# Set of slides for the Factsheet Oncology

**The impact of gender in oncology**

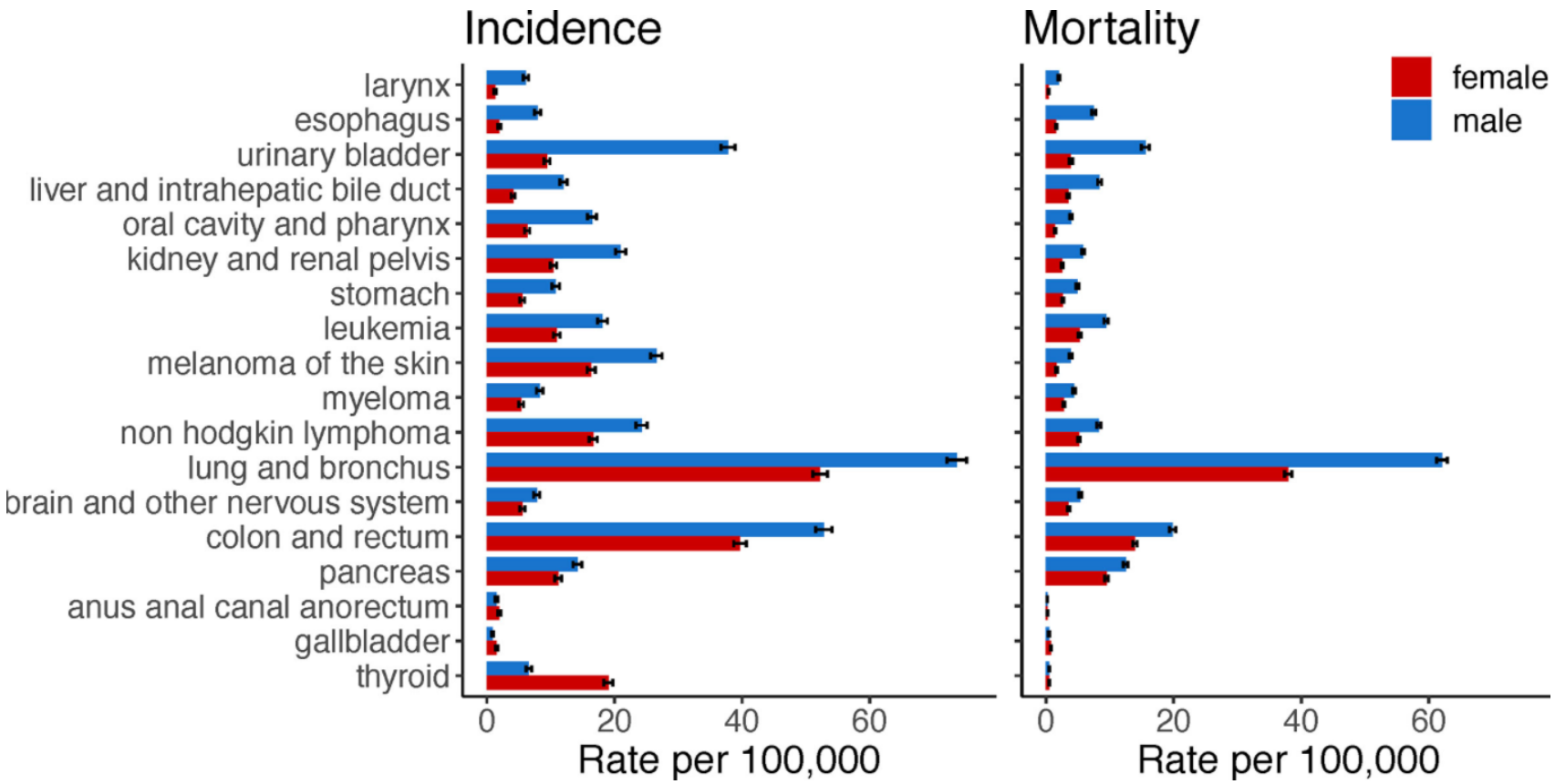
Author(s): PD Dr med Alessandra Curioni-Fontecedro

