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Sex differences in drug effects and/or toxicity in oncology

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ABSTRACT

The prevalence, incidence, and severity of a wide variety of diseases and ailments are significantly influenced by the significant disparities that occur between the sexes. The way that men and women react to pharmacological treatment also varies. Therefore, it is crucial to comprehend these reactions in order to conduct risk assessment correctly and to develop safe and efficient therapies. Even from that limited vantage point, the manner and timing of our drug usage might have unintended and unanticipated consequences. There are sex-specific differences in the incidence and mortality of certain malignancies. One of the most important discoveries in cancer epidemiology is the gender inequalities. Cancer incidence differences between the sexes are thought to be regulated at the genetic and molecular levels and by sex hormones like oestrogen. Differences based on sex and gender are among the least investigated factors impacting cancer susceptibility, progression, survival, and therapy response despite their established importance in clinical care. The molecular mechanisms underlying sex differences in particular are poorly known, hence the majority of precision medicine approaches employ mutational or other genetic data to assign therapy without taking into account how the patient's sex may affect therapeutic efficacy. In patients receiving chemotherapy, there are definite gender-dependent disparities in response rates and the likelihood of side effects. This review explores the influence of sex as a biological variable in drug effects or toxicity in oncology.

1. Introduction

1.1. Gender medicine and its importance and its prerequisite in oncology

As the world's population ages, cancer incidence is constantly rising, making it a significant cause of mortality. The WHO's Global Health Observatory has reported that cancer is responsible for about 13% of all fatalities (Luo et al., 2022). 1.75 million was the anticipated cancer-related fatalities in 2012, with males accounting for 56% and women for 44% of these deaths [Fig. 1]. There can be a significant rise in the new cases in males and females, age [0–85], by 2040, as reported by International Agency for Research on Cancer, WHO, and demonstrated in Fig. 2. Cancer occurrence, progression, and therapeutic responses are all known to be influenced by gender (Morgan et al., 2022). When analyzing the impact of gender on cancer, genetic variations should be taken into account, in addition to physical and hormonal variances. The existence of sex-driven disparities in immunological responses is also supported by mounting evidence (Xi and Xu, 2021). Gender imbalance has previously existed in clinical trials and animal model research. Sex should be a significant stratification factor in all randomized clinical trials, considering the disparities between sexes observed in cancers to understand better biological distinctions between men and women, which may result in more effective targeted therapy (*Global Cancer Observatory*, n.d.-a).

For several malignancies, there are distinguishing characteristics among sexes in terms of cancer occurrence, aggressiveness, and course of the disease. Despite this, the gender imbalance has existed in clinical trials and animal model studies. In order to comprehend the molecular basis underlying the gender disparities in the outcome and responsiveness to cancer therapy, gender-specific oncology must re-establish a balance. Understanding the molecular processes underlying sex-biased disparities may improve cancer treatment and lead to the creation of individualized therapeutic approaches.

Biological sex differences, gender identity, roles, and relationships all have an impact on disease and health, and these variations might have consequences to screen, diagnose, prevent and treat, according to a novel approach to medicine known as sex and gender-sensitive medicine. This

