Assessing the Role of Sex-Gender in Cancer Disparities

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Pathways to Discovery: Multidisciplinary Translational Research

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Health Disparities in Cancer

- Despite major advances during the 20th century about the burden, determinants, prevention, and treatment of cancer, social disparities remain

- Important gaps in knowledge of the causes of social disparities exist along the cancer control continuum

THE CANCER CONTROL CONTINUUM

Cancer Continuum

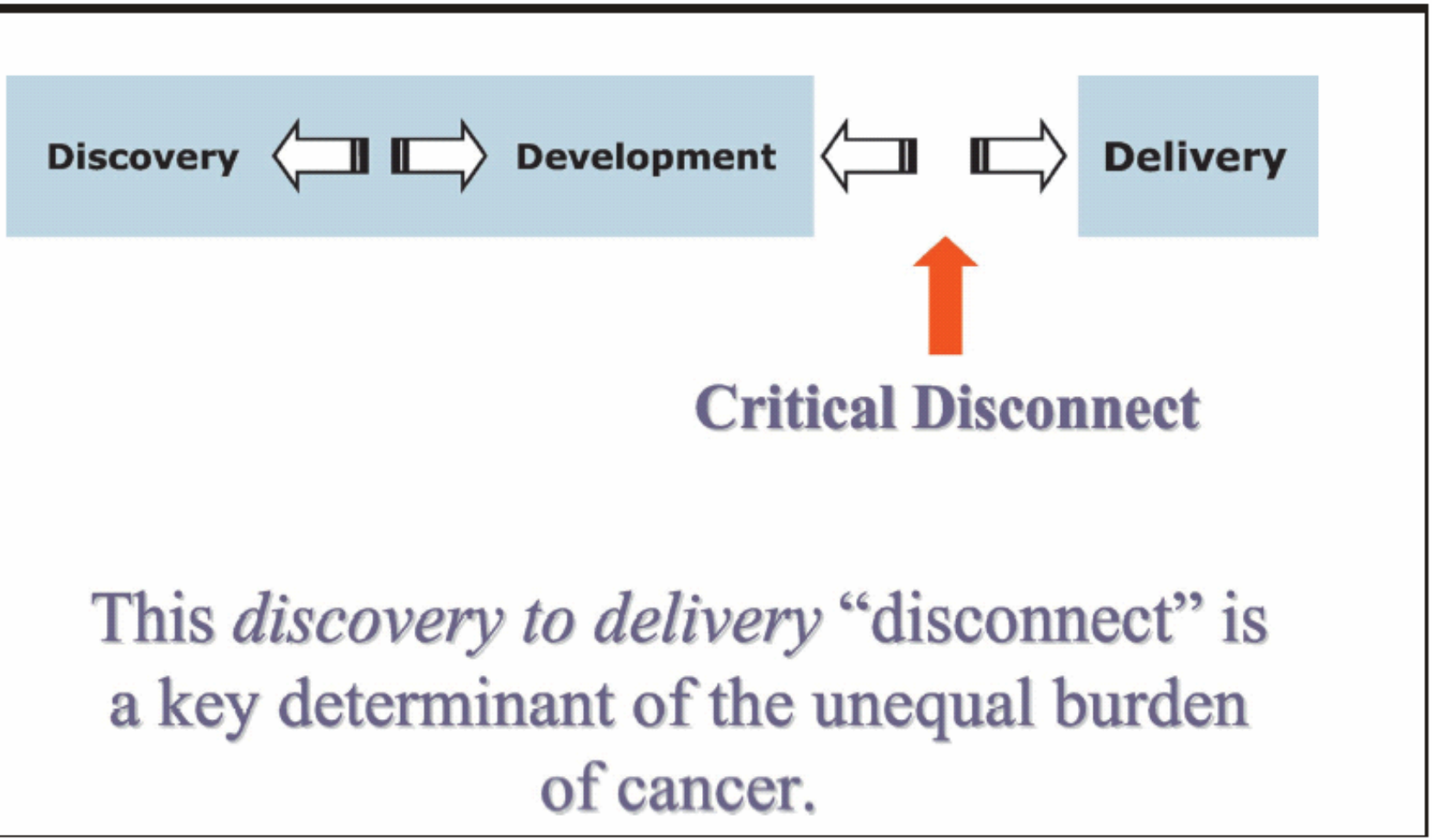


FIGURE 1 The Discovery-Delivery Disconnect.
Source: Adapted from Freeman HP.[1]

Freeman HP, CA Cancer J Clin 2004;54:72–77

Inequalities in Cancer Burden

- SES and racial/ethnic inequalities in cancer incidence, survival and mortality are well documented

- Clarity about what constitutes and causes these inequities in health is necessary for research and actions to address social disparities in cancer