Department of Medical Oncology and Hematology

Comprehensive Cancer Center Zurich

University Hospital Zurich

# Cancer Incidence

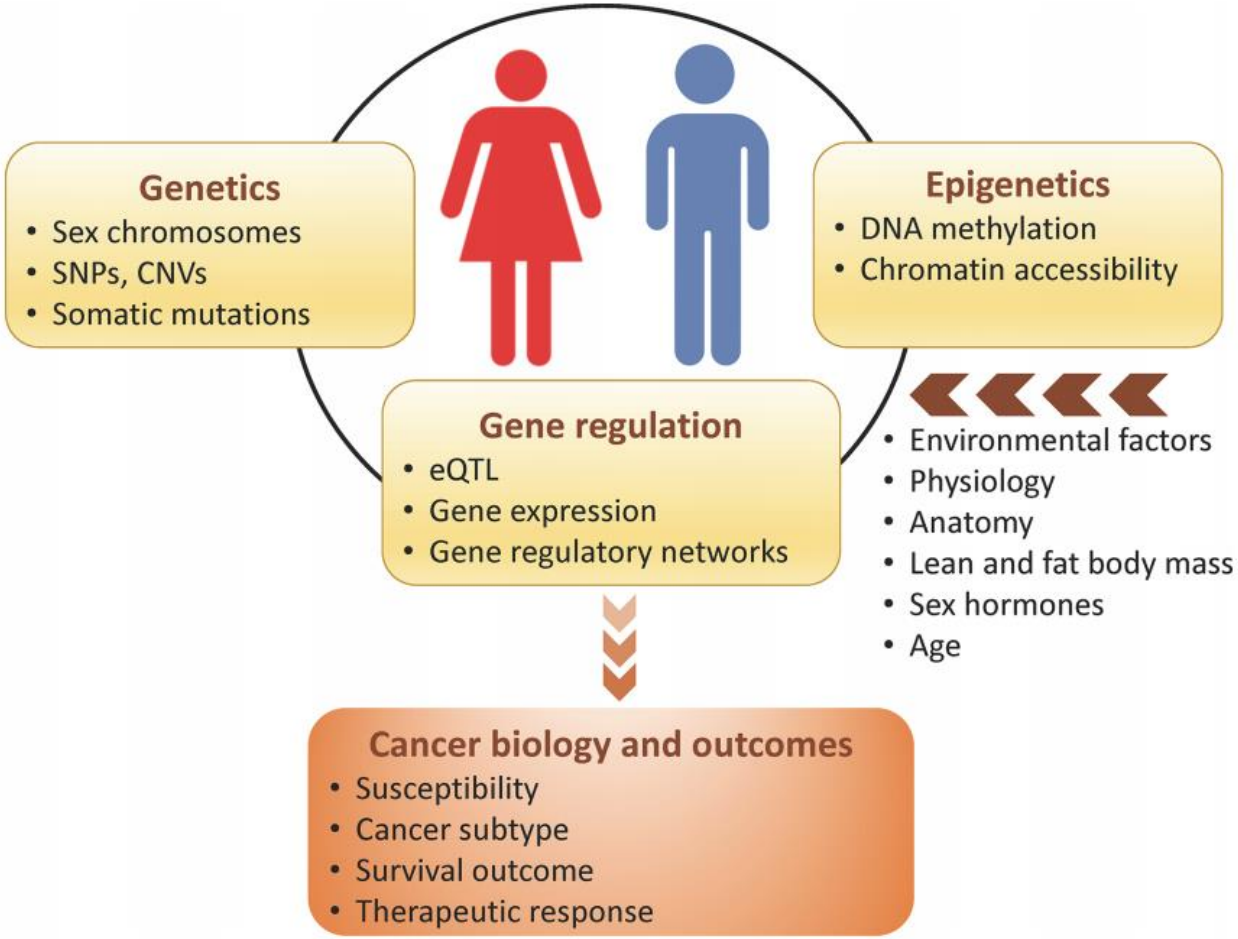



C. Lopes-Ramos, Front Oncology 2020

# Factors for disparities in incidence and mortality

- **X Chromosome (tumor suppressor genes)**
- **Metabolism**
- **Drug Metabolism**

