprotection



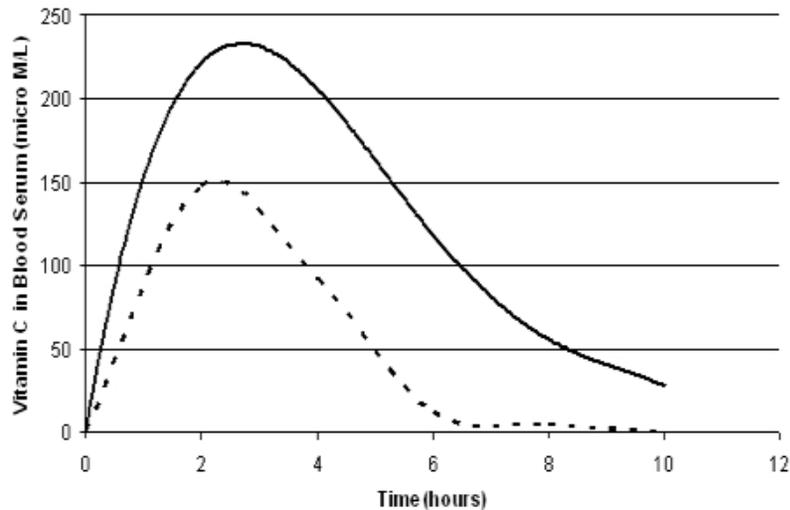
# Oral pre-medication of antioxidants:

- Advantages:

- Safety (many Health Canada approved nutraceuticals)
- Low cost
- Ease of administration
- Good distribution; can be purchased over the counter—  
pharmacy, internet
- Fits the oral premedication paradigm used for contrast reactions

# Basic pharmacokinetics

“Quickly absorbed/excreted within 24 hours” category



Some examples:

- Vitamin C, E
- N-Acetylcysteine
- Carotenoids
- Lipoic Acid

“Building concentration over several days” category

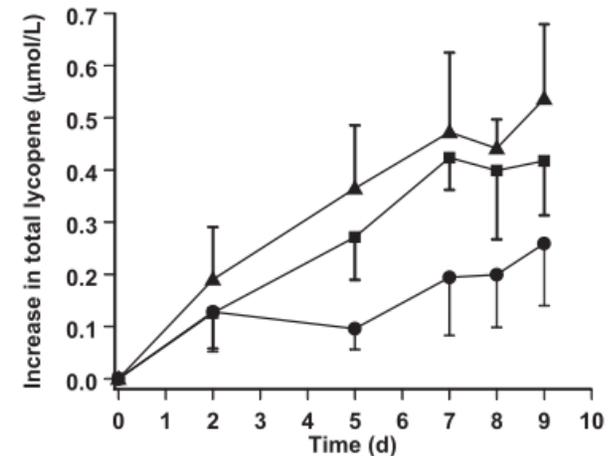


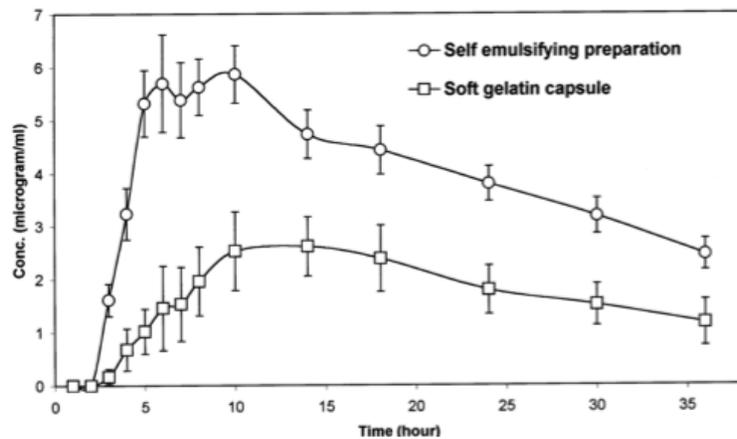
Fig. 2 Mean (SD) dose-normalized incremental increase in plasma concentration of total lycopene during the lycopene dosing phase of the study. (●) Tomato juice group, (▲) Tomato soup group, (■) Lycopene tablet group

Some examples:

