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# OncoSexome: the landscape of sex-based differences in oncologic diseases

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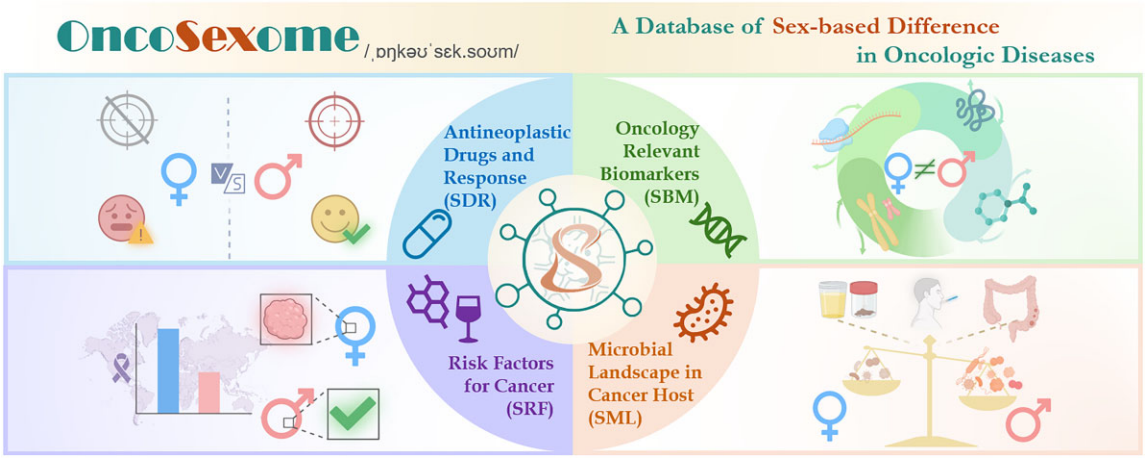
## Abstract

The NIH policy on sex as biological variable (SABV) emphasized the importance of sex-based differences in precision oncology. Over 50% of clinically actionable oncology genes are sex-biased, indicating differences in drug efficacy. Research has identified sex differences in non-reproductive cancers, highlighting the need for comprehensive sex-based cancer data. We therefore developed *OncoSexome*, a multidimensional knowledge base describing sex-based differences in cancer (https://idrblab.org/OncoSexome/) across four key topics: antineoplastic drugs and responses (SDR), oncology-related biomarkers (SBM), risk factors (SRF) and microbial landscape (SML). SDR covers sex-based differences in 2051 anticancer drugs; SBM describes 12 551 sex-differential biomarkers; SRF illustrates 350 sex-dependent risk factors; SML demonstrates 1386 microbes with sex-differential abundances associated with cancer development. *OncoSexome* is unique in illuminating multifaceted influences of biological sex on cancer, providing both external and endogenous contributors to cancer development and describing sex-based differences for the broadest oncological classes. Given the increasing global research interest in sex-based differences, *OncoSexome* is expected to impact future precision oncology practices significantly.

## Graphical abstract

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## Introduction

Cancers are the second leading cause of death; non-reproductive cancers exhibit remarkable sex differences, with a general global male predominance showing male-to-female incidence ratios of 2:1 overall and exceeding 4:1 in cancers such as esophagus and bladder, while thyroid cancer has higher incidences in females (1). In major cancer types, such as colorectal cancer (CRC), males had consistently higher mortality rates across different regions (2,3). As for prognosis, male sex was predictive of worse survival in lung cancer (4), hepatocellular carcinoma (5) and pancreatic cancer (6). Constructive efforts have been made to understand the mechanisms underlying such sex-differential landscape in cancer. The US National Institutes of Health launched a policy on sex as biological variable (SABV) in 2016, which highlighted the importance of sex-based differences in precision oncology (7) and asked for adequate consideration of the influences of sex in cancer trials (8,9). It was reported that >50% of clinically actionable oncology genes were found to be sex biased (10). For example, PD-1 and CTLA-4 are key immune checkpoint proteins, the inhibition of which showed significant sex-based differences in drug efficacy (11). Studying SABV in cancer treatment is intended to understand the mechanisms by which biological sex influences treatment benefits or toxicity and to summarize sex-divergent drug response patterns, thereby improving outcome prediction in clinical practice (12,13). This is crucial for moving away from one-size-fits-all treatment approaches and toward more individualized, sex-based dosing optimization (14,15), which will ameliorate therapeutic outcomes for each patient.

In addition to research on antineoplastic drug response (16,17), many studies have also explored the multifaceted sex-based differences in oncological molecular features (18,19), environmental risk factors for cancer (20,21) and microbial landscape in the cancer host (22,23). Such studies have been widely used to promote the discovery of sex-biased anticancer drug prescription (24), prediction of sex-specific carcinoma prognosis (25), identification of sex-specific risk factors for cancer diagnosis (26) and sex-dependent regulation of the microbiome for enhancing drug efficacy (27). These studies have highlighted the demand for a database that has accumulated sex-based difference data. Moreover, with the booming application of AI (28–33) and OMIC technologies (34–41) in basic biomedical research (42,43) and drug discovery (44–46), it was imperative to construct a molecular biology database that was designed to enhance the understanding of sex-specific molecular and pharmacological patterns (47–50), thereby advancing precision medicine in oncology (51).

So far, a number of knowledge bases have been constructed to offer information related to sex differences (52–54). Some described sex-biased features (sex-differentially expressed genes) based on transcriptomic analysis and literature reviews, such as *SAGD* (52), *HMDD* (53), FlyAtlas (55) and *SDC* (54); some carefully provided the sex-dimorphic drug response/adverse drug reactions, such as *DrugCentral* (56) and *GenderMedDB* (57); the remaining added the metadata of sexes into their ontological/metagenomic/phenotypical data to facilitate possible future analysis of sex differences, such as *HPO* (58), *GMrepo* (59), *GRAND* (60) and *MPD* (61). These available databases explicitly describe sex-based differences in antineoplastic drug responses or oncological molecular signatures, attracting great interest and scientific discussion and inspiring sex-aware AI modeling for precision oncology (62,63). However, data on environmental risk factors and microbial landscapes for cancers is largely missing from these existing databases, and therefore, these databases do not reflect the multifaceted characteristics of sex-based differences in cancers. Moreover, both the environmental risk factors and microbial landscape are known to be indispensable external contributors to cancer and complement endogenous factors via gene-environmental interaction (64). Recognizing, identifying and appropriately managing sex-specific risk factors for cancers are critical steps for advancing cancer care for men and women who are at higher risks (65). Therefore, a comprehensive database capturing the multifaceted aspects of the sex-based differences in cancer, including both external and endogenous factors, is essential, yet up to this point remains to be developed.

In this study, a multifaceted knowledge base, entitled *OncoSexome*, was constructed to describe sex-based differences in oncological drug responses, molecular biomarkers, risk factors and host microbiome. Particularly, *OncoSexome* covers **four** key topics of sex-based differences in a pan-cancer manner, which include sex-based differences in (**a**) antineoplastic drugs and responses (**SDR**), (**b**) oncology-related biomarkers (**SBM**), (**c**) risk factors for cancer (**SRF**) and (**d**) microbial landscape in cancer host (**SML**). These four topics are also defined in Figure 1. **SDR** provides the sex-based differences in drug efficacy, adverse reactions, pharmacokinetics (PK), hormonal interactions (HI) and target variations (TVs) for 2051 anticancer drugs, highlighting how biological sex influences pharmacology and treatment outcomes. **SBM** describes 12 551 sex-influenced molecular biomarkers regarding immune responses (IR), omics variation (OV), endocrine regulation (ER), clinical relevance (CR), *etc*. **SRF** illustrates 350 sex-dependent risk factors (i.e. environmental carcinogens, cancer-causing viruses, lifestyle risk factors, etc.) that might increase the chances of developing cancer. **SML** demonstrates 1386 microbial organisms with sex-specific abundances or have sex-differential correlations to the risk of cancer development. Based on our collected data, a total of 71 oncological classes (defined by the WHO *International Classification of Diseases*) were covered with their sex-specific prevalence provided, including lung cancer, colon cancer, etc.