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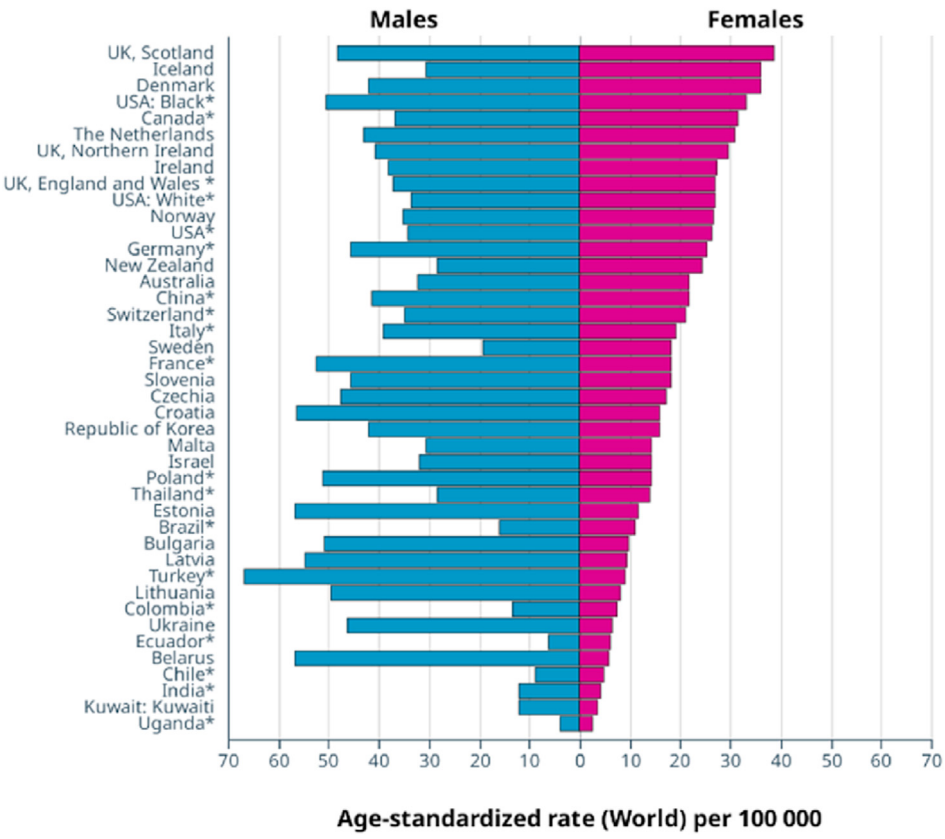

Fig. 1. Age-standardized rate (world) per 1,00,000 incidence, males and females, in 2012. [Figure legend x-axis refer*- Subnational data, reproduced from the source with the CC BY-NC-SA 3.0 IGO license, which allows users to copy freely, reproduce, reprint, distribute, translate and adapt the work for non-commercial purposes] [source: Data Source from International Agency for Research on Cancer, WHO, Reproduced from the source](*Cancer Over Time*, n.d.; *Global Cancer Observatory*, n.d.-b).

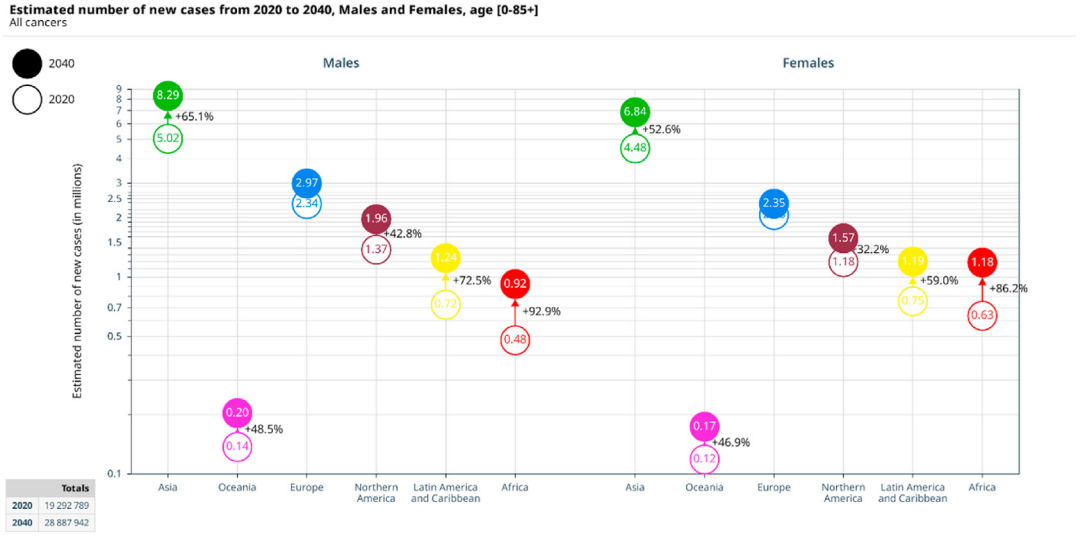

Fig. 2. Estimated number of new cases from 2020 to 2040, Males and Females, age [0–85+]. [source: Data Source from International Agency for Research on Cancer, WHO, reproduced from the source with the CC BY-NC-SA 3.0 IGO license, which allows users to copy freely, reproduce, reprint, distribute, translate and adapt the work for non-commercial purposes](*Cancer Over Time*, n.d.; *Global Cancer Observatory*, n.d.-b).