# Factors for disparities in incidence and mortality

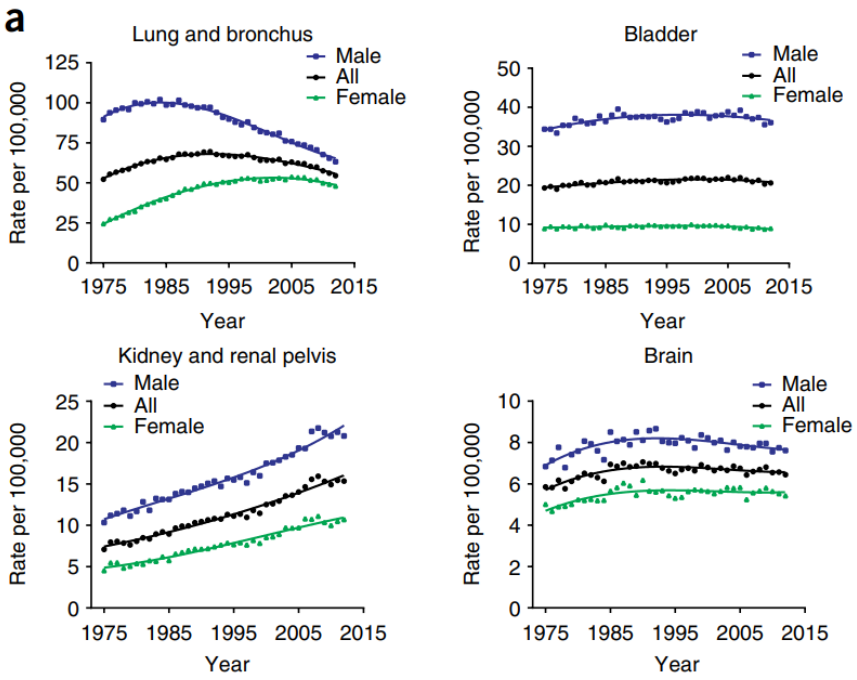



C. Lopes-Ramos, Fron Oncol 2020

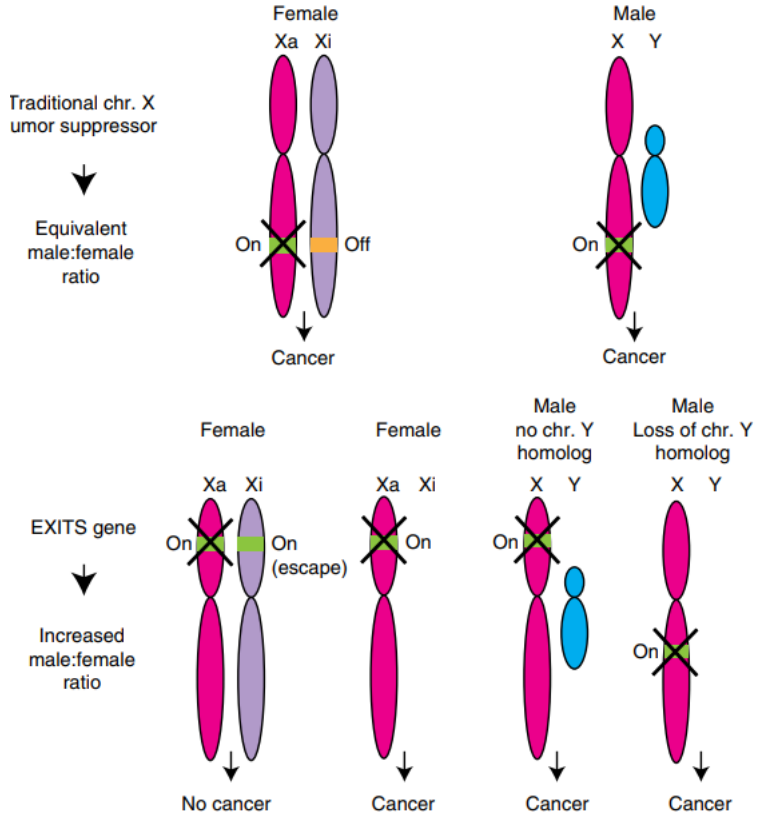
# Factors for disparities in incidence and mortality

– **X Chromosome (tumor suppressor genes)**

Escape from X-inactivation tumor-suppressor (EXITS) genes




A. Dunford Nat Genetics 2017

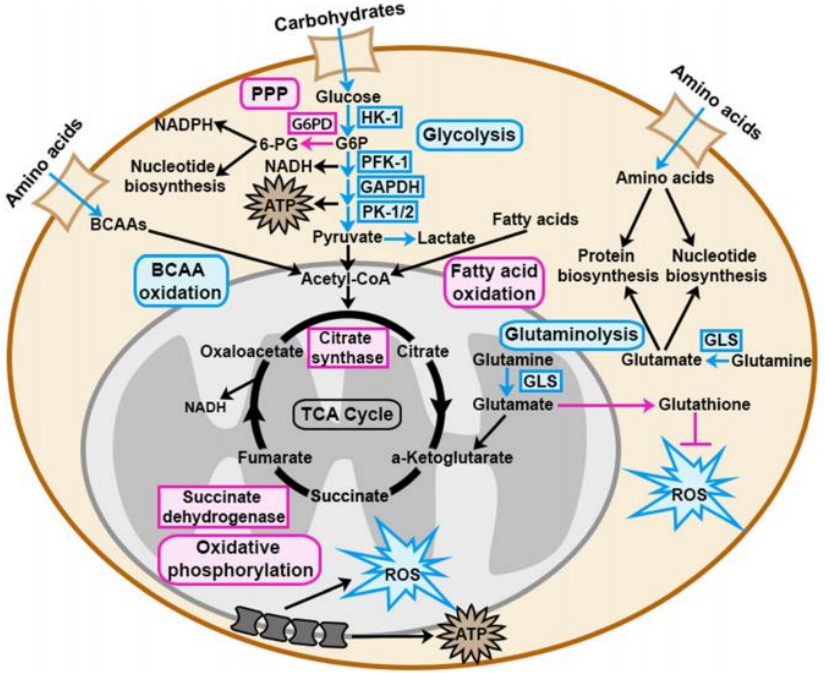


# Factors for disparities in incidence and mortality

- **X Chromosome (tumor suppressor genes)**

- **Metabolism**

JCI Insights J Ippolito 2017: In glioma → Sexual dimorphism in pyruvate metabolism.




