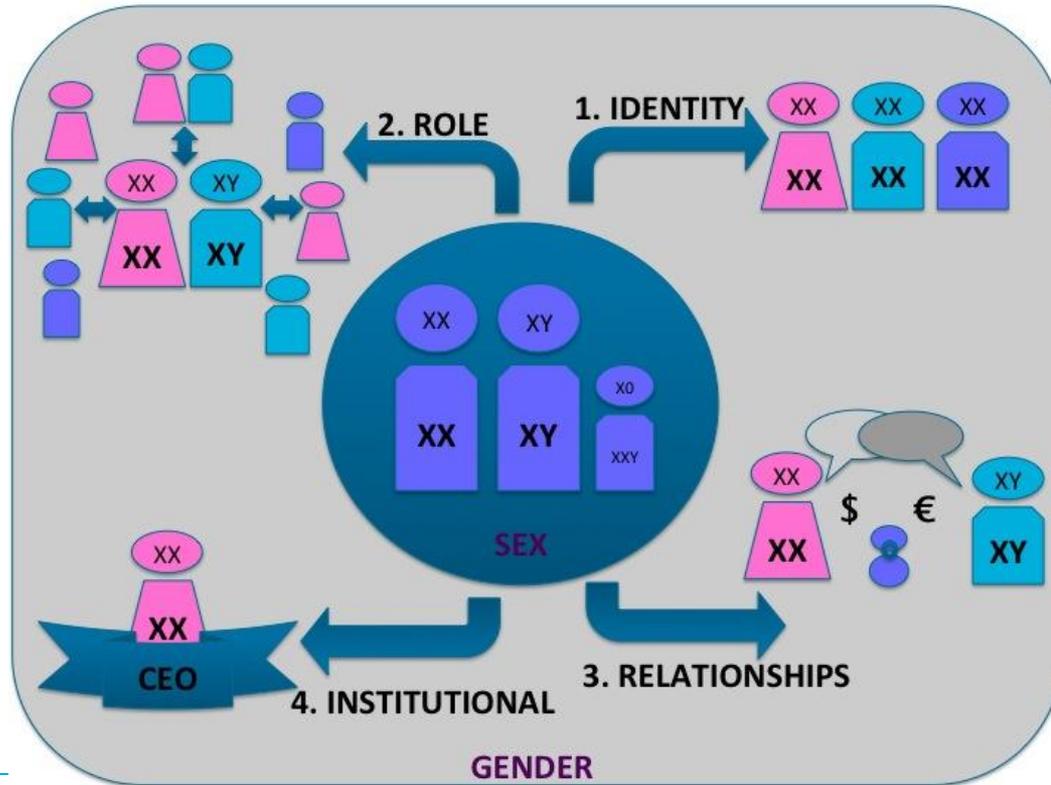


Why consider sex and gender in oncology ?