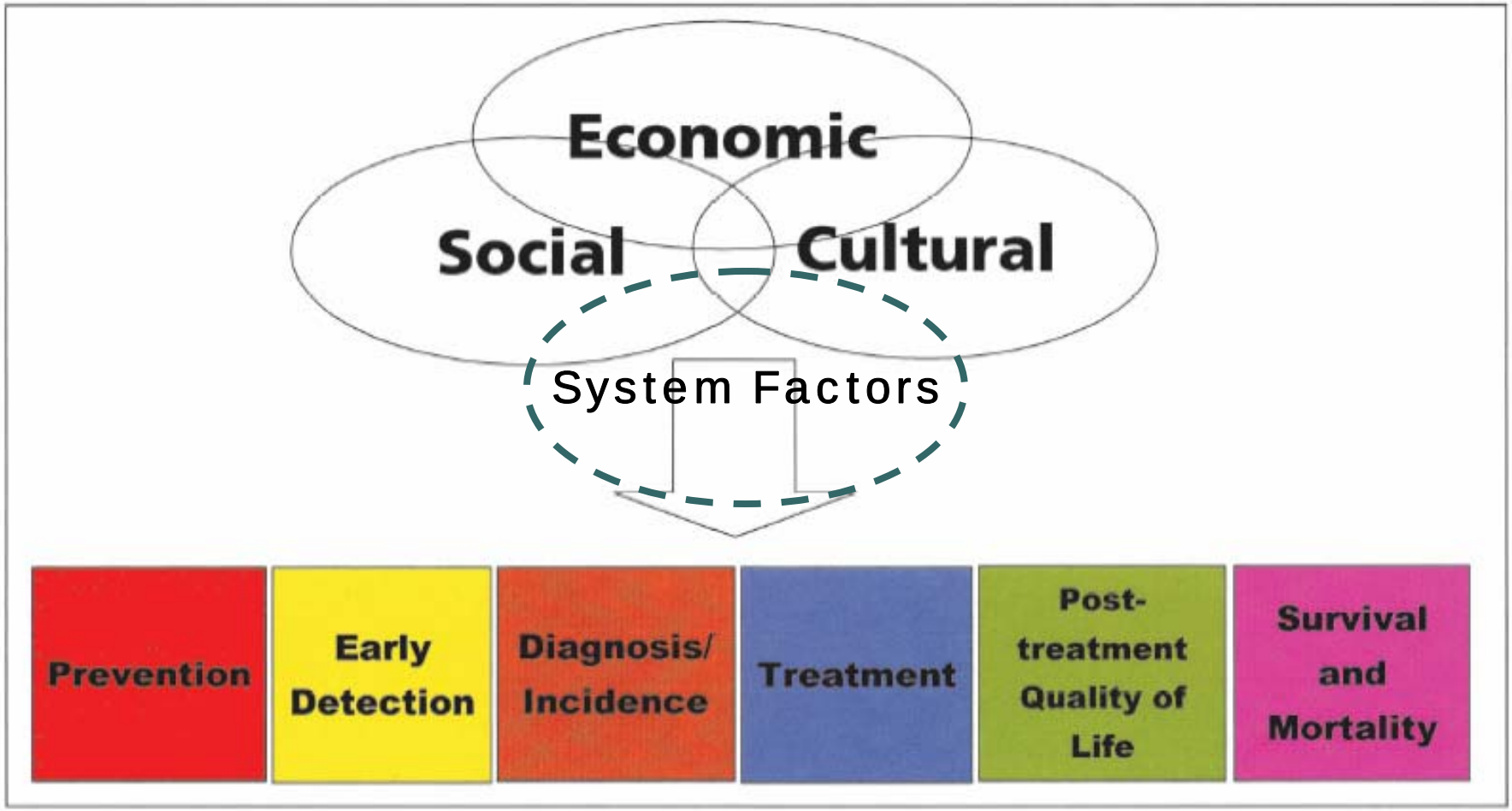


FIGURE 1 Factors That Influence Social Disparities.
Source: Adapted from Freeman, HP[3] and Institute of Medicine.[7]

Modified from: Ward E, et al. Cancer J Clin 2004;54:78–93.

Definition of Health Disparities

- Disagreements, confused terminology, and vagueness about the meaning of ***'cancer disparities'*** in scientific literature and government documents

Terms Commonly Used

- Health disparities
- Social disparities in health
- Health inequalities
- Social inequalities in health
- Health inequities
- Health variations
- Health differences

Measuring Health Disparities

- What do we mean for "**eliminating health disparity"?**
  - Everyone to have the same level of health?
  - All individuals/social groups should have the same health, regardless of how healthy or sick they might be?
  - Improving the health of the most disadvantaged individuals/social groups to approach the health of the more advantaged (i.e., priority to the worst-off/least healthy)?

Harper S & Lynch J, SRP-APR DCCPS, NCI, NIH, 2006

Measuring Health Disparities

- The health disparity concept involves both descriptive and normative elements
- Task:
  - To understand what the elements are
  - To develop sensible measures

Measuring Health Disparities

- In U.S. the term “disparity” implies two main concepts
  - It suggests that there are health “differences” between individuals or social groups
  - It suggests that such differences are unfair and against our moral concepts of social justice

Harper S & Lynch J, SRP-APR DCCPS, NCI, NIH, 2006

Measuring Health Disparities

- The term ***disparity*** often mixes ideas of ***inequality*** and ***inequity***
  - ***Inequality*** meaning that two quantities are not the same
    - Measurable, observable quantity that can be reasonably and unambiguously judged
  - ***Inequity*** implies an ethical judgment about those differences
    - Is not unambiguously measurable or observable
    - Judgment rely on social, political, and ethical discourse about what a society believes is unfair

Harper S & Lynch J, SRP-APR DCCPS, NCI, NIH, 2006

Measuring Health Disparities

- Other dimension of inequity and concepts of justice are ***avoidable*** and ***unavoidable*** determinants
  - ***Avoidability*** implies capacity to intervene (via social policy, medical care, etc.) with respect to the determinants of disparity
- Difficult to identify the determinants of disparities or to distinguish between avoidable and unavoidable determinants

Harper S & Lynch J, SRP-APR DCCPS, NCI, NIH, 2006

The Healthy People 2010

- Eliminating health disparities within a number of different types of social groupings
  - Gender
  - Race/ethnicity
  - Income
  - Education
  - Disability
  - Racism
  - Geographic location
  - Sexual orientation

Harper S & Lynch J, SRP-APR DCCPS, NCI, NIH, 2006

The Healthy People 2010

- Groupings were chosen because
  - Represent important normative dimensions of U.S. society
  - Health differences have been shown repeatedly between these social groups
- Grouping have implications for measuring and monitoring health disparities
  - Dimensions of SES position—education and income—have an inherent ordering
  - No inherent way to rank individuals by their race, ethnicity, disability status, or sexual orientation

Harper S & Lynch J, SRP-APR DCCPS, NCI, NIH, 2006

Measuring Health Disparities

- Clarification and Development of Theoretical Frameworks and Constructs of Cancer Disparities
  - Definition and Framing
  - Identification of relevant determinants
  - Ensuring the validity of methods, measures, analyses and interpretations

U.S, Official Definitions of 'Health Disparities'

National Institutes of Health (NIH, 1999)

- ‘Health disparities are differences in the incidence, prevalence, mortality and burden of diseases and other adverse health conditions that exist among specific population groups in the United States. The NIH Program of Action initially will focus on ***racial and ethnic minority populations***: African Americans, Asians, Pacific Islanders, Hispanics and Latinos, Native Americans and Native Alaskans. Research on health disparities related to ***socioeconomic status*** will also be addressed.’

NIH National Center on Minority Health and Health Disparities

- Mission concerned with: ‘reducing the profound disparity in health status of America’s ***racial and ethnic minorities, Appalachian residents, and other health disparity populations, compared to the population as a whole***’

US Department of Health and Human Services, Healthy People 2010

- Second overarching goal:
  - ‘to eliminate health disparities among ***segments of the population***, including differences that occur by ***gender***, race or ethnicity, education or income, disability, geographic location, or ***sexual orientation***’

NCI Division of Cancer Control and Population Sciences

- ‘Health disparities are differences in the incidence, prevalence, mortality, and burden of cancer and related adverse health conditions that exist among ***specific population groups*** in the United States. These population groups may be characterized by ***gender***, age, ethnicity, education, income, social class, disability, geographic location, or ***sexual orientation***’

Definitions

- Provide little insight into why these particular groups are at issue
- The definitions are descriptive, not analytic
- In the U.S., ‘population groups’ and ‘special populations’ figure prominently without any explicit explanation of why certain ‘population sub-groups’ are singled out and considered ‘special’

Proposed Analytic Definition of Cancer Disparities

- ***Social disparities in cancer refer to health inequities spanning the full cancer continuum, across the life course***
  - prevention, incidence, prevalence, detection and treatment, survival, mortality, and burden of cancer and other cancer related health conditions and behaviors
- Arise from inequities in:
  - Adverse working and living conditions
  - Inadequate health care linked to experiences and policies involving socioeconomic position (e.g., occupation, income, wealth, poverty, debt, and education) and discrimination

Krieger N, Cancer Causes & Control, 2005

Critical Components of a Research Agenda on Cancer Disparities

- Theory
- Monitoring
- Etiology
- Prevention

Krieger N, 2004

Critical Components of a Research Agenda on Cancer Disparities

- **Theory**
  - Clarification and development of theoretical frameworks and constructs needed to improve
  - How cancer researchers define and frame the problem of cancer disparities
  - Identify relevant determinants
  - Ensure the validity of methods, measures, analyses and interpretations