All in all, with such a substantial volume of structured data from various aspects, *OncoSexome* is unique in (**a**) illuminating the multifaceted influence of biological sex on cancer, (**b**) collectively providing both the external and endogenous contributors that promote cancer development and (**c**) describing the sex-based difference data for the broadest oncologic classes and thus outperforming existing databases. Due to the increasing research interest in sex-based differences, *OncoSexome* is expected to have significant implications for the future practice of sex-aware precision oncology.

## Factual content and data retrieval

Along with the growing body of evidence that supports the need for more sex-based biomedical research, scientists in this community have constantly improved guidelines on studying and reporting sex differences to promote rigor and precision (66,67). Therefore, we implement these recommendations to build the fundamentals of *OncoSexome* by defining, identifying, collecting and describing sex-based differences for the

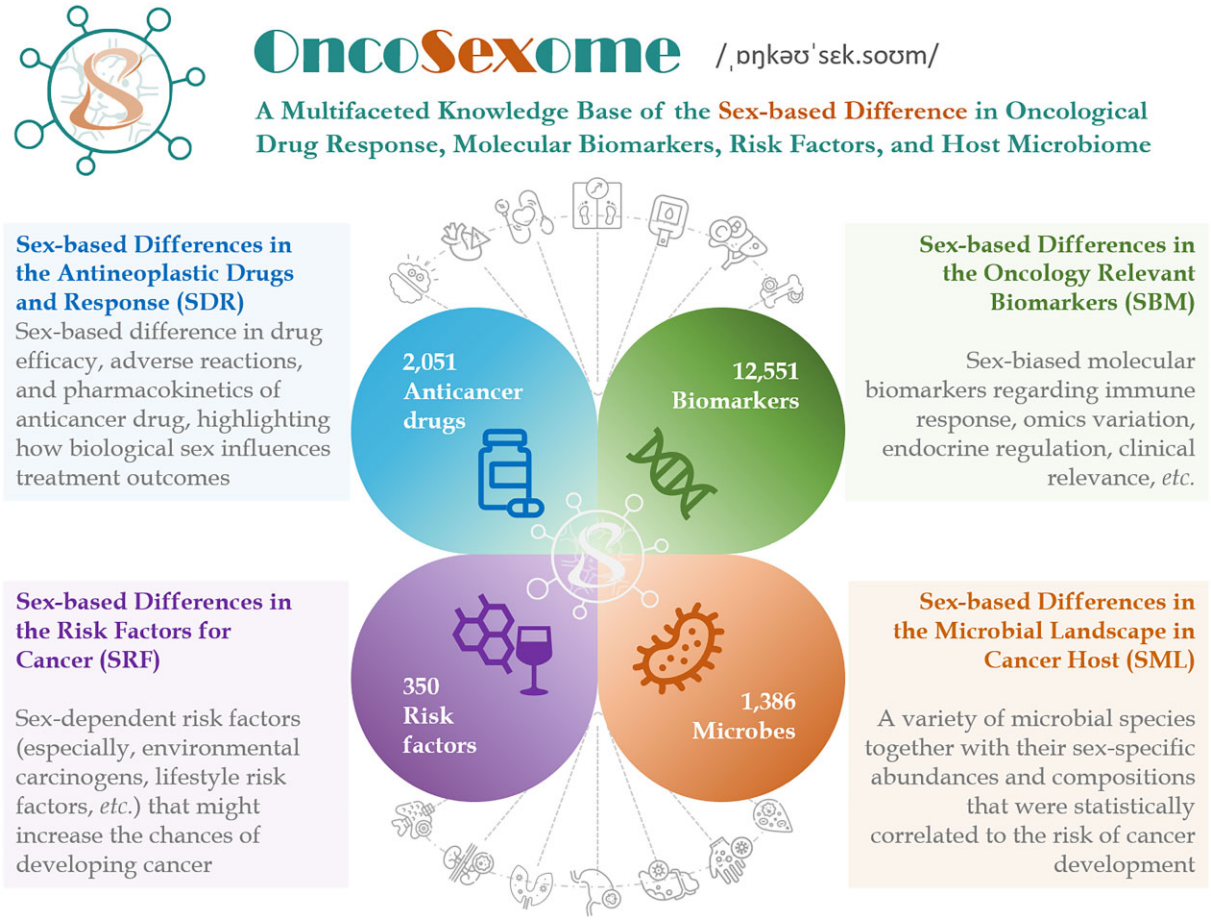


**Figure 1.** The four types of sex-based differences in cancer regarding antineoplastic drugs and response (**SDR**), oncology-related biomarkers (**SBM**), risk factors for cancer (**SRF**) and microbial landscape in cancer host (**SML**). A comprehensive understanding of the multifaceted characteristics of sex influences on cancers is essential for improving care for cancer patients, assigning more targeted therapy and having more accurate cancer prevention and screening programs.

abovementioned four topics (**SDR**, **SBM**, **SRF** and **SML**) using the following procedures. Definitions of sex differences mainly include two types of phenomena: (1) sex-biased effects, wherein effects are observed in both sexes yet with different magnitudes and (2) sex-specific effects, wherein effects are observed in one sex but not in the other (67). In terms of identification, these phenomena are always identified by the statistically significant testing result that directly compares males to females or by the interaction test of sex as an effect modifier following sex-stratified analysis. It is important to acknowledge that a minor subset of three-variable studies (i.e. examining sex, treatment and outcome) may be susceptible to a statistical error known as the 'Difference in Sex-Specific Significance' (DISS) (68). To recognize and address the DISS issue while keeping these potentially valuable data points, we annotate a 'Sex-based Results Quality Evaluation (SR-QE)' function to these data in *OncoSexome* so that users can interpret the data more precisely.

Building upon the well-established PubMed searching strategy for identifying sex-specific literature (69), we used search terms listed in Supplementary Table S1 for the systematic data collection of literature-reported findings. The filtered information was categorized into four topics. A brief introduction with examples is provided for each domain/topic in Table 1. For data extracted from older studies where the terms 'sex' and 'gender' were often used interchangeably and without clear distinction (67), we have added a '*Sex terminology*' annotation in our database. This annotation alerts users to instances where the original study may not have differentiated sex and gender identity, or where the terminology was not specified to allow users to interpret the data with appropriate context regarding the evolving understanding of sex and gender concepts in scientific literature. Based on these data preparations, the following sections describe the four types of sex-based differences in cancer.