Joshua B. Rubin Biology of Sex Differences (2020)

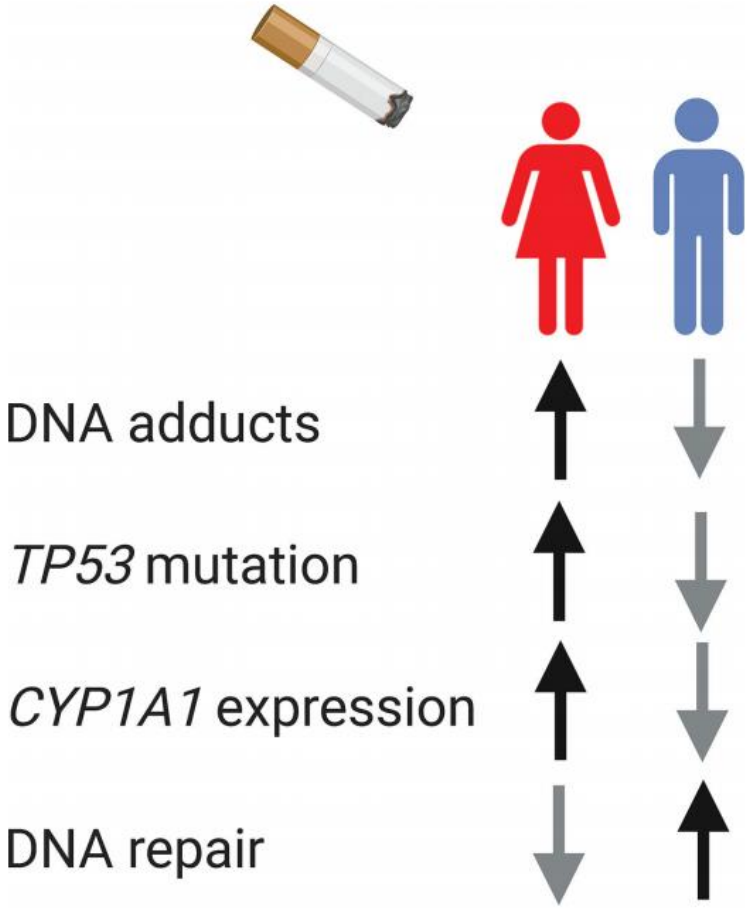
# Factors for disparities in incidence and mortality

- X Chromosome (tumor suppressor genes)
- Metabolism
- Drug Metabolism

| Enrichment in males | | | Enrichment in females | | |
|---|---|---|---|---|---|
| Pathway | NES | FDR | Pathway | NES | FDR |
| Acute myeloid leukemia | −2.207 | 0.000 | Oxidative phosphorylation | 2.637 | 0.000 |
| Endometrial cancer | −2.230 | 0.000 | Parkinson disease | 2.485 | 0.000 |
| Chronic myeloid leukemia | −2.157 | 0.001 | Ribosome | 2.287 | 0.000 |
| Notch signaling pathway | −2.114 | 0.002 | Alzheimer disease | 1.957 | 0.003 |
| Phosphatidylinositol signaling system | −2.062 | 0.002 | Proteasome | 1.968 | 0.004 |
| Erbb signaling pathway | −2.006 | 0.002 | Peroxisome | 1.914 | 0.006 |
| Pancreatic cancer | −2.012 | 0.003 | Huntington disease | 1.872 | 0.008 |
| Focal adhesion | −2.018 | 0.003 | Terpenoid backbone biosynthesis | 1.807 | 0.015 |
| Colorectal cancer | −2.026 | 0.003 | Metabolism of xenobiotics by cytochrome p450 | 1.791 | 0.015 |
| Prostate cancer | −1.962 | 0.003 | Steroid hormone biosynthesis | 1.761 | 0.018 |
| Jak stat signaling pathway | −1.923 | 0.004 | Protein export | 1.734 | 0.021 |
| Adherens junction | −1.914 | 0.004 | Histidine metabolism | 1.736 | 0.022 |
| Arrhythmogenic right ventricular cardiomyopathy arvc | −1.917 | 0.004 | Amyotrophic lateral sclerosis als | 1.677 | 0.034 |
| Fc gamma r mediated phagocytosis | −1.886 | 0.005 | Drug metabolism cytochrome p450 | 1.648 | 0.041 |
| Chemokine signaling pathway | −1.849 | 0.007 | Tyrosine metabolism | 1.590 | 0.064 |