Krieger N, 2004

Critical Components of a Research Agenda on Cancer Disparities

- **Theory** (2)
  - Controversies over how best to conceptualize and measure race/ ethnicity, racism, socioeconomic position, ***gender***, ***sexuality***, disability, and other domains of inequality
  - When to measure, at what points in the life course, and at which levels of social organization
  - Choice of reference group

Krieger N, 2004

Critical Components of a Research Agenda on Cancer Disparities

- **Monitoring**
  - Data on population trends reveal whether health inequities are increasing or decreasing
  - Tests of etiologic hypotheses
  - How to incorporate key data typically not included in cancer registries
    - socioeconomic position and social context
  - Geographic level (block group, census tract or ZIP Code) most apt for monitoring SES disparities

Krieger N, 2004

Critical Components of a Research Agenda on Cancer Disparities

- **Etiologic Research**
  - Necessary for testing hypotheses about the causes of social inequalities in population distribution of cancer
    - Incidence
    - survival,
    - Mortality
    - Access to and provision of appropriate health care

Krieger N, 2004

Critical Components of a Research Agenda on Cancer Disparities

- **Prevention Research**
  - Develop, evaluate and improve methods to assess programs, projects, and policies that affect cancer disparities

Krieger N, 2004

A systematic approach to identifying research questions:

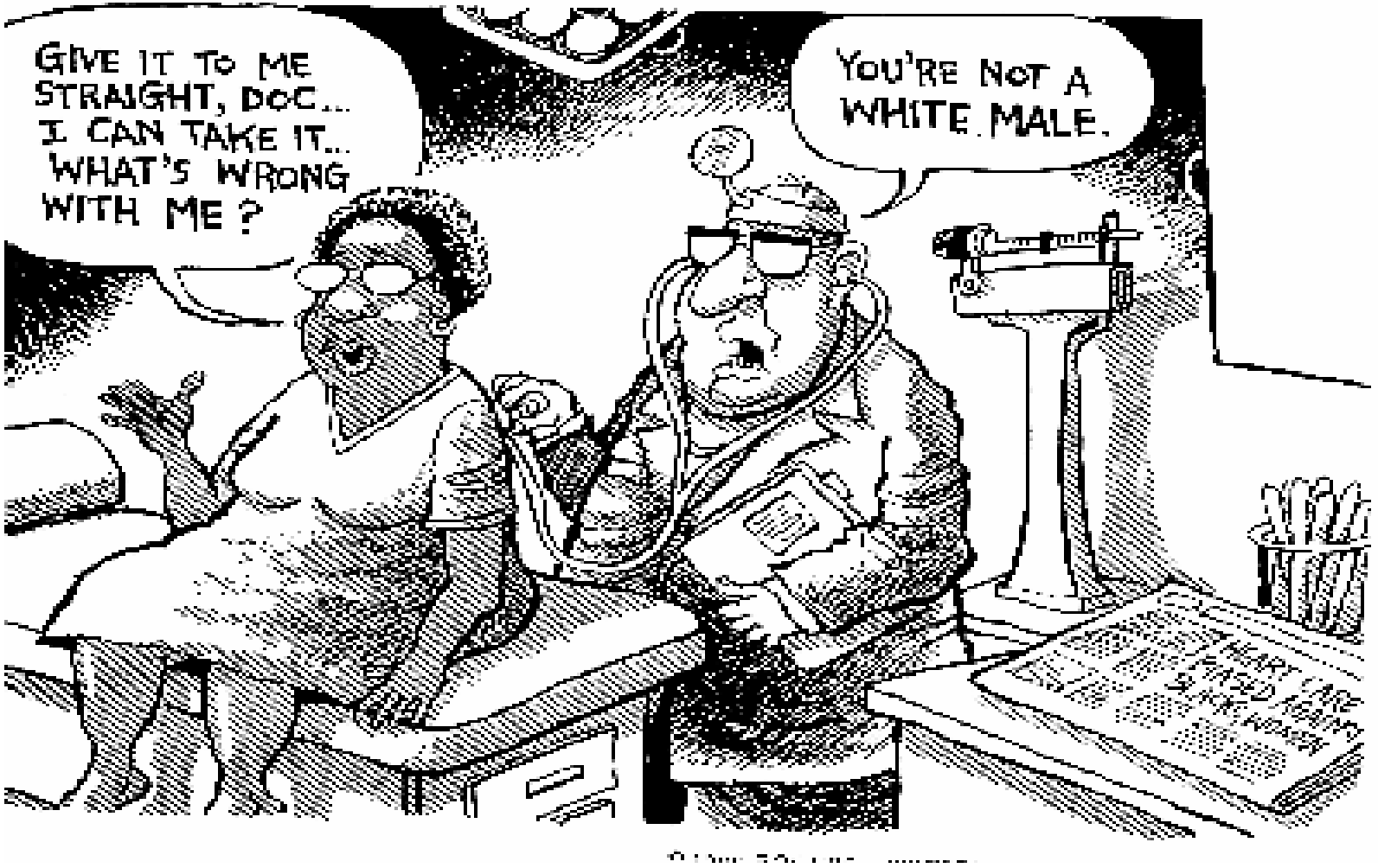
DOMAINS OF SOCIAL INEQUALITY: singly & combined, involving adverse conditions & discrimination at multiple levels (person, place, institutional, societal), across the lifecourse	CANCER CONTINUUM									
	Prevention (primary, secondary, tertiary)	Incidence	Etiology	Screening	Diagnosis	Access to clinical trials	Treatment	Survival	Morbidity	Mortality
Race/ethnicity & racism										
Socioeconomic position										
Gender										
Sexuality										
Age										
Language										
Literacy										
Disability										
Immigrant status										
Insurance status										
Geography (urban/rural)										
Housing status										

Note: research on cancer disparities encompasses epidemiologic, clinical, and intervention research; filling out the grid can highlight areas requiring emphasis (either because of the identified burden or because of gaps in knowledge), plus point to research requiring interdisciplinary expertise, premised on a population health perspective.

Fig. 2. 'Cancer disparities' analytic grid.

Krieger N, Cancer Causes & Control, 2005

Sex & Gender Cancer Disparities


GIVE IT TO ME STRAIGHT, DOC... I CAN TAKE IT... WHAT'S WRONG WITH ME?
YOU'RE NOT A WHITE MALE.