discipline's ultimate goal is to enhance patients' quality of life by learning from these distinctions (or the lack of them). Gender has been defined by WHO as socially constructed roles, activities, behaviors, and characteristics that a given society thinks are proper for both sexes. "Sex" is referred to biological grounds that support the anatomy and physiology of the sexes. Therefore, every human is gendered even though every cell is sexed (Canadian Institute of Health Research). There is constant interaction between the two in live humans. Gender is a continuum, unlike sex, that is typically categorized as binary.

In addition to the expanding collection of information about different genomes showing the existence of disparities in cancer risk between men and women that go beyond those that influence reproductive tissues, there is a shred of substantial evidence compiled from clinical and epidemiological studies suggesting variation in malignancy that is connected to a person's gender or sexual orientation. Males and females react differently to genetic and epigenetic changes and environmental stressors. Therefore, genetic traits linked to cancer genesis, prognosis, and therapy response may affect men and women differently. For

instance, alterations in the expression of the gene act as prognosticative indicators exclusively for one or both sexes. When examining several different sorts of omics data, such distinctions between male and female malignancies have been found to exist in mutation, methylation of the genome, chromatin accessibility, mRNA expression, miRNA, and protein. Integrating various data help us understand the molecular processes that underlie the sex-related disparities in cancer. An examination of the network of gene regulators exclusive to one gender or the other, for instance, can reveal the biological processes that are differently regulated by sex, the relationships between sex-biased patterns, and the sex differences seen in carcinogenesis and clinical outcomes. The prevalent paradigm in precision medicine typically disregards an individual's sex, even though there is evidence that sex affects the occurrence of cancer, metastasis, and therapeutic outcome. There are methodological and conceptual gaps regarding including sex in therapeutic practice and research (Wilson and Buetow, 2020; Woitowich et al., 2020). Further research on sex and variations in cancer risk between the sexes will help develop sex-specific prevention of cancer, early diagnosis tactics, and more sophisticated precision medicine therapeutic approaches that would enhance therapy and outcomes, including survival.

The optimization of drug dose in the field of cancer is substantially behind drug development in comparison. The prescribed therapeutic doses with mostly men might result in higher serum drug levels and toxicity in women because of variations in body composition between males and females. The biological sex and gender of a patient must be considered when choosing a course of therapy. As a result, there has to be a more excellent representation of women in clinical trials. Those trials must be set up to enable functional sex-based subgroup analysis for treatment outcomes and drug toxicity. Compared to the existing Body surface area (BSA)based or fixed-dose, prospective trials exploring the Fat-free mass (FFM)-based drug dosing for those that are cytotoxic and targeted treatment could offer a promising alternative and dramatically enhance the toxicity and efficacy ratio of anti-cancer treatment.

2. Sex and gender differences in epidemiology and tumor biology

Cancer is one of the main reasons for mortality worldwide. There are gender-specific variations in the occurrence of certain cancers as well as the mortality rate associated with them. Of all the known inventions in cancer, epidemiology is the gender inequalities most crucial one. Cancer deaths are more common in men, especially hematological malignancies. Cancer incidence differences between the sexes are thought to be regulated genetically, molecularly, and by sex hormones like estrogen. Men and women experience cancer incidence differently due to gene polymorphism, changed enzymes involved in drug metabolism, and other genetic/molecular factors. Sex significantly influences the incidence, prognosis, and death of numerous cancer (Siegel et al., 2016). From 2009 to 2013, males had a 20% greater cancer incidence than females and a 40% greater fatality rate (Siegel et al., 2017). Genetic and molecular variations influence cancer susceptibility in gender.