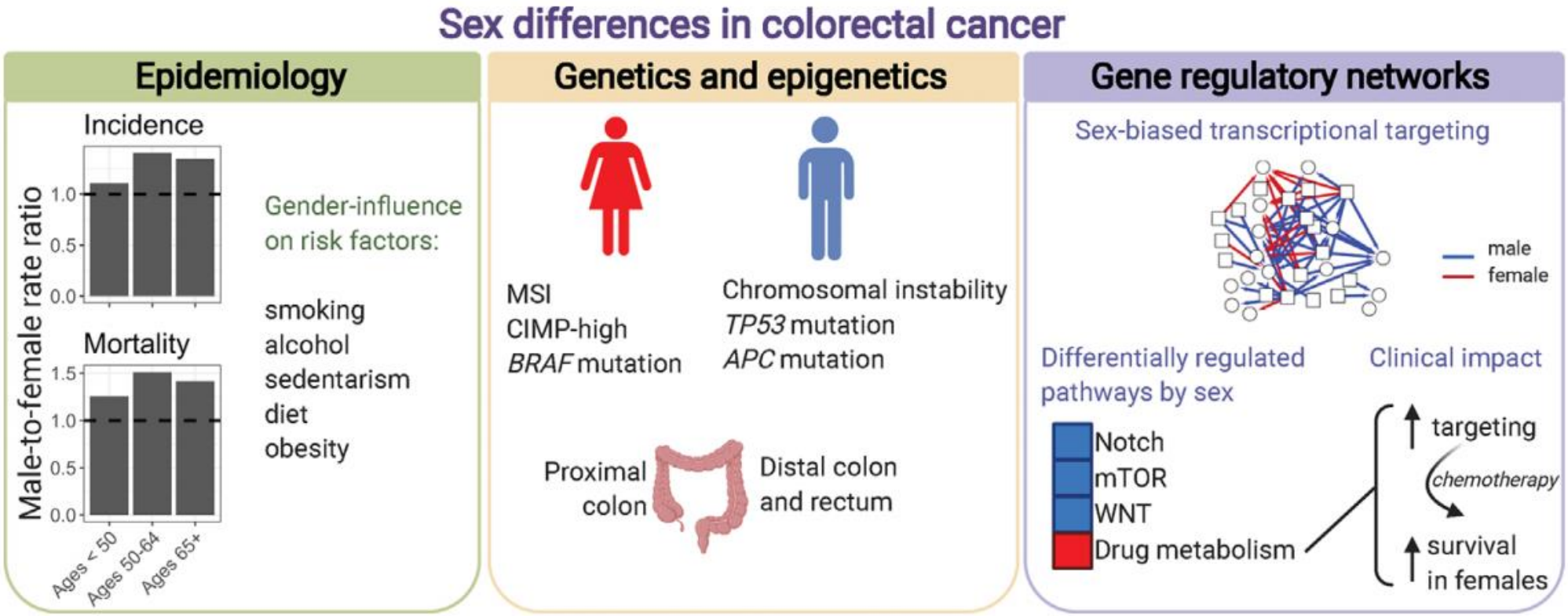
C Lopes-Campos Cancer Research 2018

# Factors for disparities in lung cancer




C. Lopes-Ramos, Fron Oncol 2020

# Factors for disparities in colon cancer




C. Lopes-Ramos, Fron Oncol 2020

# Cancer-related genes: differences

| Gene | Type of alteration | Prognostic value | Cancer |
|---|---|---|---|
| *RPL37A* | expression | only in females | colon |
| *SRGAP1* | expression | only in males | colon |
| *ACTL7B* | expression | both sexes, but in opposite directions | colon |
| *TRRAP* | expression | both sexes, but in opposite directions | colon |
| *LATS1* | CNA and expression | only in females | kidney clear cell |
| *UBAC1* | CNA and expression | only in females | kidney clear cell |
| *C16orf45* | CNA and expression | only in females | kidney papillary cell |
| *LCMT1* | CNA and expression | only in females | kidney papillary cell |
| *BRAF* | mutation | only in males | colorectal |
| *BAP1* | mutation | only in females | kidney clear cell |
| *TP53* | mutation | only in females | colon |
| *miR-192*, *miR-206*, *miR-194*, and *miR-219* | expression | only in females | colorectal |

C. Lopes-Ramos, Fron Oncol 2020

# Actionable genes in cancer: differences

| Gene | Molecular alteration | Sex bias | Cancer | Drug | Therapy type |
|---|---|---|---|---|---|
| *TOP2B* | methylation | female | BLCA | Valrubicin, Doxorubicin HCl liposome, Epirubicin | Chemotherapy (anthracyclines) |
| | mRNA | female | KIRP | | |
| *PDCD1* | methylation | female | BLCA | Pembrolizumab, Nivolumab | Immunotherapy |
| | CNA | male | KIRC | | |
| *AR* | protein | male | KIRC | Flutamide, Enzalutamide | Hormone therapy |
| *CTNNB1* | mutation | male | LIHC | Idelalisib | PI3K inhibitor |
| | | | | Erlotinib | EGFR inhibitor |
| *EGFR* | mRNA | female | LUAD | Cetuximab, Erlotinib, Gefitinib, and Lapatinib | EGFR inhibitor |
| | methylation | female | BLCA | | |
| *NF1* | mRNA | male | LUSC | Trametinib | MEK inhibitor |
| | mRNA | female | KIRP | Vemurafenib | RAF inhibitor |
| | | | | Idelalisib | PI3K inhibitor |
| *CDKN2A* | mRNA | male | HNSC | Palbociclib | CDK inhibitor |
| | CNA | male | KIRC | | |
| *TSC2* | methylation | female | KIRP | Everolimus, Temsirolimus | mTOR inhibitors |
| | methylation | female | KIRC | | |
| *BRCA1* | methylation | female | HNSC | Olaparib | PARP inhibitor |
| | mRNA | female | KIRP | | |