Sex & Gender Health Disparities

- A growing literature on the social determinants of health, suggests explanations for many population and individual level health outcomes are not attributable to biology
- Income, income inequality, social connectedness, and social capital all show some association with health and illness
- The association of ***sex*** & ***gender*** with health can not be adequately examined independently of each other
- Gender interacts with biology, in every society, although the results of that interaction vary from setting to setting

Definitions

- ***Gender*** was introduced in the 1970s as an alternative to ‘sex’ to counter an implicit and often explicit biological determinism in the scientific and lay language

- ***Gender*** was expanded from referring to ‘masculine’ or ‘feminine’ to a term of social analysis

- ***Sex*** was restricted to a biological term, referring to groups defined by the biology of sexual reproduction (or, in the meaning of ‘having sex’, to interactions involving sexual biology)

Krieger N, 2003

Definitions

- ***Gender-*** a social construct regarding culture-bound conventions, roles, and behaviors for, as well as relations between and among, women and men and boys and girls
- Gender roles vary across a continuum
- Both **gender relations** and **biologic expressions of gender** vary within and across societies, typically in relation to social divisions of power and authority (e.g., class, race/ethnicity, nationality, religion)

Krieger N, 2001

- Ethnicity, SES, sexual orientation, geography and other social identifiers situate women and men differently in the social landscape
  - complicating the relationships between gender, sex and health disparities

Definitions

- ***Sex***- a biological construct determined by biological characteristics enabling sexual reproduction
- Sexual categories include: male, female, intersexual, and transsexual
- Sex-linked biological characteristics can, in some cases, contribute to gender differentials in health but can also be construed as **gendered expressions of biology** and erroneously invoked to explain **biologic expressions of gender**

Krieger N, 2001

Sex & Gender Health Disparities

- Distinguishing between sex and gender, common in the social sciences, has begun to penetrate into the language of prevention, etiology and causation within health care
  - Women's unequal status in society jeopardizes their health and well being
  - Women experience higher mortality and morbidity in states where they have lower levels of political participation, economic autonomy, and higher levels of poverty
  - The context of women's lives has a major impact on health and the ability to get care

Sex & Gender Health Disparities

- Women are more often single parents who are uninsured or underinsured and have more limited access to health care resources than men
- These factors are exacerbated in the elderly and disabled
- Use of the categories of "men" and "women" tends to ignore the complex interaction of race, sex, and social class within our health care system and may obscure the fact that differences *among* women are larger than differences between, for example, white men and white women

Uses of Term Gender in the Literature on Women's Health Over the last 20-yr

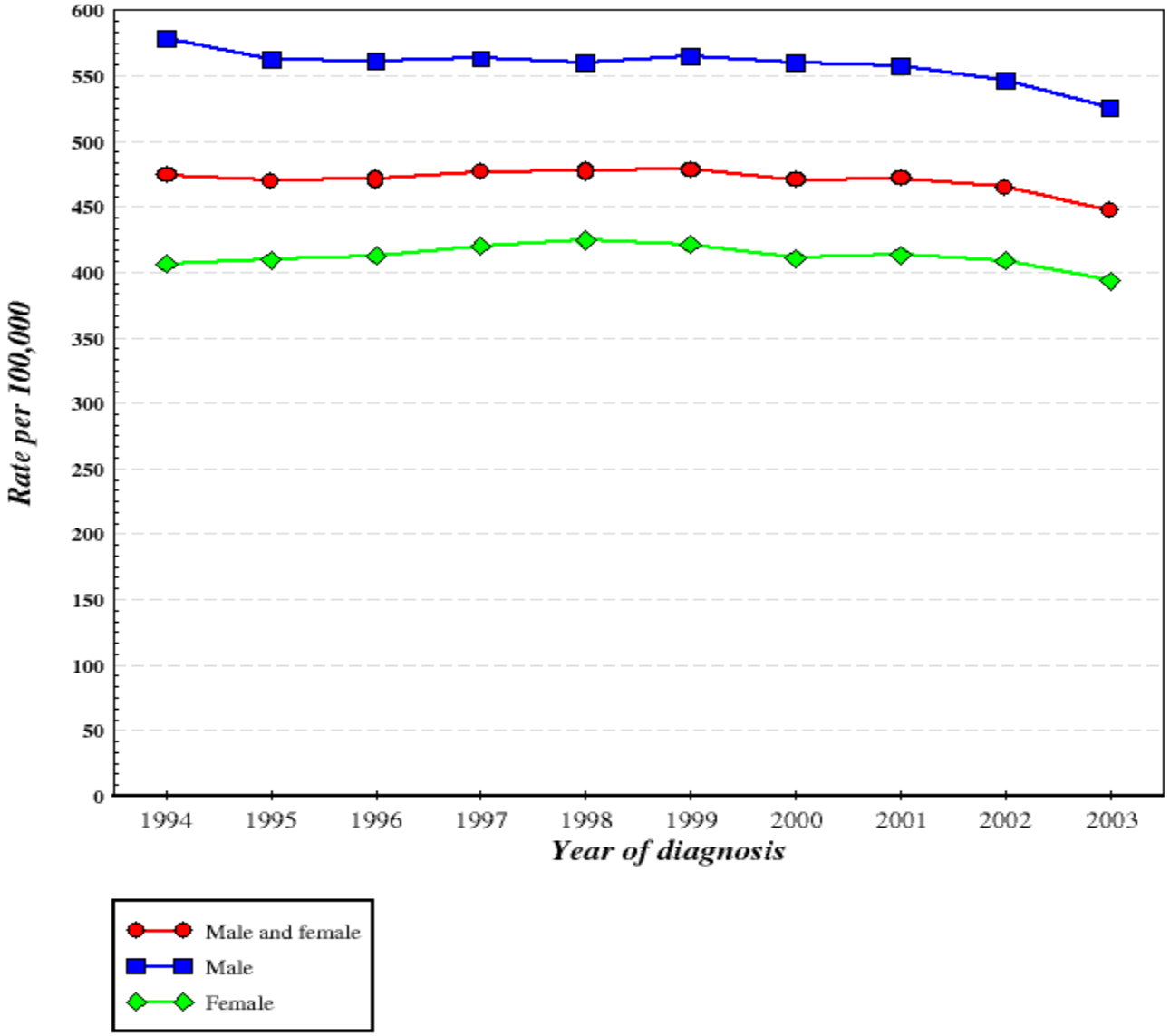
1. Does not question biology as the sole determinant of health but calls for an end to the discrimination that made the biology of women invisible
    - limitations of such an approach are two-fold
        - women continue to be defined in terms of men
        - biology defines being, while social determinants vanish
2. Introduces the term gender but uses it interchangeably with sex

