Enigmatic sex disparities in cancer incidence

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**Estimated New Cases**

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<td><strong>Prostate</strong></td>
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Intrinsic, sex-specific biological risk factors

Sex variation in risk factor prevalence or susceptibility

Aims

• Estimate **strength** of association between sex and site-specific cancer risk

• Estimate **consistency** of association between sex and site-specific cancer risk

• Identify **unexplained sex disparities** in cancer incidence for further research
Data sources

- *Cancer Incidence in Five Continents* (International Agency for Research on Cancer, IARC)
  - 1998-2002
  - Age-, sex-, and country/region-specific data
  - 35 anatomical cancer sites for analysis
  - 60 countries (almost 300 regions) for analysis

- *World Development Indicators* (World Bank)
  - Gross domestic product, GDP
  - (And a lot of other useful data)

Data analysis

- Incidence rate ratios of site-specific cancers, comparing men to women
  - Poisson models including sex, age (5-yr), GDP (worldwide quartiles), geographic region (8 areas)
  - Variation by age at diagnosis

- Consistency by GDP or geographic region
  - Interactions with sex → range of IRR estimates

- Consistency by time period
  - Subset of registries with data since 1970

Qualitative assessment

- A: Established risk factors (smoking, alcohol, occupation*) plausibly **explain** the sex disparity

- B: Established risk factors at least **partly** **explain** the sex disparity

- C: Established risk factors **do not explain** the sex disparity

*toxic metals and minerals → lung; benzene, ethylene oxide, ionizing radiation → leukemia (World Health Organization 2004)
Lymphoid leukaemia
Nose, sinuses, etc.
Kidney
Other urinary organs
Lung (incl. trachea and bronchi)
Oral cavity
Stomach
Nasopharynx
Tongue
Liver
Esophagus
Tonsil
Urinary bladder
Lip
Kaposi sarcoma
Hypopharynx
Larynx

**Thyroid**: Geographic variation in IRR

**Anus**: Geographic variation in IRR

**Non-Hodgkin lymphoma**: Geographic variation in IRR

**Lung** (incl. trachea and bronchi): Geographic var. in IRR

**Liver**: geographic variation in IRR
Larynx: geographic variation in IRR

Explainable sex disparities (N=7)

- Colon (RR_{alcohol}=1.14-1.32*, RR_{smoking}=1.2-1.6)
- Pancreas (RR_{alcohol}=0.98-1.18*, RR_{smoking}=2-4†)
- Other urinary organs (RR_{smoking}=3†)
- Nose, sinuses, etc. (RR_{smoking}=1.5-2.5†)
- Lip (RR_{smoking}+occupational exposure=1.5|)
- Oral cavity (RR_{alcohol}=1.73-5.75*, RR_{smoking}=4-5†)
- Lung (RR_{alcohol}=1.02-1.08*, RR_{smoking}=15-30†, RR_{occupation}=1.6§)

Also anus, gallbladder and biliary tract, other endocrine, eye, melanoma of skin

*RR for 25-75 g EtOH/day, Bagnardi et al., NIAAA 2001
†RR for current vs. non-smoking, Sasco et al., Lung Cancer 2004
‡RR for eight occupational lung carcinogens, Driscoll et al., WHO 2004
§mean RR for low to high exposure to three occupational leukemogens, Driscoll et al., WHO 2004

Partly explainable sex disparities (N=10)

- Kidney (RR_{smoking}=1.5-2.0†)
- Myeloid leukemia (RR_{smoking}=1.5-2.0†, RR_{occupation}=2.44)
- Salivary glands (RR_{smoking}=1.1†, RR_{smoking}>3|)
- Liver (RR_{smoking}=1.20-1.83*, RR_{smoking}=1.5-2.5†, RR_{smoking}=3-10*, RR_{alcohol}=50-100†)
- Urinary bladder (RR_{smoking}=1.04-1.17*, RR_{smoking}=3†)
- Esophagus (RR_{smoking}=1.51-4.23*, RR_{smoking}=2.3†)
- Tongue (RR_{smoking}=1.0‡)
- Kaposi sarcoma (RR_{HIV}=10,000-100,000††)
- Hypopharynx (RR_{smoking}=3-4†)
- Larynx (RR_{smoking}=1.35-3.24*, RR_{smoking}=10†)

†mean RR for low to high exposure to three occupational leukemogens, Driscoll et al., WHO 2004
‡RR for carcinogenic metals, minerals, and ionizing radiation, Guzzo et al., Crit Rev Oncol Hematol 2010
††RR for HIV infection in MSM or others, Biggar et al., Int J Cancer 1996

Explainable sites: time trends in incidence

Unexplained sex disparities (N=13)

- Tonsil
- Thyroid
- Nasopharynx (RR_{smoking}=1.5-2.5†)
- Stomach (RR_{alcohol}=1.07-1.32*, RR_{smoking}=1.5-2.0†, RR_{H. pylori}=1†)
- Small intestine
- Rectum (RR_{smoking}=1.11-1.22†)
- Non-melanoma skin
- Brain and nervous system
- Bone
- Lymphoid leukemia
- Hodgkin lymphoma
- Non-Hodgkin lymphoma
- Multiple myeloma

*O. Nyrén, personal communication

Partly explainable sites: time trends in incidence

- Esophagus
- Liver
- Kidney
- Myeloid leukemia
- Lung
- Larynx
- Gallbladder
- Pancreas
Unexplainable sites: time trends in incidence

Explanations?

- Strongly associated with disease risk
- Sufficiently unevenly distributed between males and females
- Ubiquitous and uniformly more common in one sex (if consistent across geography, GDP, and time)

Body size and basal metabolic rate?

Sex steroid hormones?

Sex chromosomes?

Infections and immunity?
Iron and oxidative stress?

Considerations

- Variable data quality
- Ecological data \(\rightarrow\) confounding
- No classification by histology, anatomic location, other disease characteristics