## Sex-based differences in antineoplastic drugs and response (SDR) across clinical trials, *In Vivo*, *In Vitro* and observational studies

Among 288 cancer trials that reported outcomes with sex comparisons, 16% had favorable outcomes in males, while 42% of results had better outcomes in females, and 15% of trials reported sex-biased side effects in which females had higher rates of adverse responses (ARs) (70). Chemotherapy-treated adult male acute myeloid leukemia (AML) patients had significantly worse survival compared to females (71). In Phase III randomized trials on CRC, female sex was a predictor of higher rates of chemotherapy-induced ARs (72). Mechanistically, these **SDR** data could be due to genetic factors and

**Table 1.** Four topics covered by *OncoSexome* highlighted the multifactorial characteristics of influences of sex on cancer onset, progression, treatment and prognosis

| Topics of OncoSexome | Definitions of the topic and affiliated data types | Typical examples of data types within the four topics |
|---|---|---|
| Antineoplastic drugs and therapeutic response (SDR) | Sex-based differences in drug *efficacy or effectiveness* (*EF*), *adverse reactions* (*AR*), *pharmacokinetics* (*PK*), *hormonal interaction* (*HI*) and *target variation* (*TV*) of anticancer drugs highlight how biological sex influences treatment outcomes. | *EF* : Males had worse post-treatment survival than females in a phase III trial studying CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) therapy (166). *AR* : A study based on 27 randomized trials suggested that female patients with colon cancer had higher risks of toxicity after receiving fluoropyrimidine- (5FU or capecitabine) based adjuvant chemotherapy (167). *PK* : Females with gastrointestinal malignancies had a higher area-under-the-concentration-time curve (AUC) of 5FU and lower elimination than males (168). *HI* : The activity of cisplatin and bevacizumab can be influenced by estrogen (169). *TV* : Erlotinib, gefitinib, and panitumumab target the epidermal growth factor receptor (EGFR), which exhibits female-biased mRNA expression in lung adenocarcinoma (10). |
| Oncology-related biomarker (SBM) | Sex-biased molecular biomarkers regarding *omics variation* (*OV*), *immune response* (*IR*), *endocrine regulation* (*ER*), and *clinical relevance* (*CR*). | *OV* : mRNA expression of CD274 (the gene encodes programmed death-ligand 1 (PD-L1)) was higher in tumors of females than in males in various cancers including esophageal carcinoma, thymoma, kidney renal clear cell carcinoma and thyroid carcinoma (17). *IR* : Serum PD-L1 levels were linked to worse disease progression only in females but not in males among patients with advanced malignant melanoma (MM) and NSCLC treated with Immune Checkpoint Inhibitors (ICIs) (170). *ER* : Androgens and AR signaling increase greater hepatic metastases tumor cell growth in males than in females (171). *CR* : Abundance of asparagine in colon tumor tissues was linked to worse prognosis in females but not in males (172). |
| Risk factor for cancer (SRF) | Sex-dependent risk factors that might increase the chances of developing cancer. | The sum of hydroxy polycyclic aromatic hydrocarbons (PAHs) in urine was correlated to higher lung cancer risks in females than in males (173). |
| Microbial landscape in cancer host (SML) | Microbial organisms with sex-biased abundance in cancer hosts or microbes linked to sex-differential cancer risks. | *Lactobacillusjohnsonii*, a probiotic enhancing immunotherapy efficacy (174), was more abundant in the feces of males with CRC than in females (23). |

hormone influences that resulted in sex differences in PK and pharmacodynamics (PD) between males and females (73,74). For instance, females had slower clearance of 5-fluorouracil (5-FU), which could predict their higher rates of 5-FU-induced toxicity (73,74). **SDR** is not limited to conventional anticancer therapy but is also substantial and prevails in targeted therapy, small molecules and currently investigational drugs (Supplementary Table S2). Therefore, we designed *OncoSexome* to collect **SDR** regarding *efficacy/effectiveness (EF)*, *AR*, *PK*, *HI*, and *TV* (Figure 2). In *OncoSexome*, we initiated data collection by defining antineoplastic agents recorded in the NCI Thesaurus (NCIt) (https://ncithesaurus.nci.nih.gov/ncitbrowser/), containing both conventional anticancer drugs and agents with other primary indications that have demonstrated anticancer activities.

The data type *AR* described how males and females differentially suffered from therapy-induced side effects and toxicity, mainly measured as AR rates by odds ratios (ORs) comparing sex (Figure 2B). DrugCentral (starting from version 2021) proposed a Log likelihood ratio (LLR) for each AR*drug combination for males and females separately (56). A higher LLR value indicates a greater likelihood that an *AR* occurred due to a specific drug. Statistically significant signals are considered for *ARs* with LLRs larger than the calculated drug-specific threshold values. In *OncoSexome*, we conducted and included the results of secondary analysis on the sex-specific *AR* data from the DrugCentral database following two steps: (1) LLRs of any AR*drug pairs that exceeded the LLR threshold and were unique to only males or females were considered *sex-specific*. (2) For the shared AR*drug pairs of both sexes, we performed Fisher's exact test for pairs satisfying the criteria adopted by Fisher *et al.* (75) to identify *sex-biased* ARs. Data processing R codes are available at: https://github.com/xs264/OncoSexome. We then identified 24 852 *sex-specific* AR*drug pairs for 5670 ARs and 207 anti-cancer drugs, including 8873 pairs that were unique to males plus 15 979 pairs unique to females. As for *sex-biased* ARs, there were 3255 *male-biased* AR*drug pairs (i.e. more frequently in males) for 123 drugs and 1109 ARs, and 1786 *female-biased* AR*drug pairs for 116 drugs and 641 ARs.

Another major part of **SDR** data was collected by a systematic literature review mainly based on the literature on clinical trials, *in vivo* experiments, *in vitro* studies and population-based studies to determine **SDR** with *PK*, *AR*, *EF* and *HI* data (Figure 2C). Supplementary Table S1 provided the search terms used for data collection. Similar to *AR*, *EF* information is usually reflected by statistically sex-differential post-treatment prognosis indicators (e.g. overall survival, disease-free survival, and recurrence-free survival) or drug response rates (Figure 2C). *PK* data contains sex differences in the absorption, distribution, metabolism and elimination based on experimental results from *in vivo* and population PK models (PopPK). We provide sufficient details of study sample characteristics (e.g. sample size, clinical stage, age) and therapy administrations (e.g. monotherapy, combination therapy, dosages, etc.) (Figure 2C).

Sex hormones and their downstream physiologic differences are indispensable for explaining sex differences in pharmacology (76) and drug response (27). In addition to the critical roles in reproductive cancers (77), targeting sex hormone