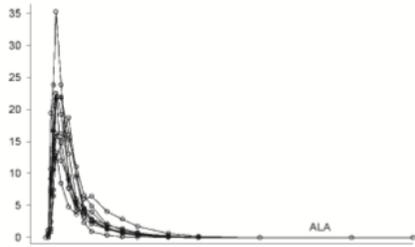
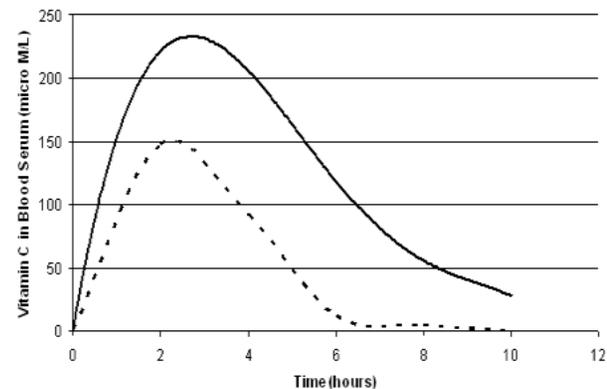
- Lycopene
- Glutathione
- Uric Acid

However, even within each category, the agents have different pharmacokinetics

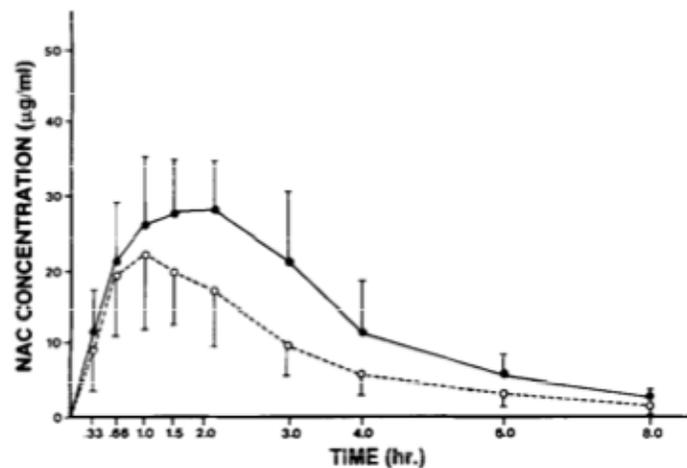
Vitamin E – 10 hours to peak



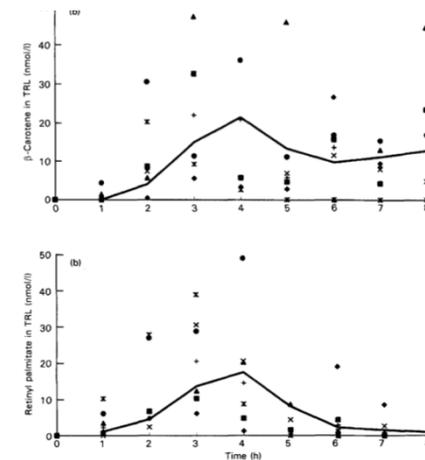
Vitamin C – 3 hours to peak



$\alpha$ -Lipoic Acid – 45 minutes to peak



N-acetylcysteine – 2 hours to peak



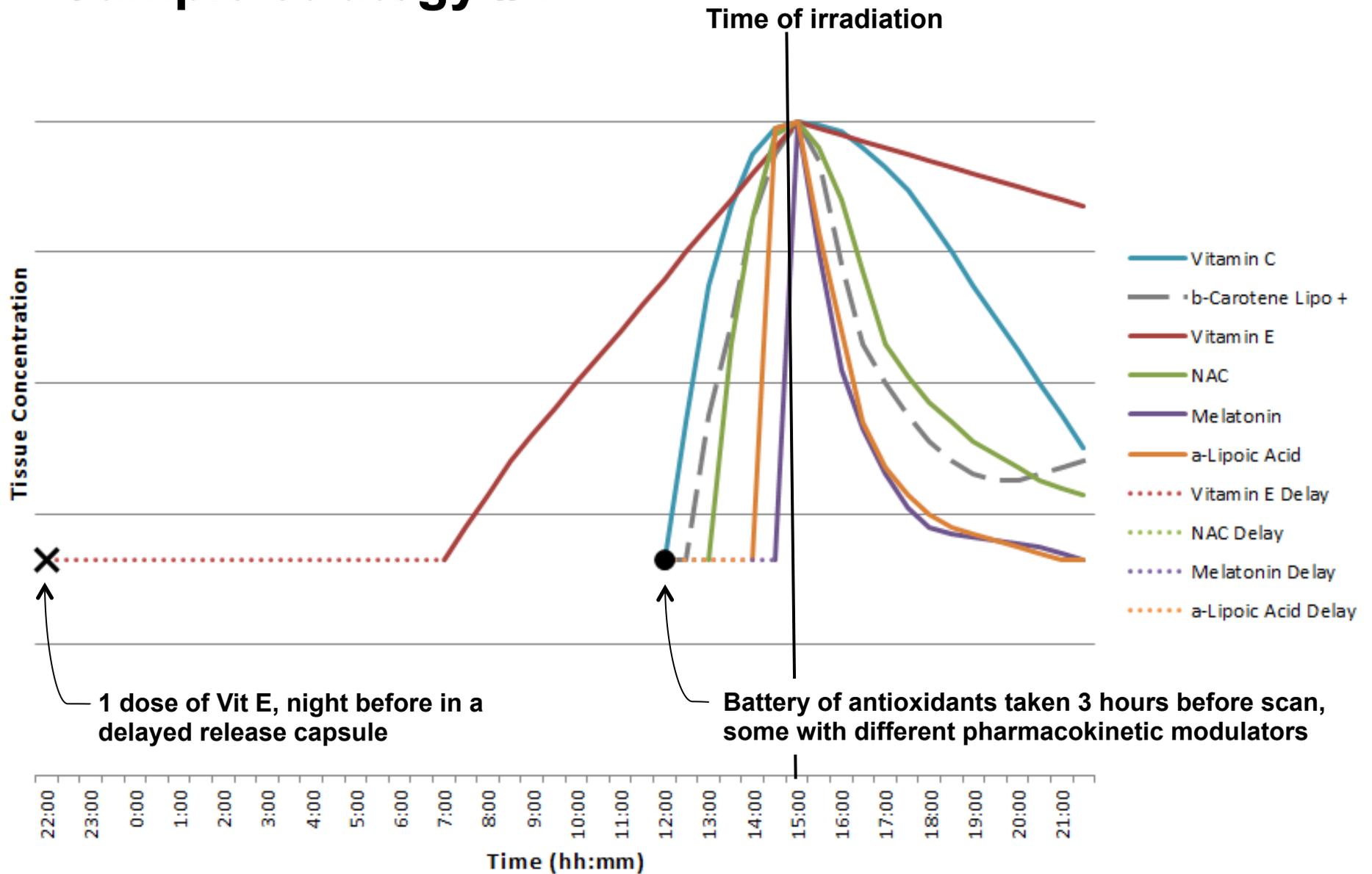
Carotenoids – 4 hours to peak



## What do we do with these varied pharmacokinetics?

- We can optimize dosing strategies:
  - **Timed dosing** so that peak blood/tissue concentration of each drug is synchronized at the time of irradiation using:
    - Simple pill schedule for patient to follow
      - Will require multiple, frequent administrations
    - Delayed release technology in tablets
    - Absorption enhancers
    - Excretion reducers
  - We only need to protect when the patient is being irradiated, which can range anywhere between a few seconds, to an hour, depending on modality

# Sample strategy #1





Advantages to Strategy #1 in previous slide