Sex hormones can have a favorable or unfavorable impact on the emergence of certain malignancies. Biological specificities determine the course of cancer and its response to treatment. The experiment's outcomes are impacted by changes in sex hormones occurring during the menstrual cycle. US FDA 0.1977 recommendation prohibited females from participating in clinical research because of the possibility of problems at the time of birth. Clinical Hold Regulations for Products Intended for Life-Threatening Diseases Amendment of 2000 (21 CFR 312.42), allows the FDA to put a clinical hold on IND studies for treating severe or life-threatening diseases if either men or women are barred from participation because of their reproductive potential. 2014 Guidance for Industry and FDA Staff on Evaluating Sex-Specific Data in Clinical Studies of Medical Devices. The FDA's requirements for sex-specific patient enrollment, data analysis, and study information reporting for medical device applications are outlined in this advice (Liu and Dipietro Mager, 2016; *Regulations, Guidance, and Reports Related to Women's Health | FDA*, n.d.).

2.1. Epigenetics and cancer

Mammals' normal development and maintenance of tissue-specific gene expression patterns depend heavily on epigenetic mechanisms. Alterations in gene function and cancerous cellular transformation can result from epigenetic process disruption. Epigenetic dysregulation has become a significant factor in cancer start and adaptation these years. Most cancer characteristics that come to have the genetic mutation can now be achieved through epigenetic pathways, as we have come to understand. This may entail the abnormal activation or silencing of specific loci or extensive epigenetic landscape remodeling. Human cancers typically contain mutations in the genes encoding histone proteins, aders, writers, and erasers of the epigenome, demonstrating a clear relationship between epigenetic instability and carcinogenesis. Recent developments in the quickly developing field of cancer epigenetics have demonstrated substantial reprogramming of every element of the epigenetic machinery in cancer, including DNA methylation, histone modifications, nucleosome positioning, and non-coding RNAs, particularly microRNA production. Nevertheless, as the review is focused only on sex differences, the detailed description was not discussed in the current section.

2.2. Sex differences in incidence and mortality of cancer

There is mounting proof that certain malignancies have different incidence and fatality rates relative to patients' gender. In the US, men have an increased risk of prostate, lung, and colorectal cancer than the other sex who have lung, breast, and colorectal malignancy (Siegel et al., 2016). There are reported gender differences in the occurrence of malignancies in the colon, lung, and liver, along with an increased risk of developing malignancy in the prostate and ovary (Tevfik Dorak and Karpuzoglu, 2012; Torre et al., 2016). Women are at a higher risk of getting thyroid cancer (Tevfik Dorak and Karpuzoglu, 2012). Men are at a higher risk of colon, stomach, and liver cancers. Additionally, more males than females have been diagnosed with leukemia and bladder cancer (Ray Dorsey et al., 2018). In individuals with colorectal cancer, females tended to express the disease more on the right side, whereas males tended to do so higher towards the left (S. E. Kim et al., 2015). Compared to left-sided sickness, colon cancer on the right side is more severe (S. E. Kim et al., 2015). The differential in estrogen levels between men and women may be what is causing the geographic disparity. Estradiol stimulates the proliferation of KAT5 cells, and the underlying process may be correlated to an increase in Bcl-xL expression. The information shines a spotlight on the molecular mechanism driving the epidemiological findings that thyroid cancer is two-to three times more common in women than in men (Ortona et al., 2019).

The primary sources of cancer deaths—lung, colorectal, and stomach cancers—Indicate a higher death rate in males. Women's cancers, including uterine corpus, breast, and ovarian cancer, have a comparatively high fatality rate. Men die more often than women from esophageal, liver, and bladder cancer. Compared to women, there was a 34% increase in the risk of men dying from melanoma (Crocetti et al., 2015). Therefore, sex inequality is demonstrated by mortality from different cancer kinds. Due to smoking, lung cancer accounted for the majority of mortality associated with cancer among males in the 20th century (Siegel et al., 2016). Decreased smoking rates, early identification, and therapy led to a drop in lung cancer deaths between 1991 and 2012.