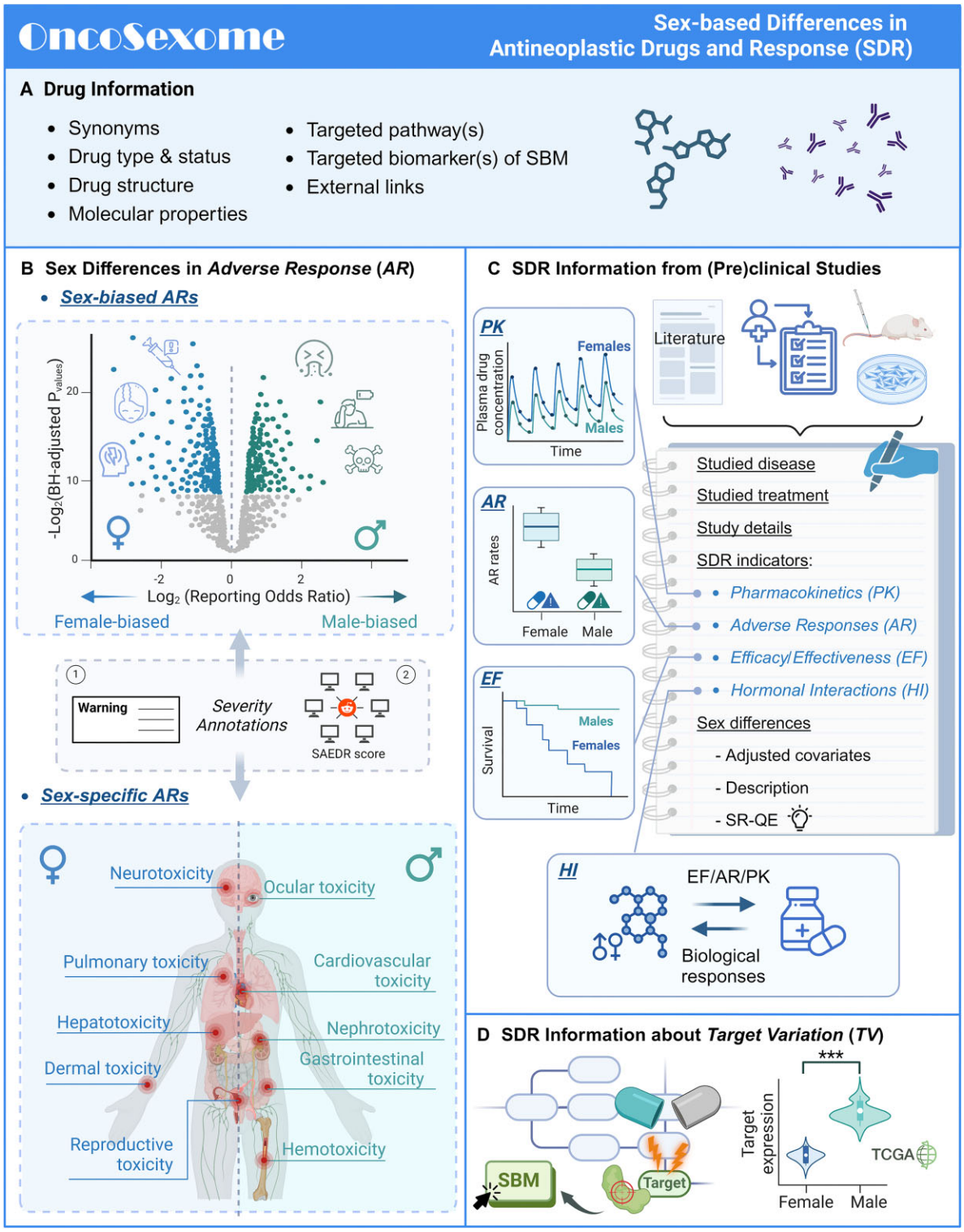


**Figure 2.** Contents of a typical page of sex-based differences in antineoplastic drugs and response (SDR). **(A)** General information on the drug with **SDR** data. This section provides comprehensive drug information, encompassing synonyms, classification, molecular structure and associated biological pathways. **(B)** Sex differences in ARs include both sex-biased ARs and sex-specific ARs. A volcano plot visually delineates sex-biased ARs linked to the selected medication into either female-biased or male-biased determined based on $Log_2$ (reporting ORs) and $-Log_2$(BH-adjusted *p* values). Sex-biased ARs were statistically linked to this drug only for males or females. Additionally, we annotate AR information with severity by both qualitative (FDA Boxed Warning (164)) and quantitative (Severity of Adverse Events Derived from Reddit scores (165)) measurements. Furthermore, section **(C)** of 'SDR Information from (Pre)clinical Studies' furnishes study details from literature, clinical trials and *in vivo* experiments, including the studied diseases, treatments investigated and **SDR** indicators for four data types. Sex-dependent PK parameters, such as the plasma concentration of the drug, describe *PK*. Sex-dependent AR rates typically illustrate AR data. EF data display sex comparisons on outcome/measurement reflecting sex-differential post-treatment survival. *HI* describes the influences of hormonal molecules on *EF*/*AR*/*PK* of drugs and how drugs induce biological and molecular responses to the endocrine system. *SR-QE* annotation evaluates the statistical rigor of sex comparisons. **(D)** The *TV* section visualizes sex-biased expression profiles of targets of certain antineoplastic drugs using RNA-seq data from TCGA database.

signaling via regulating hormone receptors, such as G protein-coupled estrogen receptor (78–80) and androgen receptor (AR) (81,82), may give insights into new therapeutic opportunities for non-reproductive cancers as well (83–86). One of the novelties of *OncoSexome* is the consideration of *HI*. Here, we categorize *HI* data into bi-directional forms (Figure 2C). The first is hormone-to-drug, which illustrates the influences of hormonal regulation on drug responses as reflected by *EF*, *AR* and *PK* alterations. The latter type is drug to hormone, which shows the drug-induced biological and molecular changes to the endocrine system. For both types, we extracted drug–drug interactions from DrugBank (87) that recorded data on interactions between drugs and hormones that are considered therapeutic agents. In addition to sex hormones, we collected interactions between antineoplastic agents and hormone-related molecules, such as gene encoding hormone receptors and enzymes for hormone synthesis (88). All in all, we collected 1 703 entries of *HI* data for 353 anti-cancer drugs and 25 sex hormone-related molecules (9 sex hormones and 16 hormonal genes).

The *TV* section displays how anticancer drug target expression levels vary by sex (Figure 2D). We first conducted differential gene expression (DGE) analysis to identify the differential expression of genes between females and males based on RNA-seq expression data from The Cancer Genome Atlas Program (TCGA) for 27 cancer types (Supplementary Table S3). We downloaded RNA-seq data of TCGA from the UCSC Xena as transcript per million format and applied the R package DESeq2 (89) adjusted for essential covariates such as tumor purity, diagnosis age and clinical stage to discover sex-differentially expressed genes. Genes with absolute $Log_2$ Fold-change (FC) values of females versus males over 1 and false discovery rate-adjusted *P* values below 0.05 are considered significantly sex-biased. These bioinformatics analyses resulted in the discovery of 4660 mRNAs and 63 miRNAs that were sex-differentially expressed in cancer samples from TCGA cohorts. Then, we downloaded targets of anticancer drugs from the Therapeutic Target Database (90) and DrugMAP (91). Eventually, we identified 1797 antineoplastic agents, which act on a total of 372 targets with sex-biased expression profiles demonstrated by RNA-seq analysis or other types of *TV* data, such as targets with sex-biased copy number alteration and single nucleotide variation (more details are described in the next section about **SBM**). This type of data offers valuable information on sex-specific considerations in drug development and clinical trial design for investigational targeted drugs when sex-based data are not yet available or thoroughly evaluated in preclinical phases.

Previously, sex differences in anti-cancer therapy have been characterized in databases such as the knowledge database Janusmed Sex and Gender (92), GenderMedDB (57) and DrugCentral (56), which described differences in treatment outcomes and PKs. However, since the last collection dates, ongoing efforts to study **SDR** have continually provided additional data that has not been adequately and timely recorded. More importantly, these databases overlooked the interactions between hormonal regulation with drugs (*HI*), and drugs with sex-biased target expression (*TV*). In contrast to these existing resources, *OncoSexome* includes 2051 antineoplastic agents, expanding the coverage of antineoplastic agents with **SDR** information by more than 7 fold. Furthermore, it includes information on 1209 clinical trial drugs and 181 investigative agents that have never been considered elsewhere (Supplementary Table S4).

## Sex-based differences in oncology relevant biomarkers (SBM)

Studying SABV is required for precision medicine (8). Sex-based differences in cancer biology have been ubiquitously revealed in gene expression and mutational profiles (93,94), epigenetics (95), IRs (96), tumor microenvironment (97), and in ER by sex hormones (98,99), some have significant impacts on cancer onset (19,100), progression (101–103), prognosis (104), and anti-cancer treatment response (7,105). Hence, in *OncoSexome*, oncological biomarkers with sex differences were categorized into OV, IR, ER, and CR (Figure 3, Table 1).