- Multiple antioxidants, each with different absorption properties
  - May offer protection in different parts of the body
- Maximize body's antioxidant capacity through synchronized timing

Disadvantages:

- Many different compounds used
- Relatively complex

Re-visiting our case scenario: Our 27 year old female has been booked for a CT thorax. This has been scheduled to take place in 45 minutes.

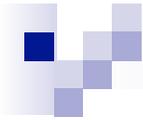
How will we protect this patient?

**Sample Strategy #2:** Give a formulation of only the most rapidly absorbed antioxidants, such as melatonin and alpha-lipoic acid, preferably in a 50 mL liquid form.

- 
- Most scans are booked weeks in advance
  - We can harness the properties of those antioxidants that can build concentration in tissues over several days

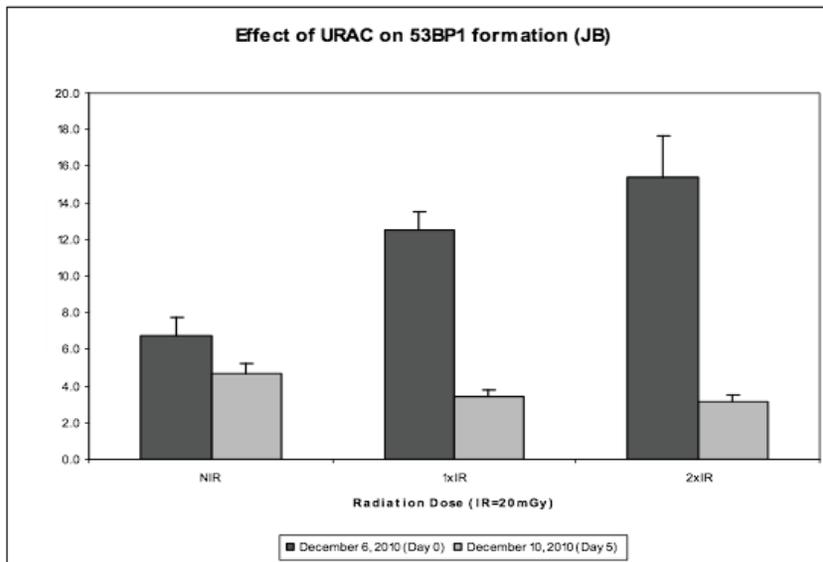
### **Sample Strategy #3:**

- *Component 1:* Daily dosing of antioxidants such as lycopene, N-acetylcysteine (glutathione pro-drug), and uric acid for 7 days prior to scan,
- *Component 2:* Sample Strategy #1 for the 24 hours prior to scan