2.3. Sex differences in sex hormones in cancer incidence

The occurrence of cancer between the sexes may be influenced by sex hormones. Due to low levels of estrogen, men are more at risk than women of developing Acute lymphocytic leukemia (ALL) (Do et al., 2010). Suppressing nuclear factor kappa B (NF–B) is a function of estrogen. NF–B regulates interferon regulatory factor 4 (IRF4)

transcription. IRF4 has a role in T and B cell development and is highly expressed in B-cell cancers due to NF–B hyperactivation. Estrogen is directly related to an elevated incidence of thyroid carcinoma in the female population (Lee et al., 2005; Tevfik Dorak and Karpuzoglu, 2012). Contrary to testosterone, estrogen boosts the growth of the cancer of papillary thyroid in human patients' cell lines and encourages the development of the anti-apoptotic Bcl-XL. Progestin enhances biliary elimination, which induces colon cancer (H. I. Kim et al., 2018).

3. Gender disparities on molecular cancer basis

According to molecular and genetic studies, the vulnerability to disease changes between the sexes. The incidence of certain cancers changes according to the sexes because of genetic and molecular variations. Bladder cancer occurs more frequently in males (Siegel et al., 2016). The genotype of the enzyme sulfotransferase 1A1 Histidine has been linked to a decreased incidence of bladder cancer in the female population (Zheng et al., 2003). SULT1A1's genetic polymorphism revealed a change from Arginine to Histidine that brought a transition from A-to-G. Only in women, the His213 allele genotype SULT1A1 markedly reduces the incidence of bladder cancer. Hence, this genome could be connected with a shielding effect in females who had bladder malignancy. Drug metabolizing enzymes are influenced by genetic variation, which affects the likelihood of carcinogenesis (Bolufer et al., 2007). Men are more likely than women to get acute leukemia, for instance. According to a study, males with the glutathione s-methyltransferase polymorphism detection of glutathione s-methyltransferase T1 were more likely to undergo biotransformation at the second phase and be identified with acute lymphoblastic leukemia compared to those who have a usual level of GSTT1. The enzyme activity was abolished by GSTT1 gene deletion. The enzyme NAD(P)H: quinone oxidoreductase 1 catalyzes the removal of free radicals. Males only, and not females, showed a greater incidence of ALL when the NQO1 polymorphism was examined (Bolufer et al., 2007). MDM2 reduces the tumor protein p53 suppressor. The p53 pathway is lessened due to an increase in the binding of Sp1 caused by SNP 309. Both the wild-type allele of p53 and the G-allele of SNP 309 attenuates the p53 DNA damage response (Bond et al., 2004).

Additionally, estrogen signaling influences MDM2 levels (Bond et al., 2004). In females bearing the G-allele of SNP309, the estrogen signaling pathway enhances tumor growth in the DLBCL, spontaneous soft tissue sarcoma, and highly invasive estrogen receptor-positive ductal carcinoma directly or indirectly. When combined, genetic and molecular variations may impact the differential in malignancy risk among sexes.

4. Sex differences in immuno-oncology and anti-cancer immunotherapy

4.1. Immune response to cancer

The immune system significantly influences cancer growth and progression. As a result, "evading immune destruction" has been recognized as a characteristic of cancer. Tumors can escape immunological responses by various methods, including inhibition of regulatory T cells (Jacobs et al., 2012), reduction of antigen processing, creation of immune-suppressive mediators, and encouragement of immune deviation and tolerance (Foell and Hewes, 2007; Rubin et al., 2020; Topalian et al., 2012).

