Role of Genetics in Cancer Risk and Outcomes: The Pathways Study

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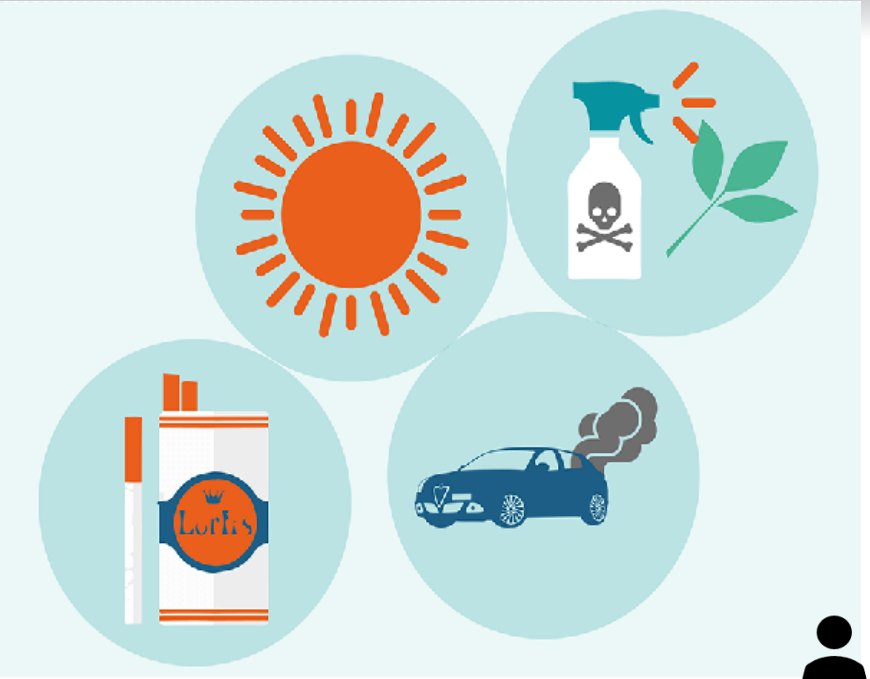
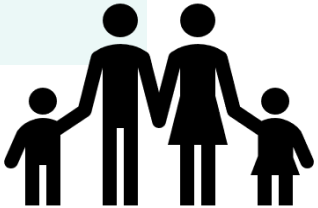
Causality of Cancer is Multifactorial





- Aging
- Exposure to carcinogens
- Viruses, Radiation
- Lack of Physical Activity
- Alcohol consumption
- Obesity
- Hormonal factors
- Dietary factors
- Family history of cancer

Role of Genetics in Breast Cancer Risk

- Rare inherited genetic mutations (BRCA1, BRCA2) 1:500 in general population
- Other gene mutations (PTEN, ATM, PALB2, CDH1)
- Genetic testing for these and other high-risk variants
- More common variants can also increase risk, combined together or with environmental exposures

Gene x Environment Interactions

Smoking causes lung cancer, but only 1 in 10 smokers get the disease

Differences in how our cells and bodies respond to carcinogenic exposures will affect risk

Biochemical Individuality[1]

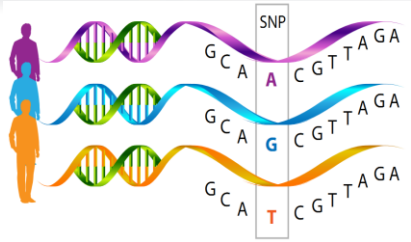
"… every individual has his own inborn metabolic characteristics."

"…every application of biochemistry to human beings must take these differences into account."

"…all diseases, such as cancer, arthritis, heart disease, etc., are related to biochemical individuality."

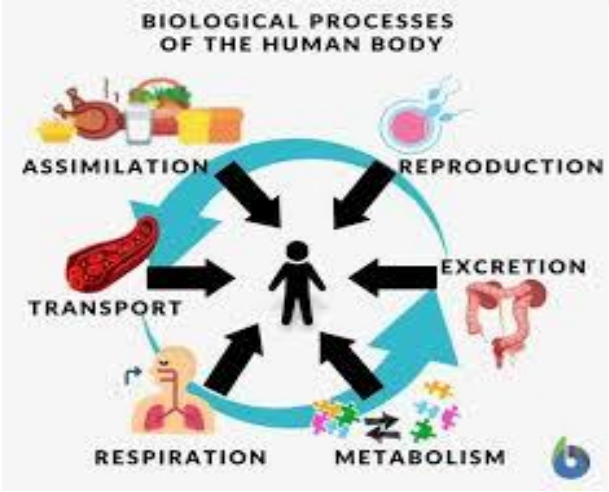
[1]Roger J. Williams, "Biochemical Individuality", John Wiley & Sons, New York (1956).

Role of Genetics in Cancer Risk



Single Nucleotide Polymorphisms (SNPs)

Common differences in code that change activity of genes (up to 50% of population)



SNPs provide variability in numerous processes, including response to exposures associated with cancer

Role of Genetics in Cancer Risk

Studies of common genetic variants in cancer risk

- Specific pathways - candidate gene approach
  - e.g. smoking and genes involved in metabolism of carcinogens, DNA repair
- Genome wide association study (GWAS)
  - Looks at all DNA across genome, testing for SNPs that are associated with risk of disease or disease outcomes

  Promise of GWAS for cancer risk limited when cancer etiology is so complex

  More likelihood of finding genetic variants in populations with known exposures; chemotherapy, radiation therapy

GWAS Findings in Pathways Study

- Overall, no single SNPs associated with survival outcomes
- Among women treated with anthracyclines and/or anti-HER2 therapy, SNP in *UACA* associated with survival UACA helps cells escape killing effects of chemotherapy
  - Findings need to be validated in other studies and tested for use in the clinic

Zhu Q et al, 2022

Polygenic Risk Scores

Total combined common variants – cumulative effect; estimates risk with those genotypes compared to risk in people with different genetic make-up – NOT causal

- Polygenic risk score for bone density and fracture risk with aromatase inhibitors (Hook C et al. 2024)
  - Endocrine therapy used to treat HR+ breast cancer – higher risk of bone loss and osteoporosis
  - Genetic estimates of bone density associated with fracture risk
- Genetically predicted metabolic traits and outcomes (Fiorica P et al. 2023)
  - PGS for cardiovascular disease, hypertension, associated with breast cancer outcomes

Known from Observational Studies

- Genetic susceptibility is not deterministic
- Multiple genetic and environmental factors may increase and/or decrease risk, combined effects
- Prognostic factors with KNOWN clear effects, repeatedly replicated – **exercise** and **physical activity** reduce risk of cancer and improve survival outcomes!

THANK YOU!!