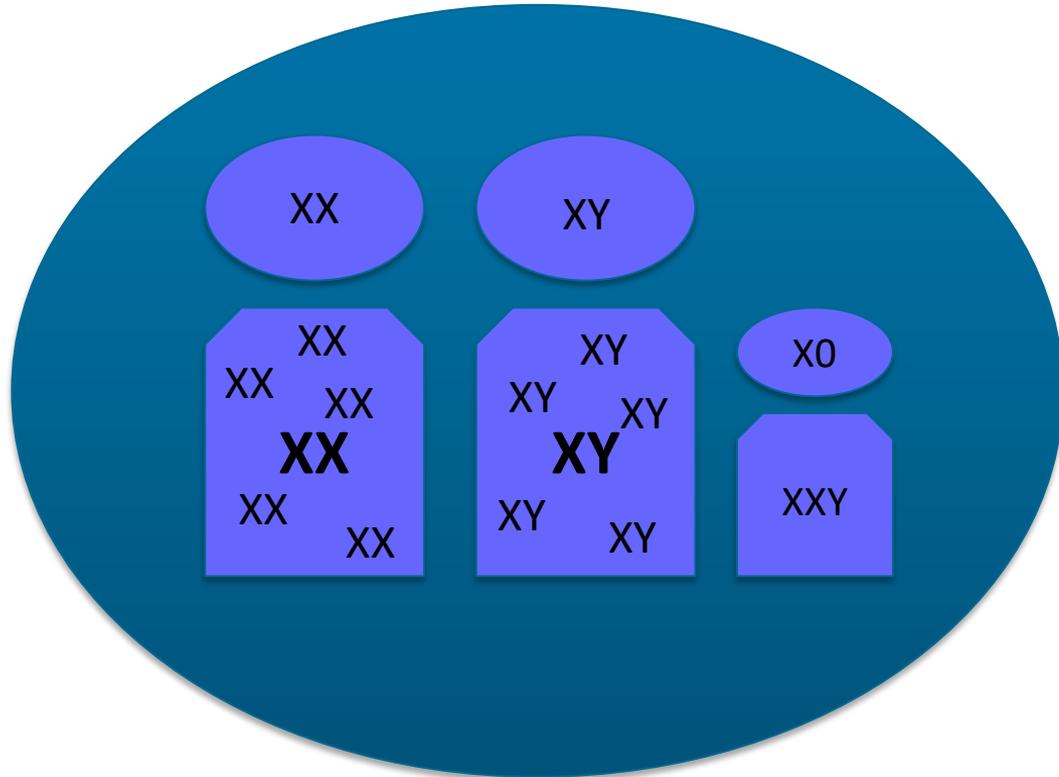
Sabine Oertelt-Prigione

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Sex and gender - terminology



Every cell has a sex



Sex differences: genes

a Receptors & associated proteins

AR	Androgen receptor
AGTR2	Angiotensin receptor 2
CSF2RA	Colony-stimulating factor 2 receptor α (granulocyte-macrophage)
GPCR	G-protein coupled receptors 23, 50, 301, 112, 159, 174 and CX-chemokine receptor 3
CYS1TR1	Cysteinyl leukotriene receptor 1
IL1RA1P1	Interleukin-1 (IL-1) receptor accessory protein-like 1
IL1RAP2	IL-1 receptor accessory protein-like 2
IL2RG	IL-2 receptor γ chain
IL3RA	
IL9R	
IL13RA1	
IL13RA2	
IRAK	
NGFRAP1	
TLR7	
TLR8	

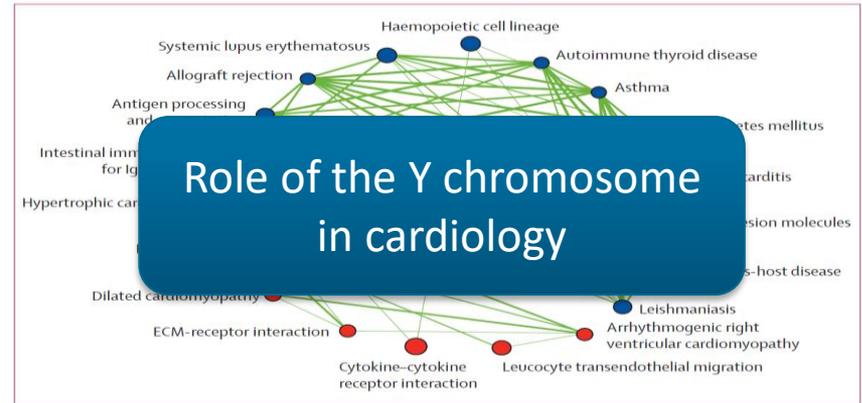
b Immune

XSCID	
BLK1	
EPAG	
GATA1	Common lymphoid progenitor
GTD	Gonadotropin deficiency
IDDMX	X-linked susceptibility to insulin-dependent diabetes
KIRP1	CD79A, immunoglobulin binding protein 1
KIRP1	Immunoglobulin superfamily member 1
ITGBBIP2	Integrin- β -binding protein 2
CD99	Also known as MIC2, associated with T-cell function
MTCF1	Mature T-cell proliferation 1
PEC	Properdin β factor, complement
TIVP1	Tissue inhibitor of metalloproteinase 1
CD40L	CD40 ligand
Z39IG	An immunoglobulin superfamily protein