Uses of Term Gender in the Literature on Women's Health Over the last 20-yr

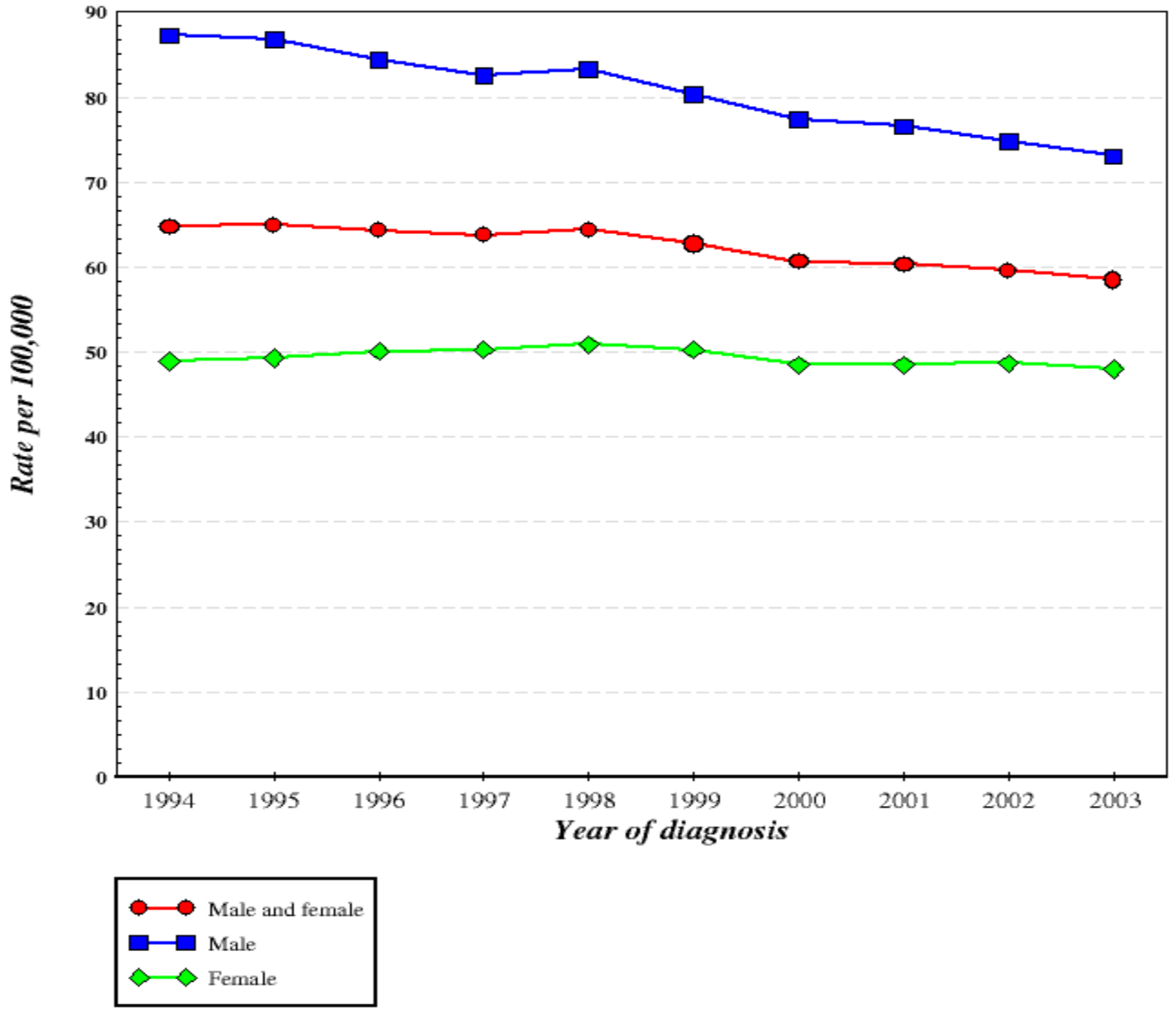
3. Links the health of women as patients to the well being of women as health care providers in a traditionally patriarchal health care delivery system
    - describing the challenges women face in advancing to leadership positions, this group suggests that only after models of care change will health outcomes for women improved
4. Defines gender as a social determinant of the health of both men and women, but deals with how sex and gender interact, and with the specifics of how gender shapes individual health

Some Examples of Sex-Gender Disparities in Cancer & Cancer Risk Factors In the U.S.

SEER Age Adjusted Incidence Rates by Sex For All Cancer Sites, All Ages, All Races SEER 13 Registries for 1994-2003
Age-Adjusted to the 2000 US Std Population



SEER Age Adjusted Incidence Rates by Sex For Lung and Bronchus Cancer,
All Ages, All Races SEER 13 Registries for 1994-2003
Age-Adjusted to the 2000 US Std Population



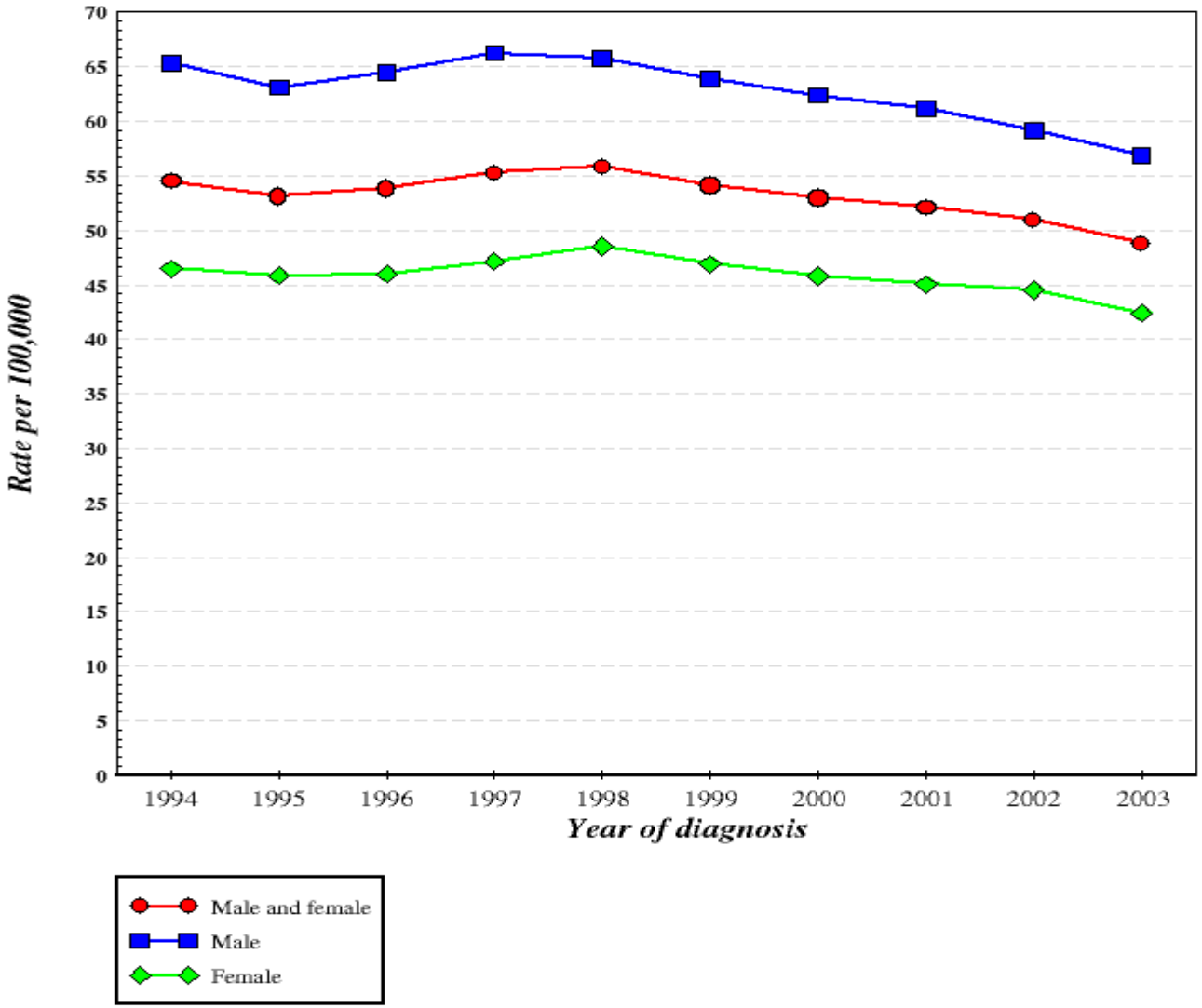
Sex & Gender Health Disparities

- Mortality from lung cancer declined significantly among men (-1.7% per year) while rates for women were still significantly increasing (1.3% per year)
- Decreasing smoking patterns among women lag behind those of men
- Women appear to be more susceptible to the damaging effects of cigarette smoke and alcohol
- Enzymatic, gene expression, and estrogen receptor-related variations may contribute to increased susceptibility

