Multifactorial Origins of Cancer Across the Life-course

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Etiology: Causes of cancer

- More than 100 kinds of cancer; causes vary

- What do we mean by "cause"?

- Most (not all) cancers arise from a collection of multiple factors, not exposure to single agents. Multi-causality.

- "Causal webs" is a dominant metaphor (note that this implies interactions among multiple contributors)

Etiology

- A common list of cancer risk factors: Tobacco, diet, nutrition, obesity, infectious agents, reproductive factors and hormones, ionizing radiation, genetics, alcohol, UV light, pharmaceuticals

- What's missing? Why?

- Candidates:
  - Environmental and workplace chemicals linked to cancer; Chemicals in consumer products
  - Non-ionizing radiation (cell phones, etc.)
  - <u>Neighborhood-</u> <u>community-</u> <u>ecosystem-level</u> variables, including pollutants in air, water, food; some communities have dramatically higher exposures than others

Rothman's "Sufficient Causal Pie Model"

A cause is not a single component, but a minimal set of conditions or events that produces the outcome of interest.
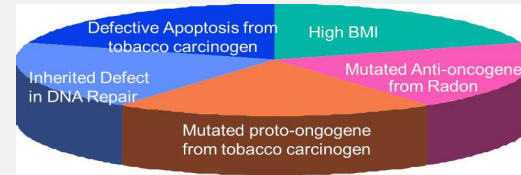Interactions among component causes are a primary feature

One sufficient causal "pie" for lung cancer
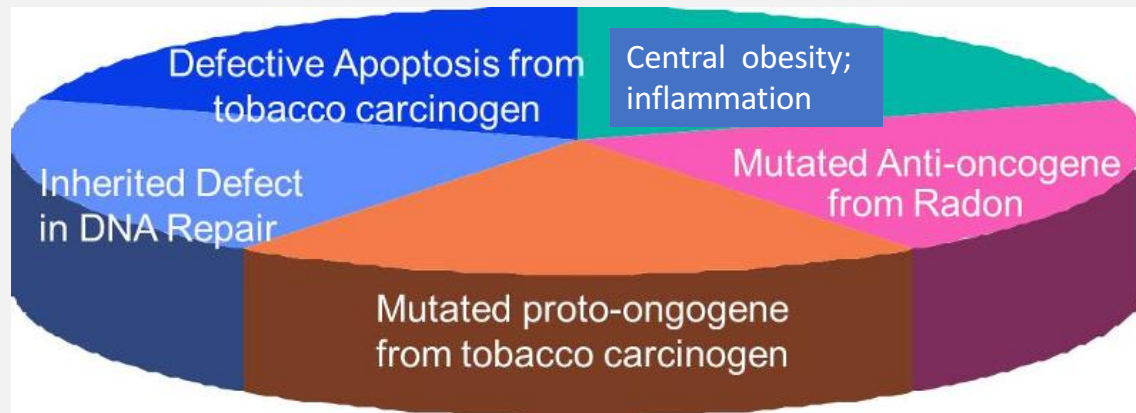
Which causal pathway <u>combinations</u> are sufficient to result in cancer development over time? What are the implications for cancer prevention?
"Intercepting" cancer before "sufficiency" is completed?

Sufficient Pie Causal Model

- Combinations of <u>other component causes</u> can also be sufficient;
    e.g., other sufficient causes for lung cancer

- Tobacco is important but, what else? Proportion of never-smokers among patients with NSCLC increasing 1990-2013. (Pelosof, 2017)

Criteria air pollutants; diesel exhaust; dozens of hazardous air pollutants; industrial chemicals, metals; asbestos; silica; radon; radiation; etc.
    (IARC; Field, Clin Chest Med, 2012)

Interactions among causal risk factors, over the life course, make it very difficult to determine valid population attributable fractions for many kinds of cancer

Key Characteristics of Carcinogens

Known human
carcinogens
have one or more of
these properties;

These are now
routinely integrated
into IARC's assessments
of potential carcinogens

Smith et al, EHP, 2016

**Table 2.** The KCs of human carcinogens (from (16))

Key characteristic
1. Is electrophilic or can be metabolically activated
2. Is genotoxic
3. Alters DNA repair or causes genomic instability
4. Induces epigenetic alterations
5. Induces oxidative stress
6. Induces chronic inflammation
7. Is immunosuppressive
8. Modulates receptor-mediated effects
9. Causes immortalization
10. Alters cell proliferation, cell death or nutrient supply