Within the umbrella of **SBM**, *OV* data mainly consists of sex-differentially distributed genetic mutations, gene expressions, proteins, and abundances of metabolites collected from literature and computational calculations (Figure 3B, **part 1**). *IR* data is defined as sex-differential IRs in cancer development as reflected by sex-biased cellular and molecular changes (Figure 3B, **part 2**). For instance, females with non-small cell lung cancer (NSCLC) tended to have greater T-cell dysfunction status (12). *ER* data present how endocrine system differences between sexes affect cancer onset and progression (Figure 3B, **part 3**). The most prominent example is the potential protective role of estrogen in CRC (106,107) and melanoma (108). For *CR* data, *OncoSexome* considers molecules correlated to cancer onset or progression in a sex-dependent way, novelly providing crosslinks between **SBM** and **SDR** (Figure 3B, **part 4**). For example, acylcarnitines are metabolites that are linked to sex differences in neoadjuvant chemoradiotherapy-induced toxicity (109). For *OV*, *IR*, *ER* and *CR data types*, we systematically reviewed literature based on *in vivo*, *in vitro*, patient cohorts and biospecimens (Supplementary Table S1). A pioneering aspect of *OncoSexome* is that we do not limit our data to individual molecules but record and annotate critical sex-differential metabolic pathways (110,111), such as male-enriched glutamine metabolism that could explain sex differences in the treatment of glioma (112). Moreover, as sex-dependent mechanisms manifest and evolve across the lifespan (113), our database meticulously records sample characteristics for most studies, especially age and menopausal status, to capture the dynamic nature of sex-specific cancer trends over time and throughout development. Therefore, similar to **SDR**, these data from pre(clinical) studies are annotated with study details, sex-related findings and pathways involved in the biological mechanisms of sex differences (Figure 3B). For the *OV* data computed by RNA-seq data, we conducted DGE analysis, as mentioned in the **SDR** section, to identify the differential expression of genes between females and males based on mRNA and miRNA expression data from TCGA databases. $Log_2$ FC $< -1$ indicates that the expression of a gene is male-biased; $Log_2$ FC $> 1$ indicates that the expression of a gene is female-biased. The DGE analysis is visualized in the 'SBM information of OV from Transcriptomics data' section (Figure 3C). Finally, *OncoSexome* reported 12 551 biomarkers with **SBM** data, including 10 444 genes (with associated mRNA expression data integrated into respective gene pages for terminology consistency and enhanced user experience), 447 proteins and 161 metabolites or compounds.

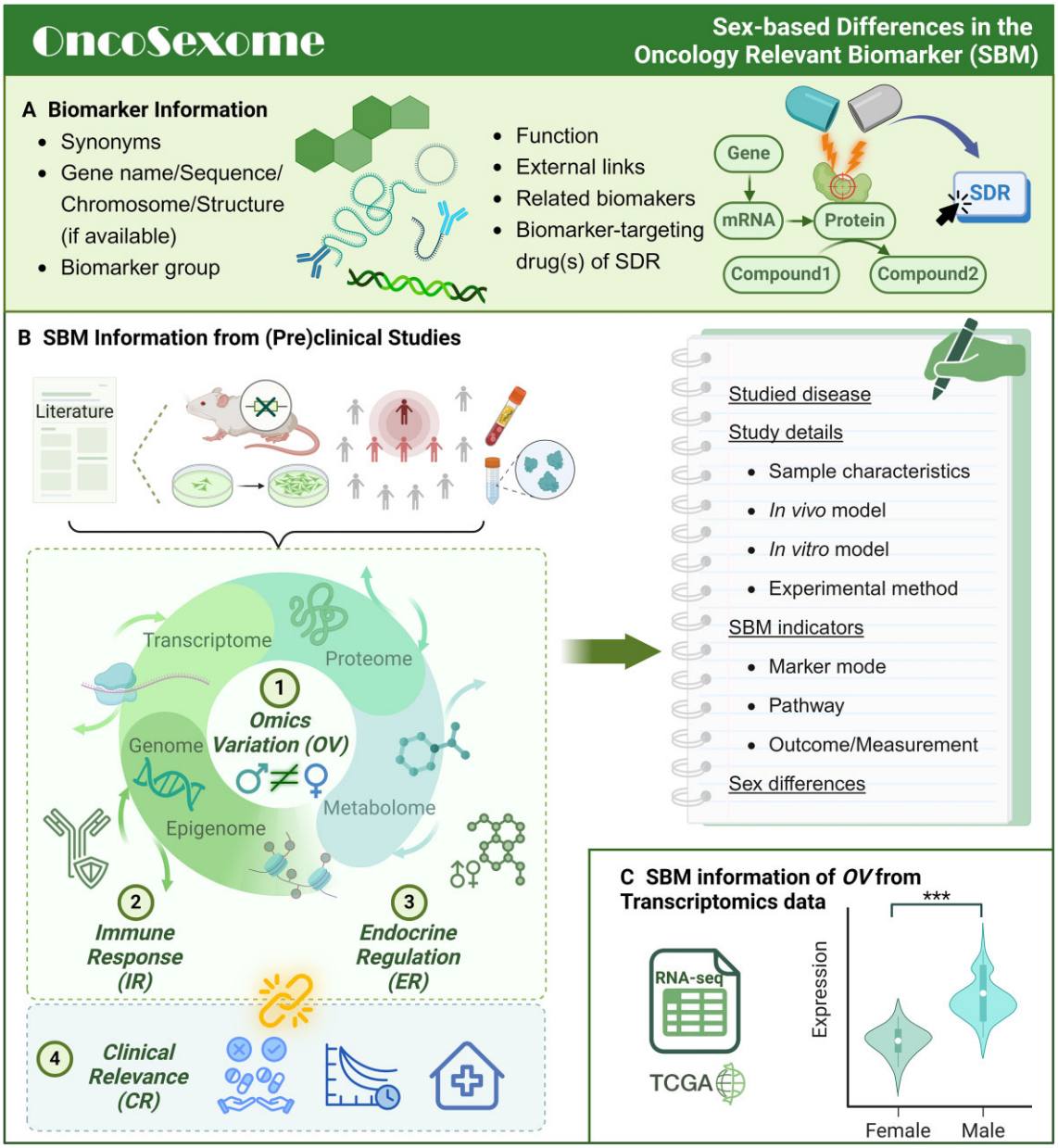


**Figure 3.** Contents of a typical page about sex-based differences in oncological-relevant biomarkers (**SBM**) start with **(A)** general information on the biomarker, including its properties, biomarker group, functions, related biomarkers and its targeting SDR drug(s). **(B)** SBM information from (pre)clinical studies was collected from literature based on *in vivo, in vitro* models and biological specimens. The information was categorized into (1) *OV*, (2) *IR*, (3) *ER* and (4) *CR* based on the topic of the findings. The data are summarized explicitly into studied disease, study details, **SBM** indicators (e.g. marker mode, pathway, outcome/measurement) and descriptions of sex differences. **(C)** SBM information of *OV* from transcriptomics data is displayed by bar plots showing significant levels.