4.2. Immune system disparities between the sexes

The immune systems of men and women differ due to genetic mediators like sex chromosomes (X, Y), hormonal mediators like estradiol, progesterone, and androgens, environmental mediators like the microbiome, social sex behaviors like smoking and alcohol intake, and age. Male mortality is higher due to hormonal regulation, immune system abnormalities, and cancer etiology. Females have higher innate and adaptive immune responses than males, lowering cancer mortality. Epigenetic, genetic, psychological, and sex hormones cause these changes. IL-2 receptor gamma subunit, TLR-7, TLR8, CD40L, and FoxP3 genes regulate immune response on chromosome X. Sex hormones affect dendritic cells, neutrophils, natural killer cells, macrophages, B and T lymphocytes, and their development, maturation, longevity, and effector activities. Sex chromosomes and hormones affect the self-renewal of systemic determinants of carcinogenesis, stem cell populations, and tumor microenvironments. Women's more robust immune response causes more autoimmune and inflammatory disorders. Women have Th1-biased immune systems. T helper1 (Th1) and Th2 cytokines (Th1/Th2) regulate Th1 and Th2 cell network functions in the immune response, and sex hormones affect this balance. Women produce IL-6 and men produce IFN- for immune response homeostasis. IL-10 is common to both but controlled by gender-specific mechanisms to restore immune system resting equilibrium. Women possess antigen-presenting cells (APCs), which are highly effective than males at presenting peptides in the innate immune system. Females have more neutrophils and macrophages than males.

4.3. Relevance to immunotherapy

The impact of sex on cancer immunotherapy was not previously studied, despite known gender differences in immune responses and functioning. Successful immunotherapy may improve the immune system's capacity to mount an efficient anti-cancer response to neoantigens or revive the immune system to create a robust immunological response (Antohe et al., 2019). The growth and operation of DC precursors and cell subsets, particularly plasmacytoid DCs, that are top targets for immunotherapy are significantly regulated by estrogens (Kovats, 2015; Laffont et al., 2017). Additionally, whereas men possess more significant numbers of $CD8^+$ and Treg leukocyte populations and females have higher $CD4^+$ T cell counts and CD4/CD8 ratios, anti-tumor immune outcomes could show sexual dimorphisms that change the effectiveness of cancer immunotherapies (Capone et al., 2018). Antigen-specific anti-tumor immunotherapy therapies include monoclonal antibodies, vaccinations, and CAR-T cells. Immune Checkpoint Inhibitors (ICIs) have been known to immensely extend patients' life in the last stage by restoring effective anti-tumor immunity. Women who receive anti-PD-1 therapy more often than men experience immune-associated side effects (Duma et al., 2019). It is yet unknown how sex disparities in response to ICI therapies are caused molecularly. Preclinical research has shown that sex hormones can control the PD-1 ligand or its pathway (Rubin et al., 2020).

5. Relation of pharmacokinetics to response to therapy

Women are more likely to experience increased bone marrow toxicity in hematological diseases. However, this higher incidence of side effects is linked to a more effective course of treatment. A better response to treatment had a greater chance of severe neutropenia in females with Hodgkin lymphoma (Klimm et al., 2005). Therefore, a difference in drug metabolism throughout therapy likely accounts for the gender-specific better life in female Hodgkin lymphoma patients. Only young men with Hodgkin lymphoma, osteosarcoma, and Ewing sarcoma showed a worse outcome; patients with acute lymphoblastic leukemia or rhabdomyosarcoma did not. Male patients between 15 and 30 accounted for most of the extra mortality. Showing that young male patients are typically underdosed with existing techniques for therapy, young female adults exhibited response rates comparable to youngsters of either sex. Changes in liver enzymes brought on by gonadal hormones throughout puberty, which have not been considered in many recent clinical trials, can be used to explain this.

According to the study, young male adults' response rates and survival have not varied in the past 20 years. Patients with colorectal cancer showed various response rates and more adverse effects when given 5FU

than male patients. Nevertheless, a combined analysis of 3302 individuals with colorectal cancer stages II and III failed to find any evidence of a sex effect in the adjuvant 5-FU treatment (Gill et al., 2004). Temozolomide increased life in glioblastoma multiforme-affected females (Stupp et al., 2005). In addition, women treated for lung cancer with carboplatin plus paclitaxel had a more prolonged median progression-free survival. Other studies have also demonstrated that female lung cancer patients respond better to treatment. It is interesting to note that adverse effects are similar between the sexes. In a few studies, cancer treatment outcomes are enhanced in females. An improved chemotherapeutic application sequence improved the response rate in male patients but did not affect the response rate in female patients.