Epigenetic alterations

- Alter gene expression without altering DNA sequence (non-mutagenic)

- Several mechanisms: DNA methylation, histone modification, non-coding RNA > gene silencing (e.g. silencing DNA repair gene)

- Or reduced DNA methylation > inappropriate gene expression (e.g. in rodent study, low-dose BPA during development > reduced methylation and over-expression of cancer-related genes in aging prostates – (Prins et al, EHP, 2017)

Epigenetic Influencers
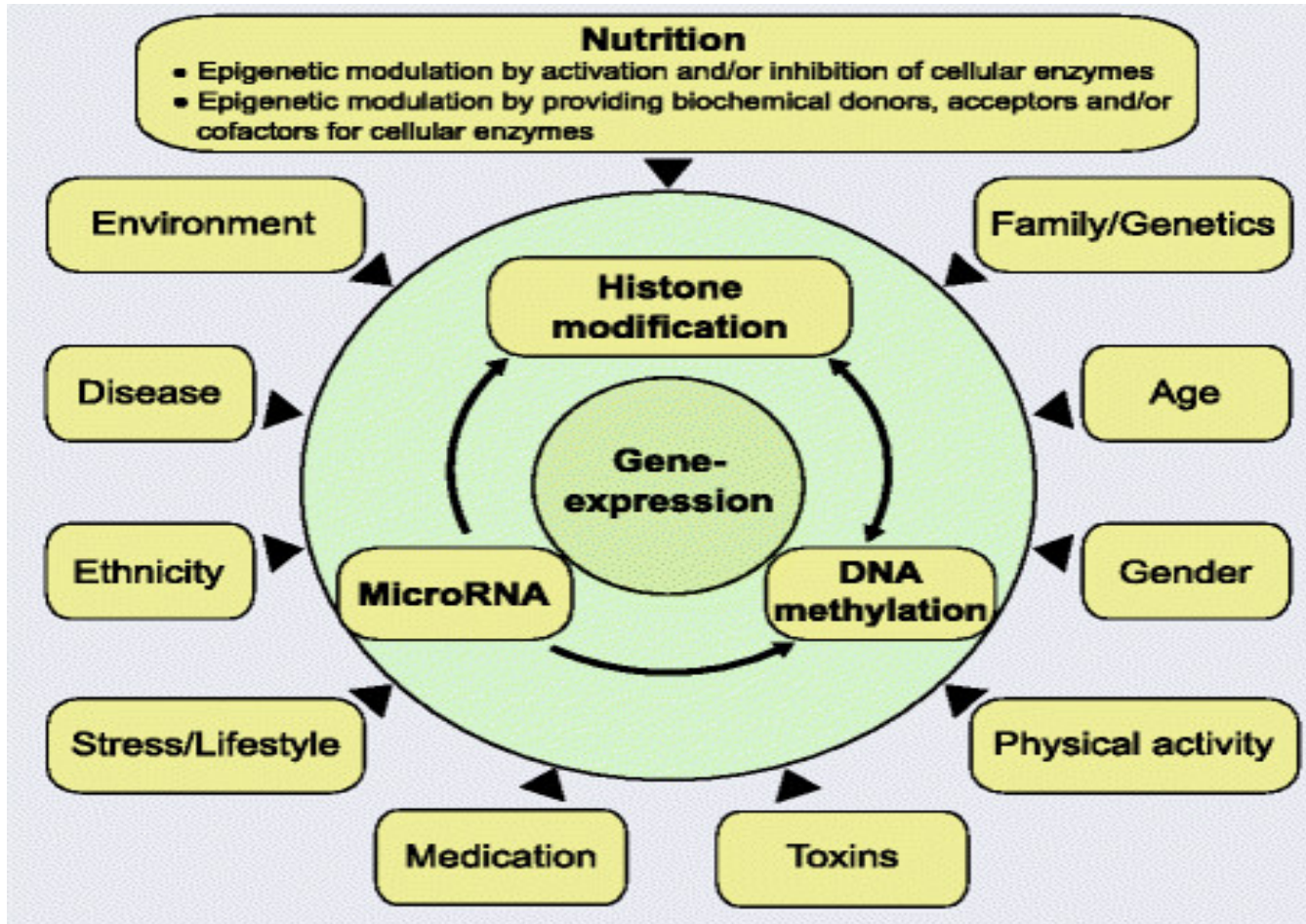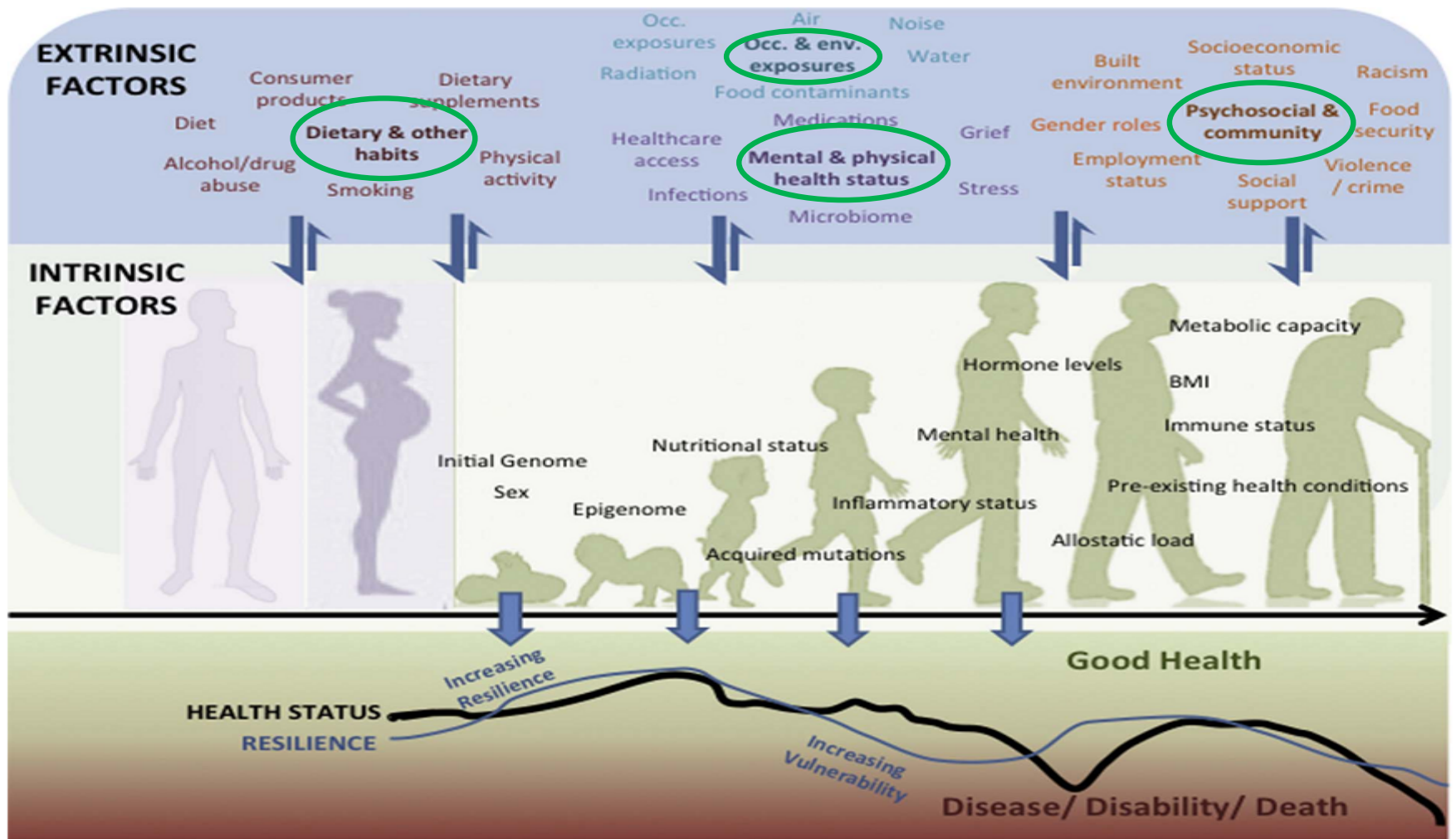
Moving from G x E to I x E (Individual, community, societal level variables) McHale; Mutat Res, 2018

Summary

Multiple, multi-level chemical and non-chemical stressors, over the life course, influence cancer risk in individuals and populations
(a quintessential "mixture" problem)

Beyond the current overwhelming emphasis on individual behaviors, this perspective adds programs and policies that also address workplace, school, community and societal level contributions to risk

Identifies additional opportunities for cancer prevention