c Transcriptional & translational control effectors

RHOA	RAS homologue (RHO) GTPase activating proteins 4, 6
CDC42GEP	Cell-division cycle 42 guanine-nucleotide-exchange factors 6, 9
ETK	Also known as BARR
BTX	Bruton agammaglobulinemia tyrosine kinase
CDK4	Caudal homeobox transcription factor 4
TRAP170	A co-factor for SP1 transcription factor activation
DUSP	Dual specificity phosphatases 9, 21
EEF	Eukaryotic translation elongation factors ϵ 13, β 4
EIF	Eukaryotic translation initiation factor $1A^*$, 2a

Role of the X chromosome in immunology

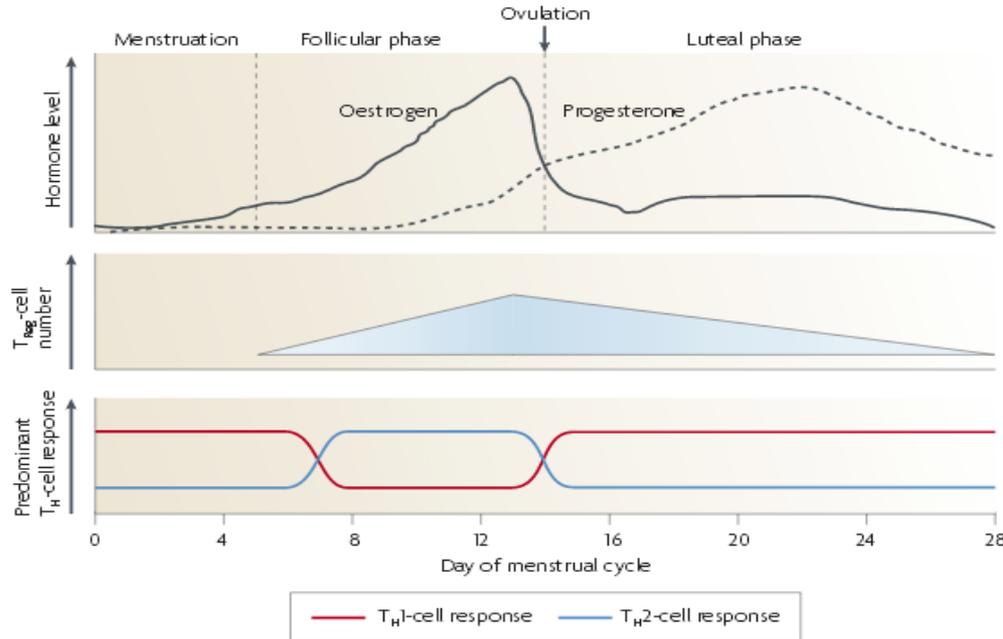


Role of the Y chromosome in cardiology

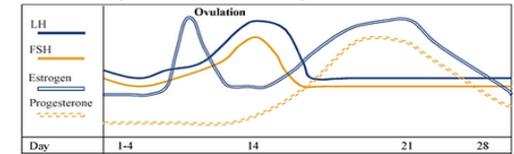
Nature Reviews | Immunology

Fish EN, Nat Rev Immunol, 2008
Charchar FJ, The Lancet, 2012

Sex differences: hormones



A Human Reproductive Menstrual Cycle



B Rat Reproductive Menstrual Cycle

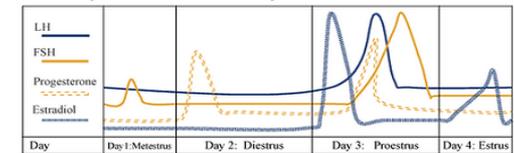


Figure 3 | Oestrogen and progesterone effects on T-cell responses during the menstrual cycle. Variations in oestrogen and progesterone levels during the different phases of the menstrual cycle influence T helper 1 (T_H1)-, T_H2 - and T regulatory (T_{Reg})-cell populations. The upper panel illustrates fluctuations in the levels of oestrogen and progesterone during the different phases of the 28-day menstrual cycle. In the middle and lower panels, the corresponding changes in the size of the T_{Reg} -cell population and the T_H -cell bias, respectively, are shown.