## Sex-based differences in diverse risk factors for cancer (SRF)

Large-scale cancer studies have shown that environmental factors are more pronounced than inherited genetic factors in cancer etiology (114,115). This suggests that exogenous environmental and lifestyle risk factors overwhelmingly contribute to cancer, and these are modifiable or actionable risk factors (116–119). However, some of these environmental factors are more prevalent among males, such as alcohol consumption, cigarette smoking and occupation-related toxin exposure (120), whereas Merkel cell polyomavirus was more prevalent in females with Merkel cell carcinoma (121), showing sex-differential cancer risk factors in males and females. On the other hand, carcinogens may have sex-dependent biological effects: for instance, oncogenes SURVIVIN/BIRC5 were more highly expressed in male diet-induced obesity rats than in female counterparts, suggesting sex dimorphic carcinogens associated with obesity (122). Additionally, sewage sludge exposure differentially affected liver polycyclic aromatic hydrocarbon (PAH) levels in females and cancer-related transcriptomic markers in males, highlighting sex-specific responses to environmental chemical exposure (21). These risk factors contribute to the underlying mechanisms responsible for the observed sex dimorphisms of both solid tumors and hematological malignancies (123). None of the previous databases on sex differences considered cancer risk fac-

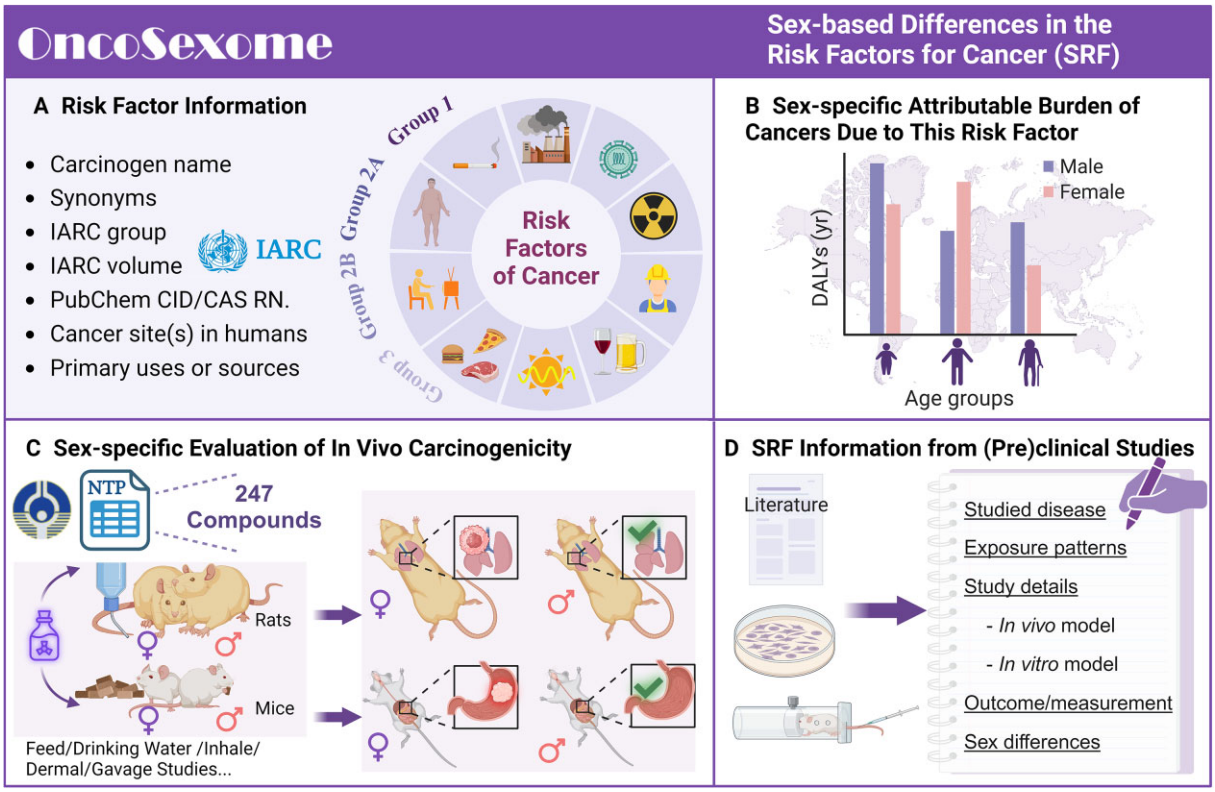


**Figure 4.** A typical page on sex-based differences in the risk factor for cancer (**SRF**) includes **(A)** general information on the risk factor, including synonyms, IARC group and volume, external links, cancer sites in humans and primary uses or sources. **(B)** The sex-specific attributable burden of cancers due to a risk factor is visualized by bar plots by age groups in different counties worldwide. **(C)** Sex-specific carcinogenicity evaluation based on *in vivo* experiments from NTP reports records potential carcinogenic compounds that have divergent carcinogenic activities by sex in various animal models with certain study conditions. **(D)** SRF information from (pre)clinical studies was collected from literature mainly on *in vivo, in vitro* and epidemiology studies that concluded with sex-differential cancer risks or disease burden due to a particular risk factor or exposure patterns of this risk factor.

tors. In addition, toxicology or exposome databases such as Exposome-Explorer (124) and CTD (88) have not sufficiently recognized the importance of sex differences. Neglecting the sex differences in cancer risk factors would hinder targeted carcinogenic exposure monitoring and the implementation of precise prevention strategies, such as cancer screening programs. Thus, the *OncoSexome* aims to merge the gaps by cataloging 350 such risk factors across various carcinogenic groups based on The International Agency for Research on Cancer (IARC) classification.

Firstly, we provide a sex-specific population disease burden scope to visualize the attributable burden due to certain **SRF** for various cancer types among different countries and age groups (Figure 4B) based on data from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) (125), the Canadian Population Attributable Risk of Cancer (ComPARe) study (126), and the Global Cancer Observatory (127). The sex-disaggregated data provide a population-level perspective on the varying impacts of cancer risk factors on males and females. Further, we display **SRF** with *in vivo* model evidence for 247 compounds with **SRF** data from 608 technical reports of long-term National Toxicology Program (NTP) toxicology and carcinogenicity studies (128). All 247 carcinogenic compounds were identified with divergent carcinogenic activity levels by sex in mice, rats, or other animal models (Figure 4C). Experiment conditions, model species, levels of carcinogenicity and sites of neoplastic lesion were listed, which supplement IARC assessments since many of the compounds have not been officially assessed by the IARC so far.

Another large body of **SRF** data was collected from literature that included diverse data sources such as preclinical studies, clinical trials, epidemiological studies, *in vivo* models, and *in vitro* experiments (Figure 4D). Based on the research focus, the evidence was categorized into different topics, such as carcinogenicity, exposure patterns and cancer risks. IARC group, IARC monographs on identifying carcinogenic hazards to humans, synonyms, cancer site(s) in humans evaluated by IARC, primary uses or sources and external links for each risk factor were provided. As a result, we included **SRF** data on 350 risk factors with sex differences, including 47 IARC group 1 agents, 24 agents of group 2A, 36 agents of group 2B, 10 agents of group 3 and 233 unclassified.

## Sex-based differences in microbial landscape in cancer host (SML) across broad taxonomic domains

Microbiota is linked to cancer development (129) and has been incorporated into cancer diagnosis (130), prognosis prediction (131) and treatment (132–134). Meanwhile, studies have shown that these microbes may not be uniformly distributed in tumor tissues and biological fluids (e.g. saliva and urine) between male and female hosts with cancers (135). Moreover, the influences of certain bacteria such as *Carnobacterium maltaromaticum* (48) and *Bifidobacterium*