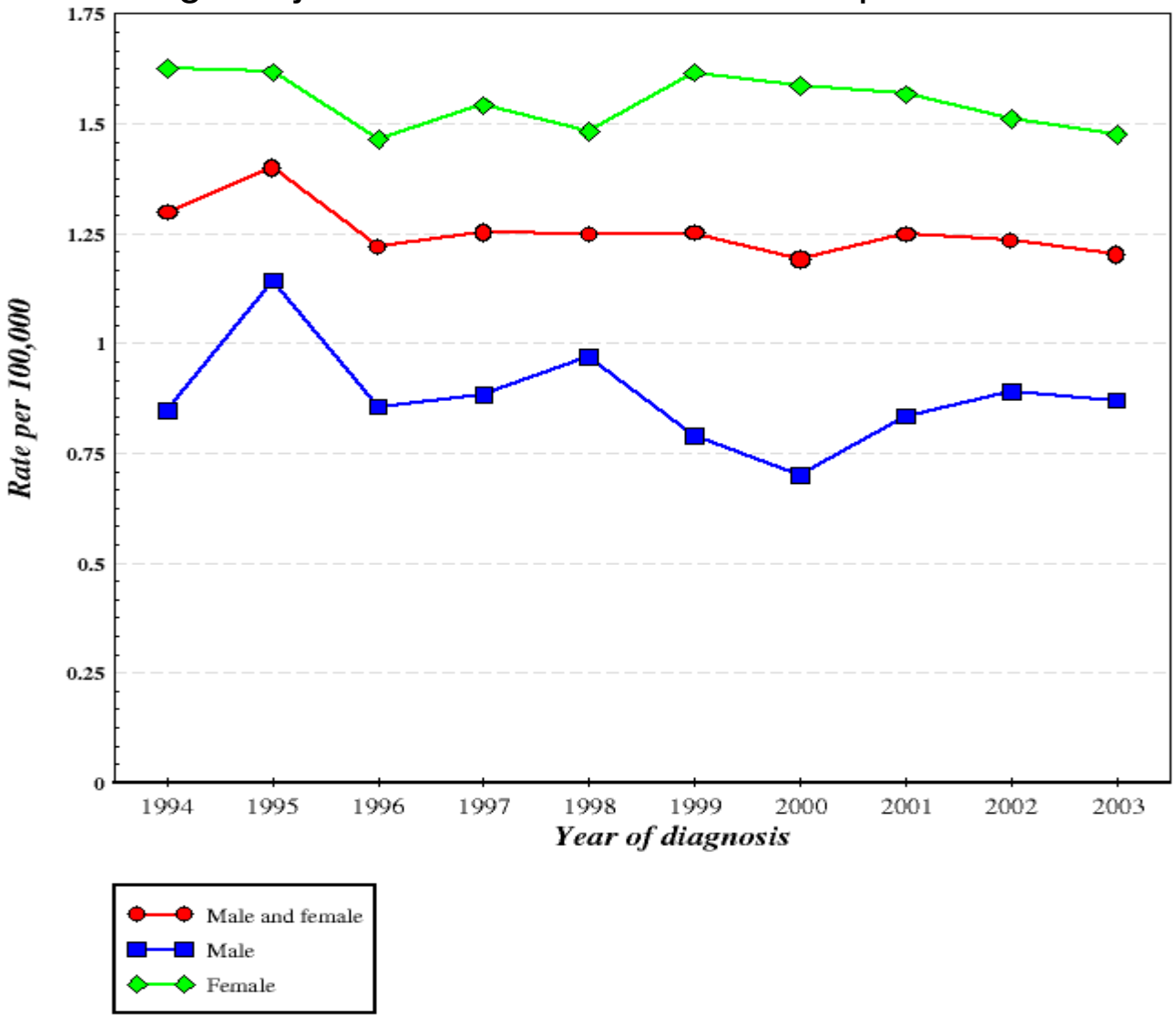
Sex & Gender Health Disparities

- Distribution of histological subtypes of lung cancer in women is different from that in men
  - Women are less likely to have squamous cell carcinoma
  - More likely to have adenocarcinoma or small cell lung cancer
- Molecular biologic substaging of patients with Stage I non-small cell lung cancer (NSCLC) demonstrates cancer-specific survival according to marker expression, gender, and histologic subtype
- NSCLC in women is more likely than in men to harbor K-ras mutations, suggesting a role for estrogen exposure, but women retain a modest survival advantage

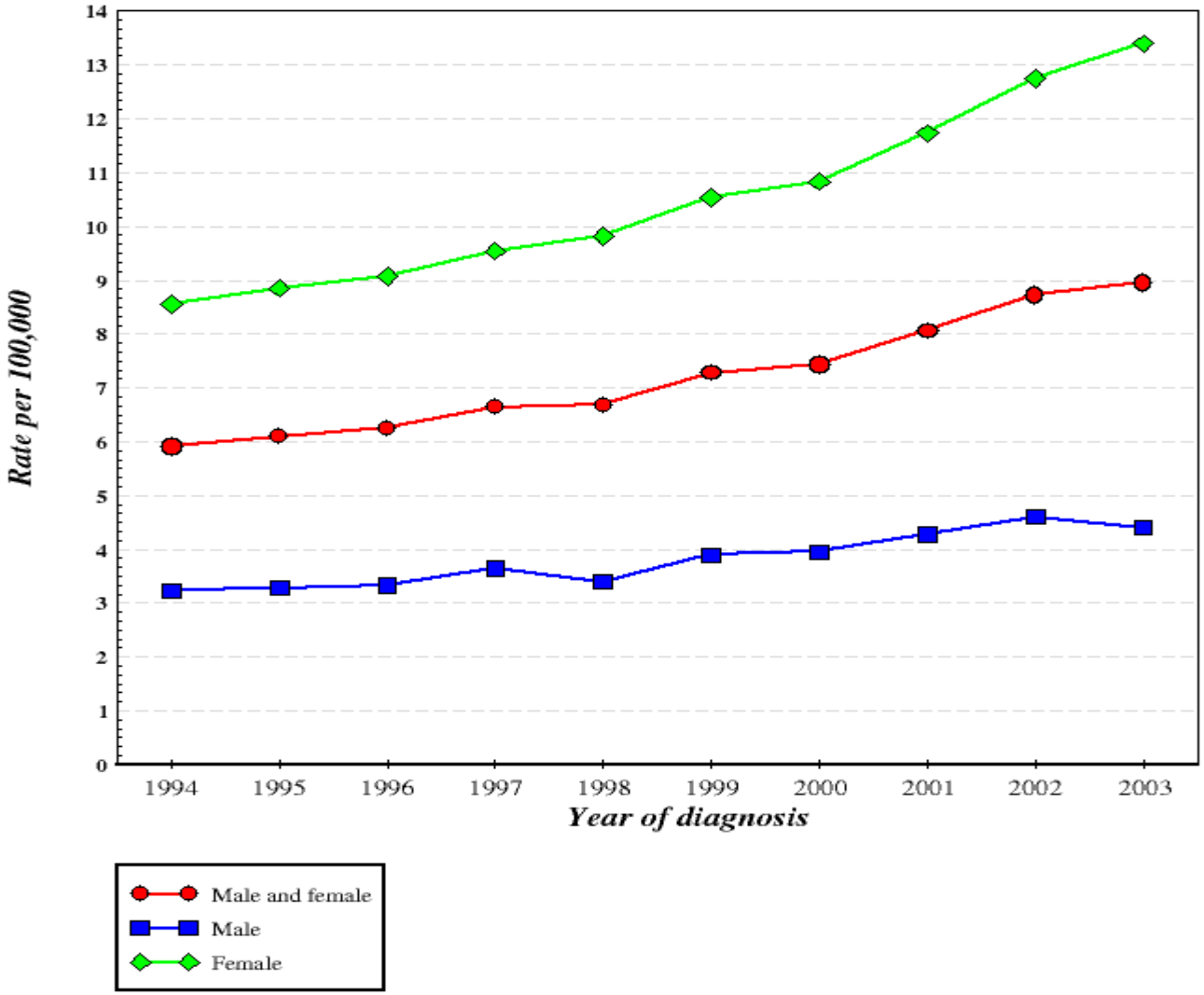
SEER Age Adjusted Incidence Rates by Sex For Colon and Rectum Cancer ,
All Ages, All Races SEER 13 Registries for 1994-2003
Age-Adjusted to the 2000 US Std Population