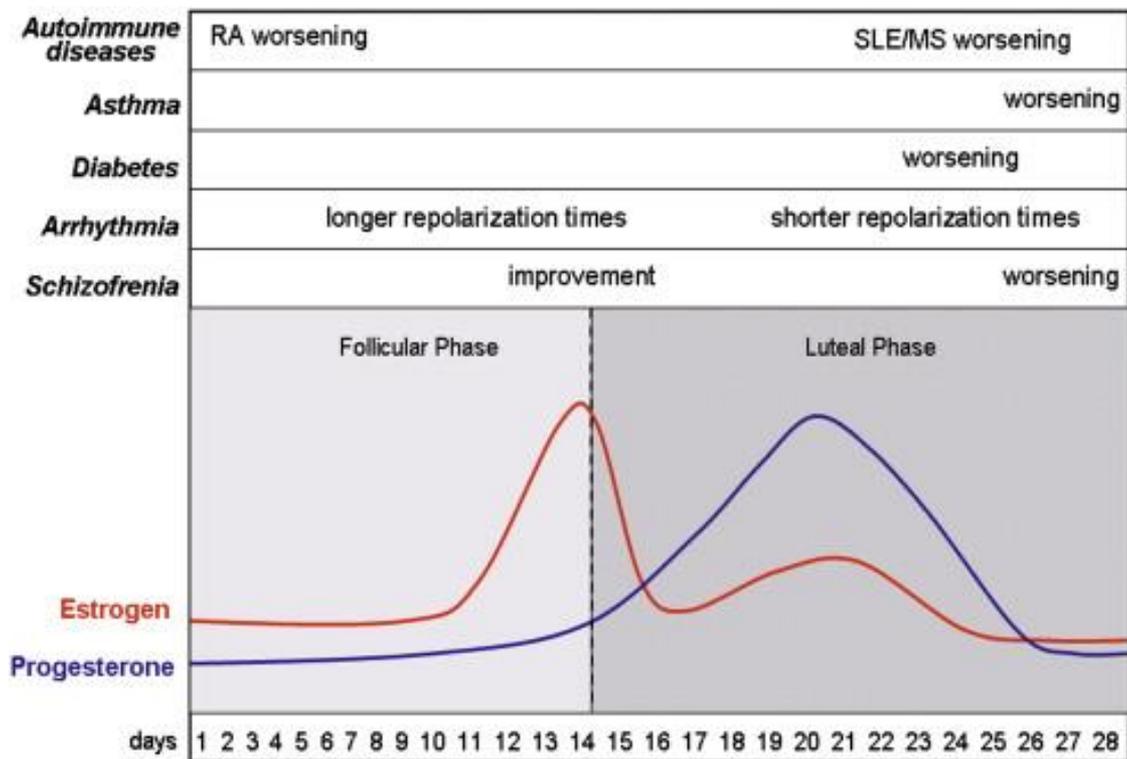
Prendergast BJ, Neurosci Biobehav Rev, 2014