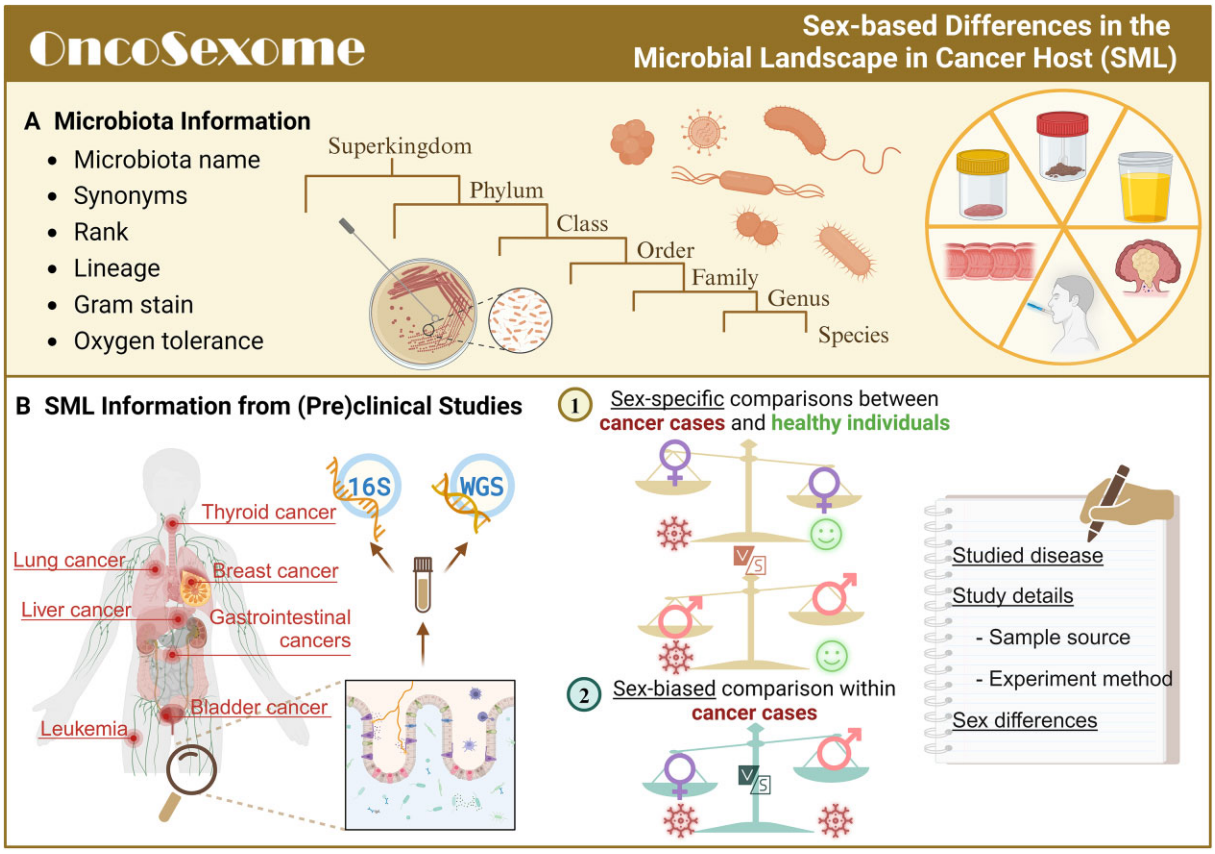


**Figure 5.** A typical page on sex-based differences in the microbial landscape in cancer host (**SML**) includes **(A)** general information on the microbiota, including synonyms, rank, lineage, gram stain and oxygen tolerance. **(B) SML** information from (pre)clinical studies was identified from literature reporting (1) sex-specific differences between cancer cases and healthy individuals and (2) sex-biased compositions or abundance of the microbe within cancerous cases. The microbes were collected from various cancer tissues and urine, stool and saliva specimens, which were then quantified using 16s RNA sequencing or whole genome sequencing techniques.

*longum* (136) could influence cancer progression in a sex-specific manner (137), leaving these previous sex-aggregate findings open to potential questions and room for improvement. Gut-derived *Akkermansia muciniphila* (*Akk*) was recently reported to have tumor suppressive roles (138) but was also found to be more abundant in males than in females with CRC (23). *Burkholderiales* bacteria that could enhance anti-cancer T cell immunity for immunotherapy potentiation (139) were widely reported with sex-biased compositions, such as in the gut of CRC patients (138), guts of murine models with pancreatic cancer (140) and liver cancer (141), human breast tissues with breast cancer (142), and urine samples in adult bladder cancer cases (143), which also suggested that the **SML** data were cancer-type-dependent. Going beyond these association-based findings, Lie et al. discovered sex-specific causal links between the oral microbiome and risks of various diseases, including CRC, esophageal cancer, pancreatic cancer, biliary tract cancer, lung cancer and hematological malignancies (137). In addition to bacterial, intratumor mycobiome and archaeome in papillary thyroid carcinoma (PTC) vary significantly by sex, with distinct microbial dysregulation patterns, particularly in female tumors, potentially contributing to sex-specific PTC pathogenesis and oncogenesis (144).

After exhausting literature searching, we concluded with two kinds of **SML**s (Figure 5B): (1) sex-specific differences between microbial abundance or compositions of cancer samples and healthy samples and (2) sex-biased microbial abundance or compositions within cancer samples. To describe the included studies, we specify sample sources, experimental methods, and necessary statistical results for sex comparisons (e.g. Linear discriminant analysis scores with *P* values after multiple comparisons). We performed data cleaning and annotation based on the National Center for Biotechnology Information (NCBI) Taxonomy (145) using the Biopython package (146). As the broadest database focusing on sex-based differences in cancer, we considered **SML** by including 1386 microbes from three domains (Bacteria, Archaea and Eukaryota), 65 phyla, 120 classes, 246 orders, 463 families, 826 genera and 145 species for 15 cancer types.

## Cancers with sex-based differences in any of SDR, SBM, SRF or SML

*OncoSexome* is structured around four key topics (**SDR, SBM, SRF and SML**), encompassing data on 71 cancer types, each associated with at least one of these topics. The first section (Figure 6A) lists general information about a specific cancer type (i.e. CRC), including the most widely used name, disease class, WHO ICD-11 and ICD-10 codes, and synonyms. The available **SDR**, **SBM**, **SRF** and **SML** informa-