5.1. Sex differences in toxicity: clinics and pathophysiology

Due to disparities in metabolism between the sexes, women have more negative adverse effects when taking cytostatic drugs. Particularly with high-dose therapy, such as those used for stem cell transplantation, the female death rate is more significant than male mortality in adolescents (Socié et al., 2001). Male patients receiving large doses of chemotherapy showed reduced lethality (Khamly et al., 2009). Several cases of oral mucositis have been observed in females during high-dose chemotherapy.

5.1.1. Differences in mucosa-associated effects

The gut mucosa in males looks more sensitive than the mouth mucosa. Women experience fewer digestive adverse effects from cytostatic drugs as part of treatment. Most xenobiotics are resorbed, with little or no stomach absorption in the jejunum and duodenum. Mucosa cells are shielded from harmful substances, and The most crucial system is involved in the redox system. Glutathione functions To render electrophiles and reactive oxygen species inactive and use a redox buffer. There have been demonstrated that glutathione S-transferase is considerably lesser as well as vibrant in the gut of males. The mucosa of the male is hence less resistant to oral toxins. Gender is a different factor of veggies and fruits boosting enzyme production, suggesting that there may be a lifestyle-related phenomenon related to glutathione S-transferase function. However, women in the postmenopausal stage experience this variation from men less noticeably. Cytostatic medications also lower the enzyme expression of ribonuclease H (Hoensch et al., 2002). By raising GST P, by contrast, cortisol derivates improve antioxidative capacity.

5.2. Sex-specific adverse effects of some drugs

Faster enhanced hepatic microsomal N-dechloroethylation caused by CYP3A4 may cause more neurotoxicity in females on ifosfamide. Females have been proven to encounter a higher degree of symptoms of colorectal cancer than men (Gusella et al., 2006). It has been demonstrated that 5-FU increases non-hematological grade 3 and 4 tumors. Hand-foot disease, hematological infection, neutropenia, and adverse effects are observed more in females than in dihydropyrimidine's enzyme activity. Newer investigations, however, have generally shown more negative hematological consequence. Morbidity and death are also prevalent among women. Adverse events from steroid use are frequently observed. The prevalence of secondary diabetes mellitus is rising.

5.3. Sex-specific side effects of some regimes

The rate of severe (grade 3 or 4) leukopenia in women receiving carboplatin and paclitaxel treatment for lung cancer was high; their median leukocyte nadir was lower. Added research revealed enhanced cyclophosphamide toxicity in female patients' hematological functions, etoposide, doxorubicin, cisplatin, and vincristine (Singh et al., 2005). Women getting chemotherapy had highly severe nausea and vomiting due to lung cancer.

5.4. Sex-specific side effects of some localized therapies

The adverse effects of localized therapy can vary significantly between men and women. One is observed with the efficacy of hyperthermic intraperitoneal mitomycin C following surgery to reduce tumor size. Neutropenia was dramatically more common in women in one trial, but there has not been a rise in mortality or hospitalization possible (Marosi, 2006). Young adults undergoing therapy for Hodgkin lymphoma, Ewing sarcoma, and neutropenia were more common in women with osteosarcoma. Men had hemoglobin levels that were lower, although female patients. In contrast, the requirement for blood transfusions was significantly reduced (Khamly et al., 2009). Less toxic in male Ewing sarcoma patients. The EURO Ewing 99 study included information on sarcoma (Joerger et al., 2006).