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Radboudumc

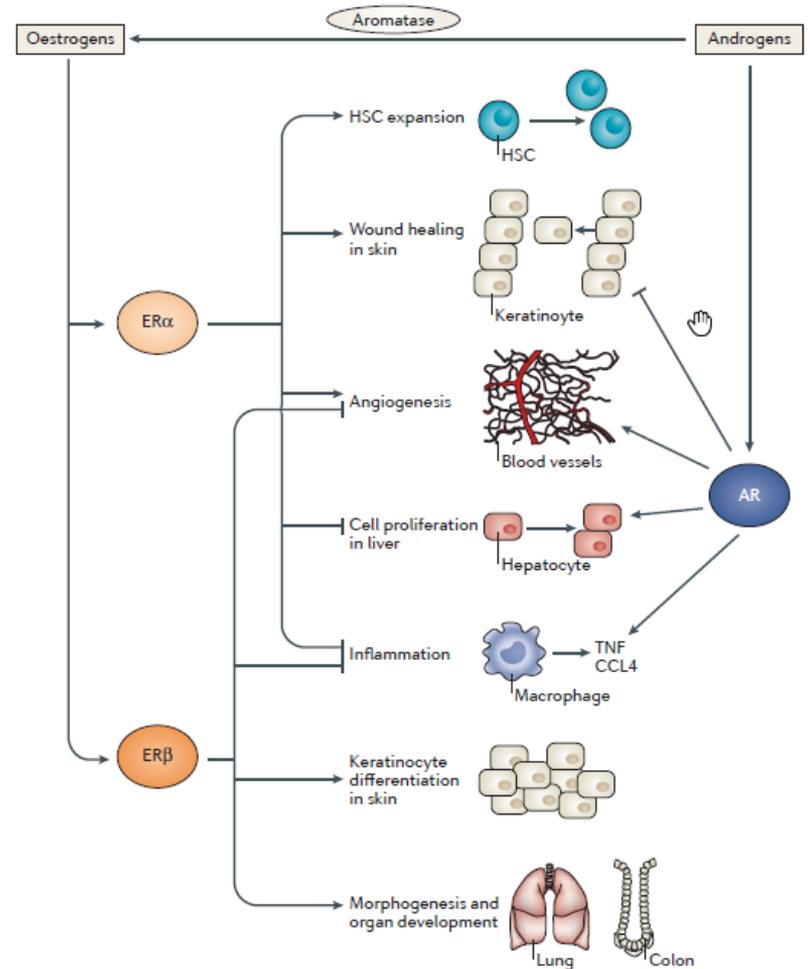
Sex differences: hormones and disease



Sexual dimorphism in cancer

Differential roles of estrogens and androgen on different cell types

Overlapping and discordant effects of ER alpha and beta on angiogenesis and inflammation



Sex differences in physiology / drug metabolism

Mechanism	Gender-specific Differences
General Differences <ul style="list-style-type: none">•Lean/fat mass ratio•Distribution volume•Drug binding	Lower lean/fat mass ratio in female Increased volume for lipophilic drugs in women Smaller and fluctuating distribution volume in females Increased volume for hydrophilic drugs in males Hormonal influences on drug binding
Gastrointestinal Differences	Longer gastric emptying time in women due to <ul style="list-style-type: none">•Slower motility•Higher pH
Metabolic differences (Phase I) <ul style="list-style-type: none">•CYP•P-glycoproteins	CYP1A2, CYP2E1, CYP2D6 all have higher activity in men CYP3A4 higher activity in females (maybe rate limiting step is P-glycoprotein)
Excretion Differences	Females generally have lower GFR, mostly due to body size Active secretion might be reduced in females
Hormonal Influences	Estrogens influence inflammation, vasodilation, apoptosis, contractility

Does body surface calculation allow for detection of sex differences in body composition ?

Both fat-free mass and fat mass are metabolically active, yet their activity differs

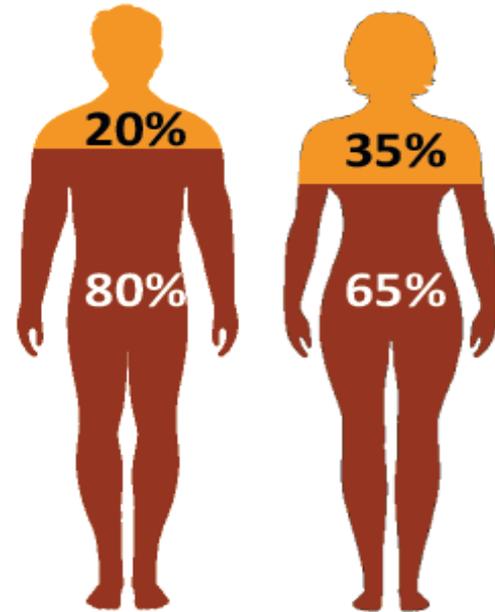
FFM – resting metabolic rate, free radical production

FM – aromatization of hormones

BWt 65 kg
Ht 1.70 m

BSA 1.75 m²
BMI 22.5 kg/m²

FFM_{male} 52 kg
FFM_{female} 42 kg



Potential consequences

Consequences of ignoring sex differences I:

Reduced reproducibility

“ We found that exposure of mice and rats to male but not female experimenters produces pain inhibition. Male-related stimuli induced a robust physiological stress response that results in stress-induced analgesia. This effect could be replicated with T-shirts worn by men, bedding material from gonadally intact and unfamiliar male mammals, and presentation of compounds secreted from the human axilla.