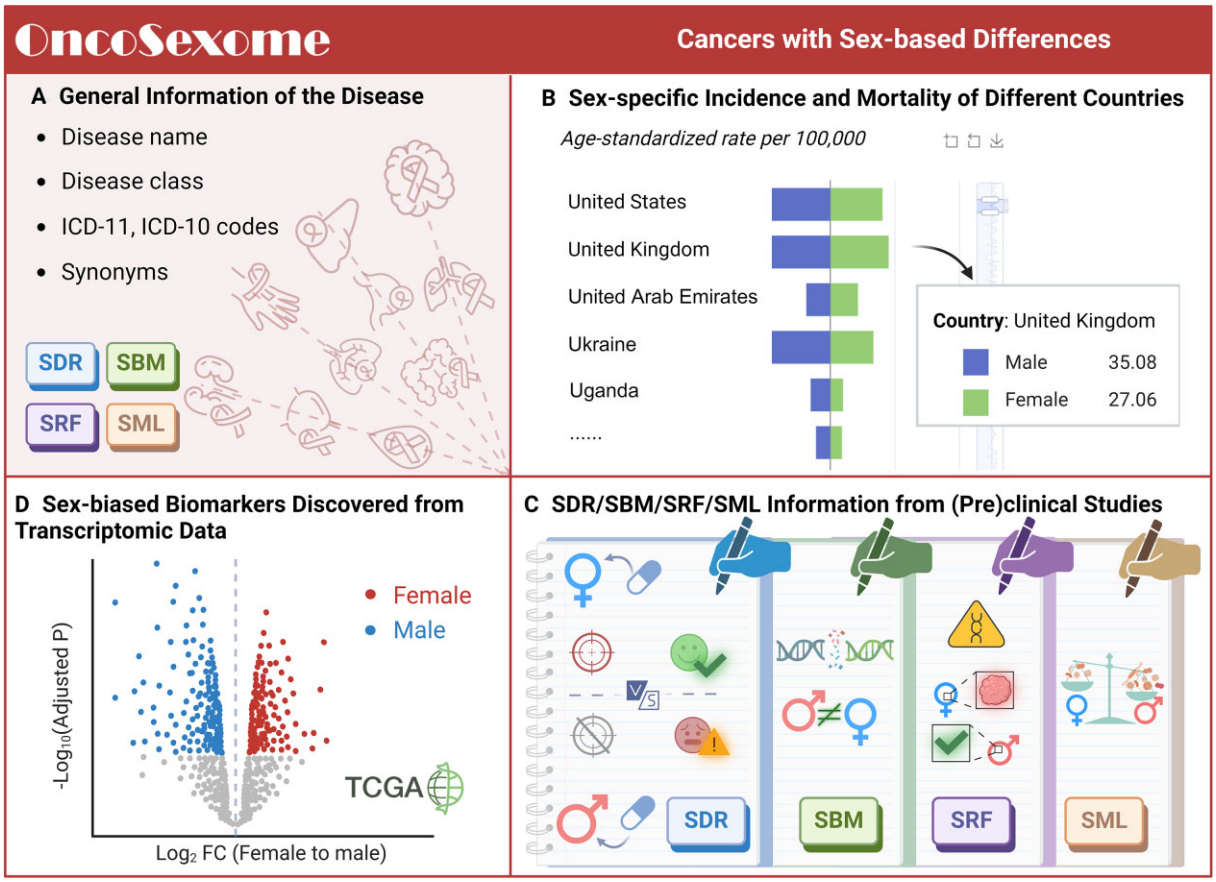


**Figure 6.** Contents of a typical page for a specific cancer type start with the (**A**) general information, including its name, class, ICD-11 and ICD-10 codes, and synonyms, followed by buttons of quick links to the four topics of **SDR**, **SBM**, **SRF** and **SML**. (**B**) Most pages of a certain cancer have two histograms showing sex-specific incidence and mortality of different countries measured by age-standardized rate/100 000. (**C**) Detailed information about all **SDR**/**SBM**/**SRF**/**SML** data related to this disease is listed in separate sections and displayed by tables similar to their individual page. (**D**) In the **SBM** section, a volcano plot displays sex-biased biomarkers discovered from transcriptomics data from the TCGA database.

tion related to this cancer can be quickly accessed via the corresponding buttons. We display sex-specific incidence and mortality data for 26 cancers in 185 countries based on IARC statistics (data in 2022) (147) with a user-friendly sliding bar for viewing countries of desire and a worldwide comparison (Figure 6B). The following part aggregates all available **SDR**/**SBM**/**SRF**/**SML** data from (pre)clinical studies related to this cancer (Figure 6C). The **SDR** data are grouped into drug types, such as small molecules and antibodies. The **SBM** section is grouped by types of biomarkers such as compounds, proteins, genes and immunological features. The data of **SRF** are ordered by the IARC group from 1 to 3. The **SML** data of various microbes is grouped by the affiliated order level in the taxonomic hierarchy. As introduced above, the **SDR** of numerous biomarkers was identified through DGE analysis utilizing RNA-sequencing data from the TCGA database. In addition to the bar plots showing sex differences in the expression of a particular mRNA, we further gathered all such mRNAs and miRNAs into volcano plots (Figure 6D). Female-biased biomarkers are in red-colored dots, and male-biased biomarkers are in blue-colored dots. Users can move mouse pointers to view detailed statistics of a specific mRNA or miRNA, including Ensembl ID, gene name, located chromosome, $Log_2$ fold change, $Log_{10}$ adjusted *P* value and link to its **SBM** page.

## Conclusion and perspectives

*OncoSexome* represents a significant advancement in understanding sex-based differences in cancer, providing a comprehensive resource that integrates data on cancer pharmacology, tumor biology, risk factors and microbial influences across 71 cancer types. By illuminating the multifaceted influences of sex on cancer, *OncoSexome* offers an unprecedented platform for clinicians and basic scientists to explore sex-specific patterns in cancer development, progression and treatment outcomes.

In practice, researchers and oncologists have proved that emerging therapies targeting sex differences in cancer are promising. The European Society For Medical Oncology has launched to promote the inclusion of sex as a stratification factor and the determination of sex-specific maximum tolerated doses (148–150). There have been positive advancements so far. The SEXIE-R-CHOP-14 trial explored sex-specific rituximab dosing in elderly men with diffuse large B-cell lymphoma, showing a 32.5% improvement in progression-free survival with increased rituximab doses for men, suggesting potential benefits of sex-specific dose adjustments (151). AR inhibition could enhance the efficacy of immune checkpoint inhibitors (anti-PD-1) by preventing CD8 + T-cell exhaustion in males specifically (152). For cancer prevention, sex-based data have been critically applied to build tools for predict-

ing lifetime cancer risk (153) and cancer screening (154). Additionally, sex-specific tumor mutational burden (TMB) cutoffs could improve immunotherapy predictions, particularly in women with NSCLC, who tend to have lower TMB (155). These examples highlight how precision oncology is beginning to be applied to clinical practice, benefiting from a deeper understanding of sex-specific biological mechanisms.

Therefore, as research interest in sex-based differences continues to grow, *OncoSexome* is poised to play a crucial role in shaping future cancer research paradigms and implementation of a life-course approach to cancer prevention and treatment by recognizing the uniqueness of women and men at different life stages (65).

Furthermore, a comprehensive examination of the complex interplay between environmental exposures and internal biological factors (156,157) promises a deeper understanding of oncogenesis, metastasis and therapeutic efficacy (158). Thus, it is insightful to consider the interactions among the four domains of **SDR**, **SBM**, **SRF** and **SML**, which have been recorded in *OncoSexome* in the following ways. **SDR*SBM** have connections to each other when the biomarkers are associated with sex-differential drug responses, including the *TV* of **SDR** and *CR* of **SBM**. For instance, elevated Granulocyte colony-stimulating factor (GCSF) and GCSF receptor (GCSFR) levels in the tumor microenvironment of colon cancer were linked to worse prognosis, while inhibition of GCSF favored female mice with more extensive benefits than males (159). **SML** can also interact with **SBM**. Gut oncogenic microbes are more abundant in males with CRC and contribute to impaired gut barrier function with enriched lysophosphatidylcholine metabolites in males (23). Furthermore, gene-environmental interactions influence cancer vulnerabilities (160), requiring more investigations on cancer exposome. **SBM*SRF** has been investigated when **SBM** discovery depends on the status of exposures to cancer risk factors such as smoking and carcinogens. In particular, sex differences in the genomic profiles of lung cancer tumors were only identified in non-smokers but not in smokers (161). Among HBV-positive hepatocellular carcinoma patients, males expressed higher levels of aflatoxin metabolism-related genes, indicating type I interferon signaling/response upregulation and antitumor immunity suppression (162). Another interaction was observed in **SRF*SML**. For example, maternal obesity enhances predisposition to liver cancer in female offspring only, where gut microbiome dysregulation plays an important role (163). Therefore, we may update the database bi-annually, expanding the data beyond the four preexisting topics and focusing more on these interactions with the growing number of scientific findings.

To ensure the database remains up to date and captures emerging findings, we will adopt a collaborative expert network pattern, where domain-specific experts (e.g. pharmaceutical scientists for **SDR** and molecular biologists for **SBM**) will curate updates for their respective fields. We will also employ click-through rate (CTR) analysis to prioritize which topics to update based on user interactions, allowing us to focus on high-interest topics, such as frequently accessed drugs, biomarkers, risk factors or microbes. The database will be updated bi-annually, expanding beyond the four pre-existing topics and incorporating new insights on the interactions mentioned above as the research volume continues to grow.

## Data availability

OncoSexome is accessible without login requirement at: https://idrblab.org/OncoSexome/.

## Supplementary data

Supplementary Data are available at NAR Online.

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## Conflict of Interest Statement

None declared.

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