Genetic/epigenetic basis of ethnic differences in cancer predisposition

Gian Paolo Dotto

Epigenetics / gene transcription
Cell-cell communication
Field cancerization

Squamous Cell Carcinoma

Ancestry

European Research Council
Cancer Prevention: linking science to society

Sharing of scientific knowledge across cultural / ethnic divides

Empowerment for individuals and societies
2 Types of Cancer Prevention:

**Primary cancer prevention** (at the level of populations)

- Life style, socio-economic factors
- Infectious diseases
- Aging
- Sex
- Ancestry

**Secondary cancer prevention** (at the level of individuals)

- Detection / treatment of premalignant lesions
- Reduced risk of cancer relapse
Differences in cancer survival between “White” and “Black” populations

All cancer types

Head & Neck Squamous Cell Carcinoma
Determinants of cancer susceptibility

Özdemir and Dotto, Trends in Cancer 2017
Squamous Cell Cancers: A Unified Perspective on Biology and Genetics

G. Paolo Dotto and Anil K. Rustgi
Cancer Cell 2016

Pattern of Frequently Altered Genes in HNSCC

The Notch / p63 signaling network
Higher genetic variability of Black African populations because of migration bottlenecks: the “Out of Africa hypothesis”

(Michael C. Campbell, 2008)

Peter B. deMenocal & Chris Stringer *Nature* 2016, 538, 49–50
Greater genetic variability of primary foreskin keratinocytes from boys of Black versus White ancestries.
Higher stem cell potential and oncogenicity of primary keratinocytes from Black versus White boys

White HKC

Black HKC

ΔN-p53 + HRasV12

HRasV12 + ΔN-p53

Pan-keratin

Pan-keratin positive area (mm²)

White (270) Black (246)
Differential expression of the *HSD17B7* gene in Black versus White keratinocytes promotes stem cell potential and oncogenesis

Xu, Tassone et al., EMBO Mol Med 2021
HSD17B7 (17-beta-hydroxysteroid dehydrogenase) is an enzyme involved in sex hormones activation and cholesterol biosynthesis.

Estrone $\rightarrow$ Androstenedione $\rightarrow$ Zymosterol $\rightarrow$ Estradiol $\rightarrow$ Testosterone $\rightarrow$ Cholesterol

HSD17B7 association with worse patients’ survival

Graph showing overall survival over months with different survival rates for different groups and a p-value of 0.0036.
Ancestry – and Sex-related differences in cancer incidence and survival

Head/Neck Squamous Cell Carcinoma

**Incidence**

Age-Adjusted SEER Incidence Rates

By Race and Sex

Oral Cavity and Pharynx, All Ages, 1975–2013 (SEER 9)

**Survival**

5-Year Relative Survival By Year Dx

By Race and Sex

Oral Cavity and Pharynx, All Ages, 1975–2012

Cancer sites include invasive cases only unless otherwise noted.

Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups – Census P25–1130). Regression lines are calculated using the Joinpoint Regression Program Version 4.2.0, April 2015.

National Cancer Institute

Incidence sources: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).

Cancer sites include invasive cases only unless otherwise noted.

The 5-year survival estimates are calculated using monthly intervals.
Sexual dimorphism in cancer

Andrea Clocchiatti, Elisa Cora, Yosra Zhang and G. Paolo Dotto
Sex Hormones and Anticancer Immunity
Berna C. Özdemir¹,² and Gian-Paolo Dotto²,³,⁴

Sex Differences in Efficacy and Toxicity of Systemic Treatments: An Undervalued Issue in the Era of Precision Oncology
Berna C. Özdemir, Lausanne University Hospital; and International Cancer Prevention Institute, Lausanne, Switzerland
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Gian-Paolo Dotto, International Cancer Prevention Institute; University of Lausanne, Lausanne, Switzerland; and Massachusetts General Hospital, Charlestown, MA
Anna Dorothea Wagner, Lausanne University Hospital, Lausanne, Switzerland
Sex bias in cancer development

Interplay between sex hormones and chromosomes

- Cancer target cells
  - Ubiquitous
    - Cell cycle
    - Apoptosis
  - Cancer type specific
  - Sex hormones (protein and steroid)
    - Epigenetics
  - Sex chromosomes
- Cancer stroma
- Field cancerization
  - Systemic
    - Immune system
    - Metabolism
- Angiogenesis
- Inflammation

SEX BIAS IN CANCER DEVELOPMENT

Clocchiatti et al., NCR 2016
Androgen Receptor, a double-edged role in senescence and cancer
Reduced androgens levels in aging populations and cancer risk

**Total and Free Testosterone Levels in Men by Age**

- **Total T (ng/dl)**
- **Free T (pg/ml)**

**Average Number of Cases per Year**

- Male Rates
- Female Rates
- Male Cases
- Female Cases


Aging

- Androgen replacement therapy (ART)
- Androgen deprivation therapy (ADT)

Cancer
there can be a continuum between male and female sex determinants at the individual level of importance for personalized medicine
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