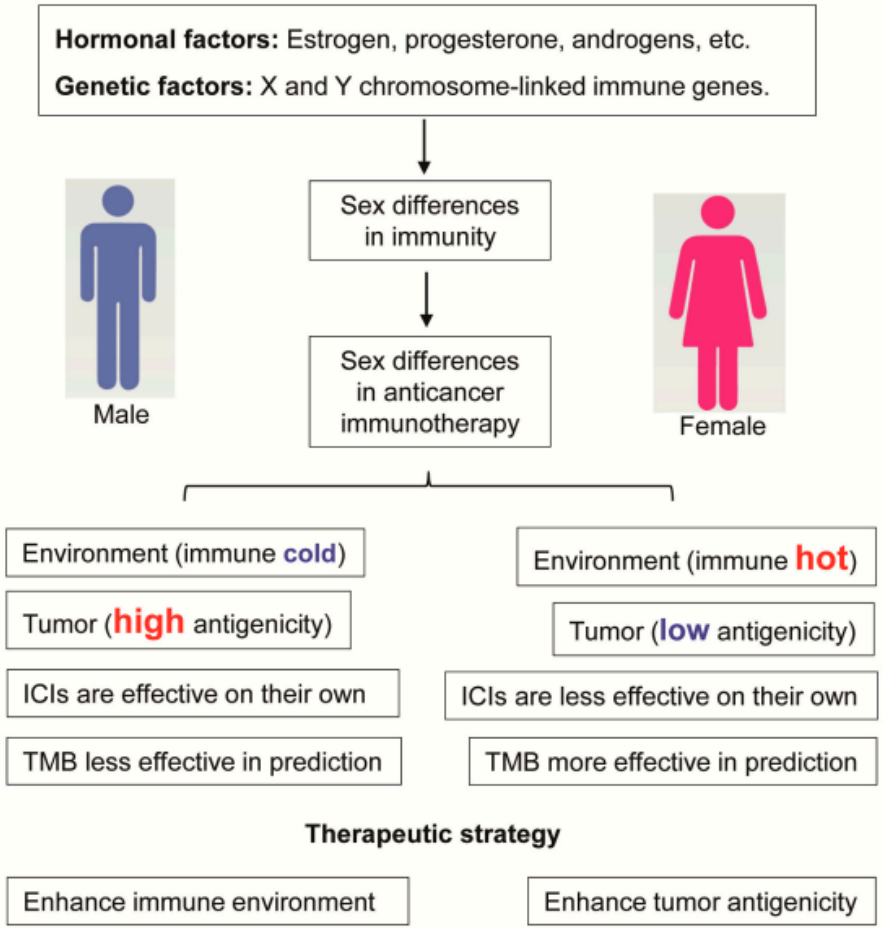
C. Lopes-Ramos, Fron Oncol 2020

# Anticancer agents: differences in clearance

| Class/drug, name | Indication | *n* (men)/ (women) | Variability on CL (CV%) | Relative change in women versus men | |
|---|---|---|---|---|---|
| **Angiogenesis inhibitors** | | | | | |
| Aflibercept [47] | Advanced solid tumours | 767/739 | 31% | Clfu Vfu | −16% −19% |
| Bevacizumab [48, 49] | Gastric cancer; solid tumours | 1101/949 | 26% | CL | −14% to −27% |
| **Antineoplastic agents: antimetabolites** | | | | | |
| 5-Fluorouracil [50, 51] and metabolite | GI malignancies; metastatic colo-rectal cancer | 74/42 | 22%–40% | CL CLmet | −14% to −27% −18% |
| **Myeloablative agents** | | | | | |
| Busulfan [52] | Marrow transplantation | 904/689 | 22% | V | +7% |
| **Antineoplastic agent: alkylating agents** | | | | | |
| Temozolomide [53, 54] | Glioma, glioblast-oma, melanoma | 303/177 | 5%–10% | CL | −19 to 27% |
| Mephalan [55] | Advanced malignancies | 22/42 | 45% | CL | −19% |
| Trabectedin [56] | PD study | 232/467 | 51% | V Keo | −17% +22% |
| **Antineoplastic agents: alkaloids** | | | | | |
| Paclitaxel [57, 58] | Solid tumours | 159/160 | | CL Vmax | −30% +14% |
| Irinotecan (SN38) [59–61] | Solid tumours, glioblastoma | 67/58 | 47% | CL | −30% to 38% |
| **Antineoplastic agent: antibodies** | | | | | |
| Rituximab [62] | Lymphoma | 16/13 | 19% | CL | −21% |