# Validation Through Human Clinical Studies

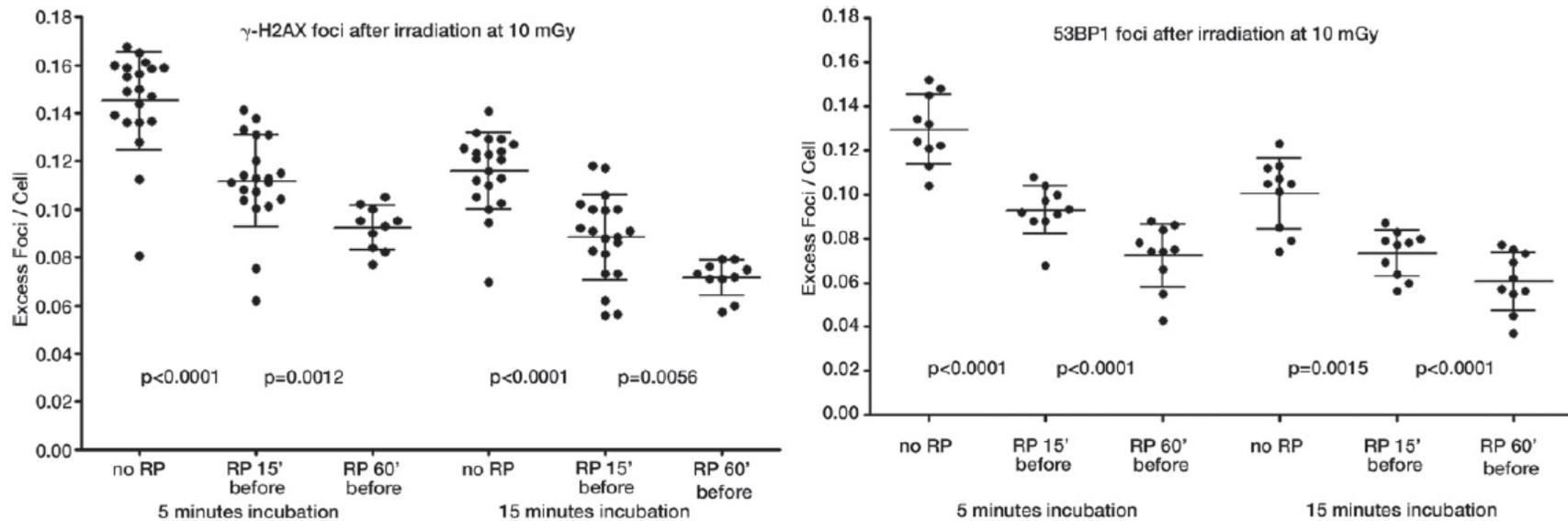
- The effects of antioxidants on reducing DNA injury and long-term cancer risk caused by ionizing radiation has been characterized in animal models, and at high, non-clinically used radiation exposures (*Miller et al., 2013, Carcinogenesis*)
- The challenge is in conducting this work in humans with a true clinical model at diagnostic radiation doses



Our initial work focused on a mixed in vivo/in vitro model. The volunteer shown consumed a uric acid based antioxidant cocktail for 5 days, after which blood was drawn and irradiated ex vivo, at 0, 20, and 40 mGy.

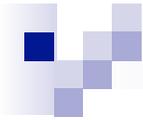
53BP1 foci, which form at sites of DNA injury/repair, were measured to show a reduction in DNA injury after 5-day premedication of antioxidants

**Figure 2**



Kuefner et al. (2012) *Radiology*

- Another group did an in vivo/in vitro study following ours, with a larger sample size (n=17).
- Results show a 58% decrease in gH2AX foci (DNA double-stranded break marker) following an oral pretreatment with an antioxidant mixture 60 minutes before ex vivo irradiation of blood with 10 mGy of gamma radiation



# Future Directions



# Where do we go from here?

- Our team at UHN is working on a completely *in vivo* study to measure DNA injury following diagnostic imaging, and our ability to mitigate that injury using antioxidant premedication
  - Funded by the Peter Munk Cardiac Centre Foundation
- Projected that 29 000 excess cancers were caused in the USA by CT scans in 2007 (*National Cancer Institute*)
- If antioxidant premedication is shown to significantly reduce DNA injury after imaging studies, it suggests that we may be able to significantly reduce the number of excess cancers caused by imaging, and effectively tackle this large public health concern

*Thank you!*