Re-envisioning Carcinogenicity Assessment @ NTP

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NTP Board of Scientific Counselors
June 18, 2019
“To improve public health through the development of data and knowledge that is translatable, predictive and timely.”
“To improve public health through the development of data and knowledge that is *translatable, predictive* and *timely.*”

Human Relevant & Impactful
“Cancer” is a collection of over 100 related diseases.
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Types of Breast Cancer

- Ductal Carcinoma In Situ (DCIS)
- Invasive Ductal Carcinoma (IDC)
- IDC Type: Tubular Carcinoma of the Breast
- IDC Type: Medullary Carcinoma of the Breast
- IDC Type: Mucinous Carcinoma of the Breast
- IDC Type: Papillary Carcinoma of the Breast
- IDC Type: Cribriform Carcinoma of the Breast
- Invasive Lobular Carcinoma (ILC)
- Inflammatory Breast Cancer
- Lobular Carcinoma In Situ (LCIS)
- Male Breast Cancer
- Molecular Subtypes of Breast Cancer
- Paget's Disease of the Nipple
- Phyllodes Tumors of the Breast
- Metastatic Breast Cancer
How many cancers are caused by exposure to carcinogens in the environment?

~4-20%

But the precise causes of most cancers are not known

What Are the Costs of Cancer?

The Agency for Healthcare Research and Quality estimates that the direct medical costs (total of all health care expenditures) for cancer in the US in 2015 were $80.2 billion.

According to a recent study by American Cancer Society epidemiologists, at least 42% of newly diagnosed cancers in the US – about 729,000 cases in 2018 – are potentially avoidable.
I’m always amazed by the disconnect between what we see in the news and the reality of the world around us. As my late friend Hans Rosling would say, we must fight the fear instinct that distorts our perspective:

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**Causes of death in the US**

*What Americans die from, what they search on Google, and what the media reports on.*

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*This represents each cause's share of the top ten causes of death in the US plus homicides, drug overdoses, and terrorism. Collectively these 13 causes accounted for approximately 64% of deaths in the US in 2018. More breakdowns of causes of death can be found at the CDC WONDER public health database: [https://wonder.cdc.gov/](https://wonder.cdc.gov/)*

*Data refer to 2018.*

*Graphs and figures are created by Hannah Ritchie and Max Roser.*

June 11, 2019
Causes of death in the US

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<thead>
<tr>
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<tbody>
<tr>
<td>Heart Disease</td>
<td>Heart Disease</td>
<td>Cancer</td>
<td>Cancer</td>
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<tr>
<td></td>
<td></td>
<td>37%</td>
<td>12.7%</td>
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<tr>
<td>Cancer</td>
<td>Cancer</td>
<td>29.5%</td>
<td>37%</td>
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<tr>
<td>Alzheimer's disease</td>
<td>Lower Respiratory Disease</td>
<td>7.4%</td>
<td>22.8%</td>
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<tr>
<td>Stroke</td>
<td>Stroke</td>
<td>4.9%</td>
<td>Stroke</td>
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<tr>
<td>Diabetes</td>
<td>Diabetes</td>
<td>3.8%</td>
<td>Diabetes</td>
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<tr>
<td>Homicide</td>
<td>Homicide</td>
<td>3.2%</td>
<td>Homicide</td>
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<tr>
<td>Drug overdose</td>
<td>Drug overdose</td>
<td>2.8%</td>
<td>Drug overdose</td>
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<tr>
<td>Terrorism</td>
<td>Terrorism</td>
<td>7.2%</td>
<td>Terrorism</td>
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<tr>
<td>Pneumonia &amp; Influenza</td>
<td>Pneumonia &amp; Influenza</td>
<td>5.2%</td>
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</tbody>
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All data for year 2016

*This represents each cause’s share of the top ten causes of death in the US plus homicides, drug overdoses, and terrorism. Collectively these 13 causes accounted for approximately 88% of deaths in the US in 2016. Full breakdown of causes of death can be found at the CDC’s WONDER public health database: https://wonder.cdc.gov/*

Based on data from Shen et al (2018) – Death: reality vs. reported. All data available at: https://owenshen24.github.io/charting-death

All data refers to 2016.
“Does [Agent] cause cancer?”

2 year Bioassay

Rodent Carcinogen: Yes, No, Maybe

Human Carcinogen: ?
“Does [Agent] cause cancer?”

2 year Bioassay

Rodent Carcinogen: Yes, No, Maybe

Human Carcinogen: ?

How do we make this more translatable, predictive and timely?
Start incorporating human data
Identify those cancers likely associated with environmental exposures
"[Quantitative contribution] of Agent X to [cancer type Y] in [population Z]"

Develop a deep knowledge of specific cancer pathways
ER Pathway to Breast Cancer

Sources
- Local Estrogen Synthesis
- Estrogen Synthesis (ovarian)
- Xenobiotics

Macro-Molecular Response
- ER Activation
  - ER Binding to DNA (classical)
  - ER Binding to T.F. to DNA (non classical)
  - Second Messenger Production
  - Activation of Signaling Pathways

Cellular Response (Initial)
- Gene Expression
- Protein Production

Cellular Response (Primary)
- Mitochondrial Dynamics
- Proliferation
- Apoptosis
- Motility
- Oxidative Stress
- DNA Damage

Cellular Response (Cancer Cell)
- Endothelial Proliferation + Migration
- Tumor Associated Macrophages
- Cancer Associated Fibroblasts
- Cancer Associated Adipocytes

Cellular Response (Stromal)
- Angiogenesis
- ECM Composition
- Tumor Growth
- Invasion

Tissue Response
- ER+ Breast Cancer Related Deaths

Adverse Outcome

Exposure

Probabilistic

Cancer

From Morgan et al., 2016, Pharmacology & Therapeutics 165: 79-92
ER Pathway to Breast Cancer

“Tipping Point”
High likelihood of progressing to cancer

From Morgan et al., 2016, Pharmacology & Therapeutics 165: 79-92
ER Pathway to Breast Cancer

From Morgan et al., 2016, Pharmacology & Therapeutics 165: 79-92
“Does [Agent] cause cancer?”

“[Quantitative contribution] of Agent X to [cancer type Y] in [population Z]”

Or Not
Hypothesis-driven Research

- Knowledge Integration
- Chronic in vivo Studies
- Short term in vivo Studies
- In vitro Studies
- Bioactivity Screening
- Computational Toxicology
- Data / Knowledge Mining

Communicate
• Centralized cancer registries in the United States conduct population-based surveillance of cancer incidence and mortality.
• State health departments (funded by CDC’s National Program of Cancer Registries) and NCI’s Surveillance Epidemiology and End Results Program, collect cancer incidence data.

Cancer Incidence

Liver cancer

Leukemia

Kidney cancer
The All of Us Research Program is a historic effort to gather data from one million or more people living in the United States to accelerate research and improve health.

Million Veteran Program (MVP)

MVP is a national, voluntary research program funded entirely by the Department of Veterans Affairs Office of Research & Development. The goal of MVP is to partner with Veterans receiving their care in the VA Healthcare System to study how genes affect health.
• Work with internal and external stakeholders to establish a problem statement and define scope
• Survey available resources
• Identify initial areas of focus
• Develop a strategic plan to set goals and establish timelines
• Develop a communication plan
Thank you

Questions?