SEER Age Adjusted Incidence Rates by Sex For Gallbladder Cancer , All Ages, All Races SEER 13 Registries for 1994-2003
Age-Adjusted to the 2000 US Std Population



SEER Age Adjusted Incidence Rates by Sex For Thyroid Cancer, All Ages, All Races SEER 13 Registries for 1994-2003
Age-Adjusted to the 2000 US Std Population



Sex & Gender Health Disparities

- 35% of women >20 years are obese
- One in 4 women reports no regular physical activity
- The pharmacokinetics and pharmacodynamics of many prescription drugs differ between women and men
- Many women believe they are not at risk for CRC
- CRC strikes women nearly as often as men
  - 67,000 women each year are diagnosed with the disease and 40% die from it
- CRC screening is low in both men and women

Sex & Gender Health Disparities

- Women experience more severe toxicity than men receiving 5-FU–based chemotherapy for CRC and SCLC
  - Greater incidence of a wide variety of toxicity types
  - Greater average severity
- Even in cycles 2 and 3, when men received an equal or greater 5-FU dosage than women, women still experienced more toxicity than men during these cycles

Sex & Gender Health Disparities

- Potential mechanisms:
  - Levels of dihydropyrimidine dehydrogenase have been reported to differ between the sexes
  - It has been postulated that it might be related to thymidylate synthase levels (no report of sex differences in thymidylate synthase levels)
  - Lower clearance
  - Greater BMI
  - Related to a perceived differential in reporting of subjective symptoms between men and women

Sex & Gender Health Disparities

- Previous data suggest that women longer survival with advanced NSCLC than men
  - 9.2 months versus only 7.3 months
  - Cannot be explained by differences in any other known prognostic factors
  - Molecular differences have also been reported
  - Differences in drug metabolism
  - Differences in DNA damage susceptibility

Research Strategies to Address Gender & Sex Health Disparities

Gender & Sex-Based Analysis

- Approach to research and evaluation which systematically inquires about biological (sex-based) and sociocultural (gender-based) differences between women and men, boys and girls, without presuming that any differences exist

- Purpose- to promote rigorous ***sex/gender-sensitive health research*** which expands understanding of health determinants in both sexes, to provide knowledge which can result in improvements in health and health care

Canadian Institutes of Health Research (CIHR). *2005-6 CIHR Grants and Awards Guide*

Gender & Sex-Based Analysis

- GSBA is meant to be applied within the context of a diversity framework
  - Attends to the ways in which ethnicity, SES, disability, sexual orientation, migration status, age and geography interact with sex and gender to contribute to exposures to various risk factors, disease courses and outcomes
- These intersecting factors have significant impact on health and wellbeing

Canadian Institutes of Health Research (CIHR). *2005-6 CIHR Grants and Awards Guide*

Gender-Sensitive Research

- Systematically checking on the lack of attention for gender aspects or on hidden imbalances in the attention paid to aspects relevant to men and women

- To retrieve the complex interdependence of biological, psychological, social and cultural factors- and not dealing with sex as if it were a confounding variable

Canadian Institutes of Health Research (CIHR). *2005-6 CIHR Grants and Awards Guide*

Sex/Gender-Sensitive Health Research

- Sex and gender-sensitive health research produces knowledge that reflects the complexity and diversity of human health
- Investigates how ***sex*** interacts with ***gender*** to create health conditions, living conditions and problems that are unique, more prevalent, more serious, or for which there are distinct risk factors for women or men
- Responses to these factors are the result of an interaction of genetics, physiology, cultural, social and individual responses-in other words of the interplay of sex and gender

Canadian Institutes of Health Research (CIHR). *2005-6 CIHR Grants and Awards Guide*

Gender & Sex-Based Analysis

- ***GSBA is Good Science***
  - demands greater attention to the construction of measurements and variables in research
- ***GSBA is Ethical Research***
  - More inclusive research contributes to more meaningful and accurate research outcomes that ultimately contribute to a healthier population
- ***GSBA is Essential to Equity***

Canadian Institutes of Health Research (CIHR). *2005-6 CIHR Grants and Awards Guide*

Health Canada

- "the *integrated* use of GSBA throughout the research, policy and program development processes can improve our understanding of sex and gender as determinants of health, of their interaction with other determinants, and the effectiveness of how we design and implement sex- and gender-sensitive policies and programs"

GSBA Research Question

- Are sex and/or gender identified and defined?
- Are the definitions supported by recent academic literature?
- Does the proposal demonstrate awareness of what is known about sex, gender and diversity (ethnicity, socioeconomic status, sexual orientation, migration status, etc.) in this area of research?
- Are the concepts of sex, gender and diversity taken into account in the development of the research question(s)?
- Are the concepts of sex, gender and diversity applied clearly and appropriately?
- If used in the study, does the researcher identify and justify the choice of the sex of cells, cell lines, and/or animals?
- If the applicant asserts that sex and/or gender and diversity are *not* relevant to the proposed research, what evidence is presented?
- Does the research question reflect the diversity in and among females and males ?

Canadian Institutes of Health Research (CIHR). *2005-6 CIHR Grants and Awards Guide*

GSBA Data Collection

- Does the sex/gender/diversity composition of the sample reflect the research question?
- Does the sample match the researchers' plans for generalizing from the data?
- Have research instruments (i.e., surveys, measurements) been validated to reflect gender/sex and diversity?
- If sex is used as a proxy for weight, height and body fat/muscle ratios, is there an explicit explanation and analytical strategy provided for employing this approach?

GSBA Data Collection (2)

- In the case of clinical trials:
  - Does the sample reflect the distribution of the condition in the general population?
  - For proposed clinical trials, are sufficient numbers of women and men included in the sample to enable safety as well as efficacy analysis?
  - Where appropriate, how will the clinical trial track and account for female menstrual cycles?
  - Does the applicant plan to analyze results in the context of known sex-specific adverse effects, height-weight-sex relationships, and interactions with commonly used drugs?