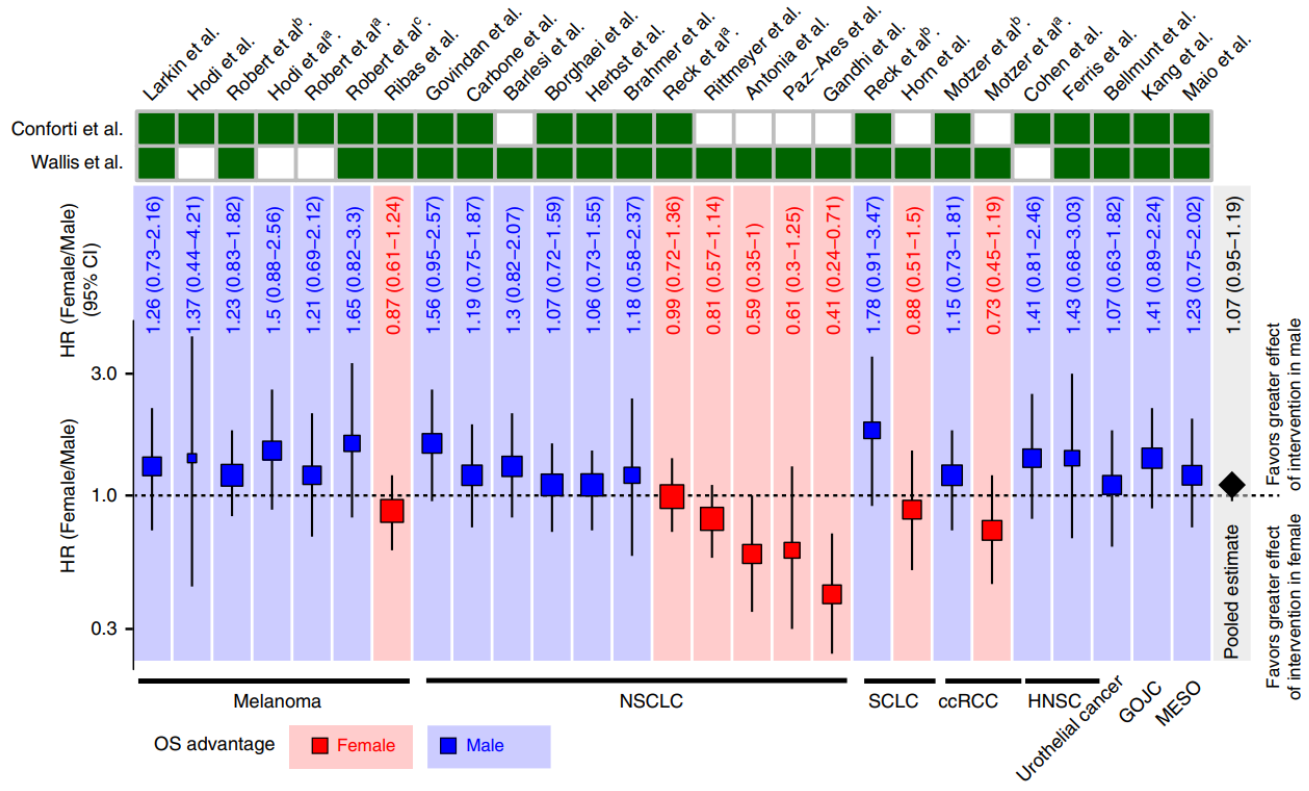
A D Wagner Annals of Oncology 2019

# Immune responses to cancer: disparities



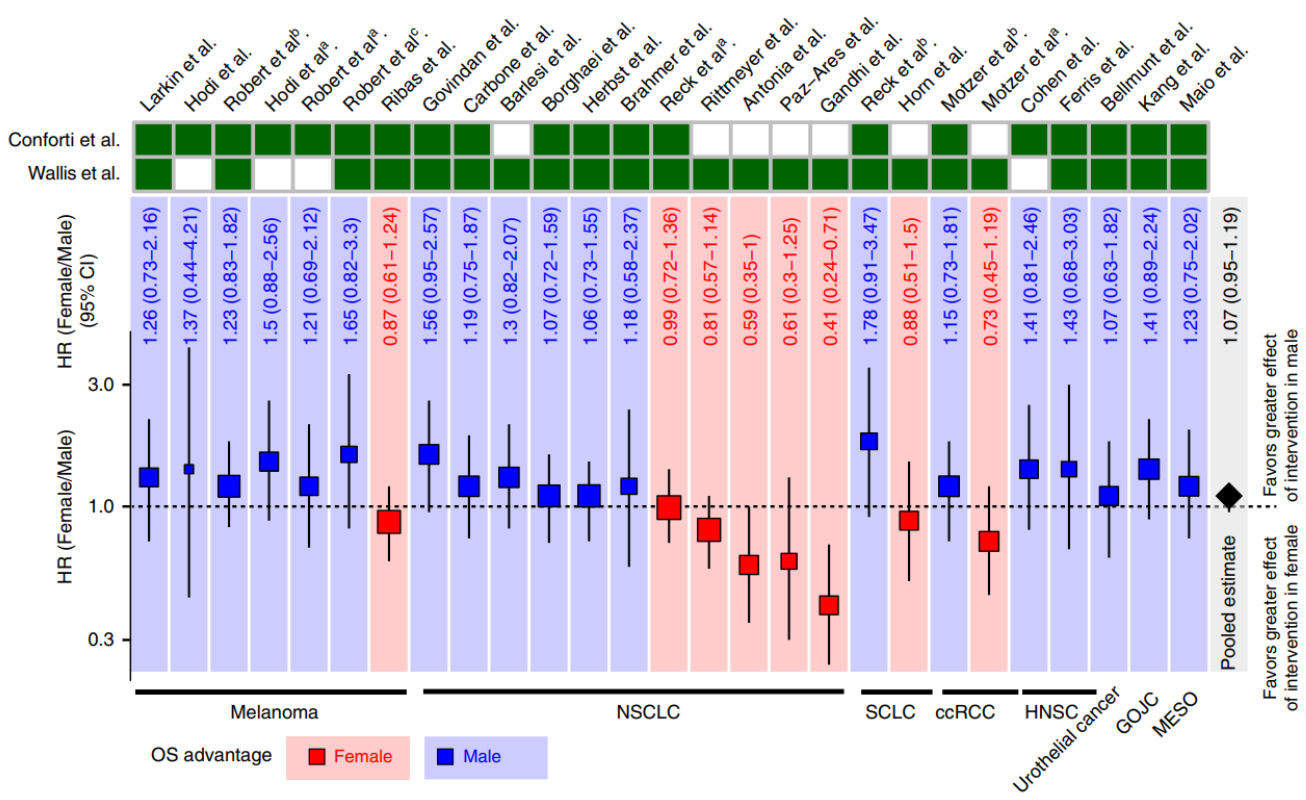

Botticelli A. Oncotarget 2017

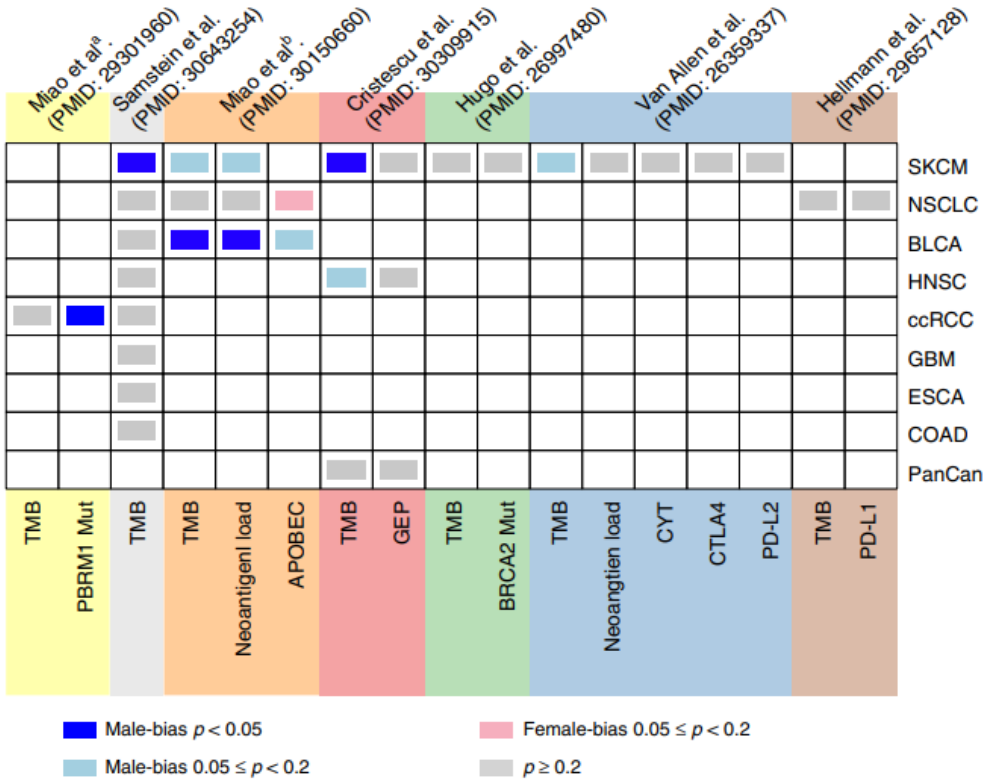
# Immune responses to cancer: disparities




Youqiong Ye, Nature Communications 2020

# Immune responses to cancer: disparities




Youqiong Ye, Nature Communications 2020

# Conclusions and outlook

- Clear disparities between female and male patients with cancer in incidence and outcome
- Prospective studies with stratification based on gender are warranted