Experimenter sex can thus affect apparent baseline responses in behavioral testing. “

Consequences of ignoring sex differences II:

Delayed diagnosis

Diagnosis in women with bladder cancer and haematuria is more likely delayed because attributed to cystitis

Although women refer more symptoms of asthma, they are less likely diagnosed. In girls wheezing is less common than in boys

Men are diagnosed later with osteoporosis and autoimmune diseases, because these are perceived as „female“

If not diagnosed correctly, men with MS are more likely referred to an orthopedic surgeon, women to a psychiatrist.



Consequences of ignoring sex differences III:

Mortality due to increase of unexpected side effects

TABLE 1. PRESCRIPTION DRUGS WITHDRAWN FROM UNITED STATES MARKET, JANUARY 1, 1997–DECEMBER 31, 2000

<i>Drug</i>	<i>Type of drug</i>	<i>Date approved</i>	<i>Date withdrawn</i>	<i>Primary health risk</i>
Pondimin (fenfluramine hydrochloride)	Appetite suppressant	6/14/1973	9/15/1997	Valvular heart disease
Redux (dexfenfluramine hydrochloride)	Appetite suppressant	4/29/1996	9/15/1997	Valvular heart disease
Seldane (terfenadine)	Antihistamine	5/8/1985	2/27/1998	Torsades de pointes
Posicor (mibefradil dihydrochloride)	Cardiovascular	6/20/1997	6/8/1998	Bradycardia in elderly and adverse drug interaction
Hismanal (astemizole)	Antihistamine	12/19/1988	6/18/1999	Torsades de pointes
Rezulin (troglitazone)	Diabetic	1/29/1997	3/21/2000	Liver failure
Propulsid (cisapride monohydrate)	Gastrointestinal	7/29/1993	7/14/2000	Torsades de pointes
Lotronex (alosetron hydrochloride)	Gastrointestinal	2/9/2000	11/28/2000	Ischemic colitis
Raxar (grepafloxacin hydrochloride)	Antibiotic	11/6/1997	11/1/1999	Torsades de pointes
Durac (bromfenac sodium)	Analgesic and anesthetic	7/15/1997	6/22/1998	Liver failure

Sex-specific pharmacotherapy? 3 Options

1. Specific therapies for women

Alosetron (Lotronex) (Camilleri, Lancet, 2000)

only for women with diarrhea-dominant IBS

withdrawn from the market due to cardiovascular side effects

2. Different dosage for women and men

Zolpidem (Ambien) (Farkas, N Engl J Med, 2013)

50% dose reduction recommended for women in USA/Canada

currently debate about risks of undertreatment in women

Rituximab (Pfreundschuh, BJH, 2017)

experimental trial with default dosage increase in men (500 mg/m², women 375 mg/m²),

improved PFS, no increase in side effects

3. Potentially different therapy due to different mechanisms (Sorge, Nat Neurosci, 2015)

In animal experiments the development of a pain response was associated with the

involvement of different cells in m/f mice (glial cells vs T lymphocytes)

What does this mean for oncology ?

1. **Gender affects exposure to risk factors (e.g. melanoma, lung cancer)**
2. **Sex hormones might influence susceptibility (e.g. menopause)**
3. **Sex / gender might influence location of the tumor (e.g. colon, melanoma)**
4. **Gender roles / relationships might influence diagnostic timing**
5. **Gender might influence access to medication**
6. **Sex might influence response to therapy (e.g. rituximab)**
7. **Immunological differences might impact progression and survival**

Thank you for your attention!

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 Sabine Oertelt-Prigione