GSBA Data Analysis and Interpretation

- Will the researchers disaggregate and analyze data by sex/gender?
- Does the use of gender as a variable mask or intersect with other potential explanatory factors such as socioeconomic status, physical attributes and/or ethnicity?
- What assumptions are being made about gender and/or sex-especially as they intersect with other diversity indicators such as ethnicity, sexual orientation, socioeconomic class, etc.-while formulating the research problem, sampling, data collection, analysis and interpretation?

FY 2006 NIH Research Priorities for Women's Health

- *The mission of the Office of Research on Women's Health (ORWH) is to stimulate and encourage meritorious research on women's health, including the role of sex and gender in health and disease*
- Four overarching themes are important for addressing research on women's health:
  - Lifespan
  - Sex/Gender Determinants
  - Health Disparities/Differences and Diversity
  - Interdisciplinary Research

The following statements, recommended by the Council on Scientific Affairs, were adopted as AMA Policy at the 2000 AMA Interim Meeting:

1. The AMA supports the recent trend of increased research on women's health and participation of women in clinical trials, the results of which will permit development of evidence-based prevention and treatment strategies for all women from diverse cultural and ethnic groups, geographic locations, and socioeconomic status

2. The AMA recommends that all medical/scientific journal editors require, where appropriate, a sex-based analysis of data, even if such comparisons are negative.

The following statements, recommended by the Council on Scientific Affairs, were adopted as Directives at the 2000 AMA Interim Meeting:

1. The AMA commends the various federal agencies and medical association and women's health organizations that are providing valuable and credible physician/patient education on sex- and gender-based differences in health and disease

2. The AMA encourages the Women Physicians Congress in its efforts to serve as a clearinghouse for organization resources and related information on sex- and gender-based differences in health and disease, including the use of various forums, such as the AMA Web site and Medem, to provide comprehensive and timely physician education resources on sex- and gender-based differences in health and disease

3. The AMA will widely distribute this report to the Federation of Medicine, Association of American Medical Colleges, women's health organizations, and other relevant groups

Association of Schools of Public Health (ASPH) 2004

1. Promote, through a public statement promulgated by the deans of the schools of public health, the incorporation of content specific to sex and gender differences in health problems into the core MPH curriculum.
2. Establish an ad hoc advisory group to guide efforts that promote integration of the aforementioned key principles related to sex and gender in the MPH curriculum.

Redefining Gender

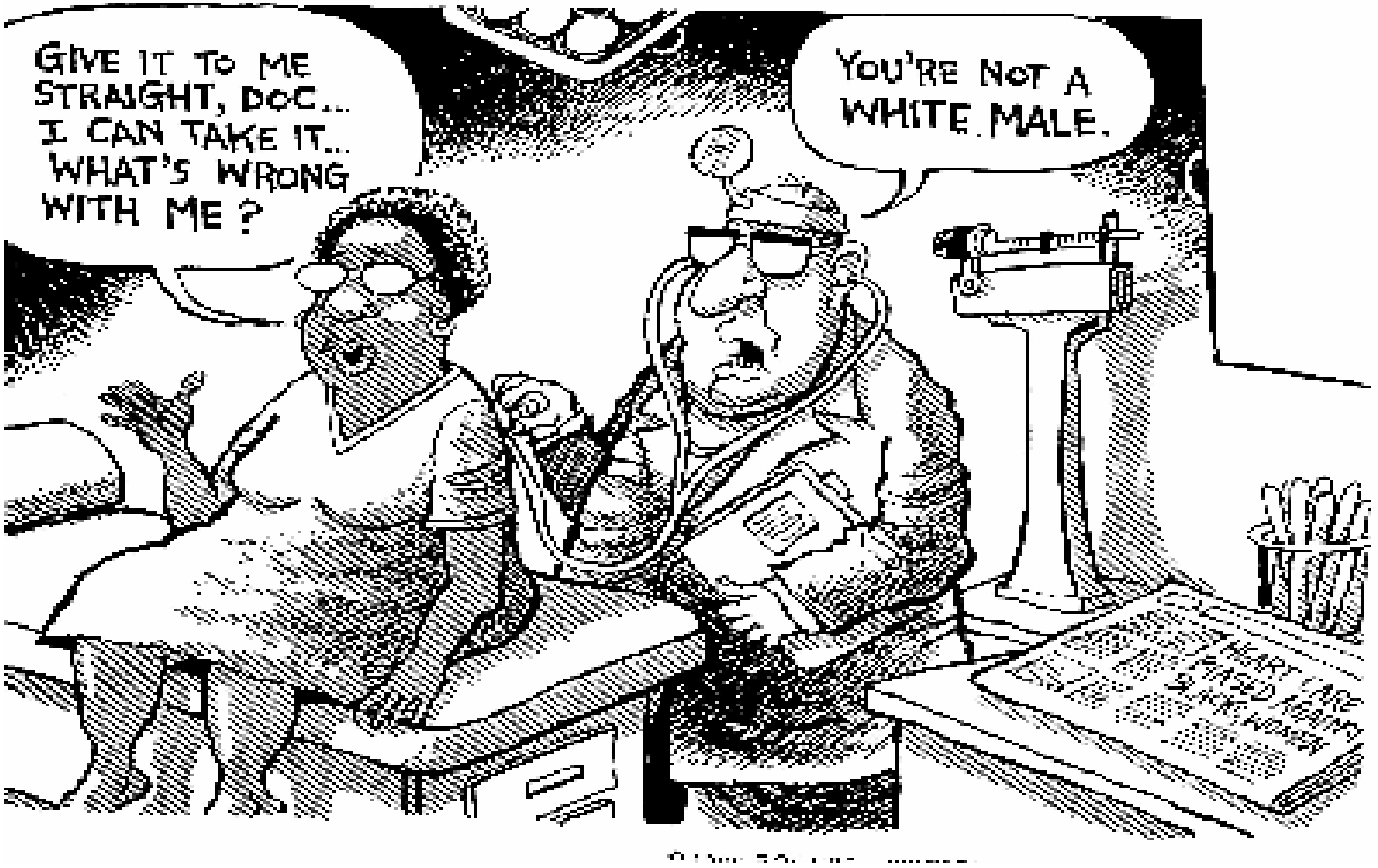
- “”Given the interconnectedness of the biological and the social, it might prove pragmatic to consider that gender encompasses both sex differences and the social constructs that give rise to gender differences
- There is no practical advantage to disentangling where sex ends and gender takes over as a cause of the sequelae of disease
- Redefining gender as the composite of both social and biological health effects associated with being either male or female, researchers may more easily move on to studying those effects, without getting stuck at enumerating sex differences

Phillips SP, 2005

Gender Index/Composite variable

- No one has proposed a proxy measure for gender
- Indicators of human rights may approximate gender when the health of women is the outcome being examined
- Similarly income, income distribution, and access to education or health care are likely colinear with gender in the measure of women's health
- Even more important may be the interaction between these variables in answering questions such as how the health of women in a relatively wealthy, but repressive country compares to women's well being in a less wealthy, but more egalitarian country
- Multilevel analyses may capture individual variations in wealth or freedom within population level research
- More problematic is identifying proxies for gender when examining men's health

Phillips SP, 2005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