6. Sex and gender differences in anticancer treatment

6.1. Oesophagogastric cancer

Sex may affect the effectiveness and side effects of chemotherapy by altering variability among patients in chemotherapy metabolism and dose response. The number of patients receiving treatment for oesophagogastric cancer who were administered first-choice chemotherapy is the highest. In addition to having non-crucially increased rates of neutropenia and febrile neutropenia, females also had a considerably greater level of GI toxicity. Women are more prone to develop GI toxicity after controlling for relevant factors. Overall, the female population gets lower chemotherapy than men, with a more significant percentage getting only one to three rounds and a lower percentage getting seven. Females received smaller percentages of the fluoropyrimidine, platinum, and anthracycline doses administered; nevertheless, this change has not achieved significance statistically. No variations in the frequency of dosage reductions or delays were found (Davidson et al., 2019).

6.1.1. Toxicity difference

Davidson et al. represented the most significant pooled analysis of the effect of sex on chemotherapy outcome and toxicity in advanced oesophagogastric cancer. Epirubicin (E), cisplatin (C), Fluorouracil (F), capecitabine (X) oxaliplatin (O) were included as treatments to form the four trials like ECF, ECX, EOF or EOX. No variation in all grade or grade III toxicity was found between boys and girls for toxicities that were recorded consistently across all four trials. But, females showed increased levels of all-grade and grade-III nausea, vomiting, all-grade diarrhea, and stomatitis. All females had greater absolute rates of grade III and febrile neutropenia, but significance could not be determined. All-grade peripheral neuropathy was substantially prevalent in men. At least one serious adverse event (SAE) occurred more frequently in females during treatment. Women more often encounter GI toxicities when predefined factors are taken into account. However, no difference was found in hematological toxicity among the sexes. There were no variations in rates of diarrhea or hand-foot syndrome among males and sexes treated with capecitabine-containing regimens (Davidson et al., 2019).

6.2. Non-small cell lung cancer

The primary leap toward tailored and precision medicine is to comprehend how sex affects the effectiveness of anti-cancer drugs. Patients with NSCLC respond to medication differently according to their gender, and this difference is unaffected by age or smoking status. The effectiveness of the medications affects the sex disparity. If the medicine is successful, female patients respond to treatment better than male patients. The women subgroup exhibited a reduced heart rate value HR compared to the male subgroup (Nipp et al., 2016). The women subgroup reacted well to chemotherapy plus cetuximab Erbitux compared to the men segment in two reports of a study of advanced non-small cell lung cancer patients receiving chemotherapy plus Erbitux (Pirker et al., 2009, 2012). The female

subgroup demonstrated a better response than the male subgroup in comparing the chemotherapy effect of erlotinib [Tarceva ®]as first-line therapy in patients with advanced EGFRmutation-positive non-small cell lung cancer (Zhou et al., 2011). In the study of erlotinib as maintenance therapy in advanced non-small cell lung cancer, the female subgroup exhibited a lower Heart rate than the male subgroup (Cappuzzo et al., 2010). The female subgroup exhibited a significantly lower hazard ratio than the males in the trial of an intercalated combination of chemotherapy and erlotinib in patients with advanced-stage NSCLC (Wu et al., 2013).

In the United States, lung cancer kills more women than breast, ovarian, and colon cancer, making it the leading cause of cancer-linked fatalities in both sexes. Hypertension and hemoptysis were more common side effects of antiangiogenesis treatment in patients who were given bevacizumab. Females receiving bevacizumab exhibited an increased rate of grade 3 hypertension than men in each arm when comparing the two genders. On the bevacizumab arm, proteinuria, hemoptysis, and other bleeding events happened equally in men and women. When treated with bevacizumab plus chemotherapy, women were more liable to experience high grade 5 neutropenia or infections with neutropenia than men. Across both treatment groups, women often reported higher nausea than men, albeit the variation was not statistically significant. Constipation was more common in women receiving PCB treatment. In line with this, women on the PCB arm also experienced more abdominal pain than men. Women on PCB may rarely have chemotherapy in the second-line context. The prescribed second-line therapy does not, however, have complete data accessible. Compared to females receiving PC alone, women on PCB also had higher toxicity and liver involvement. The difference in treatment effect between sexes marginally narrowed but remained significant after adjusting for other characteristics. At 15 mg/kg of bevacizumab, women had a statistically improved PFS compared to males, while at 7.5 mg/kg of bevacizumab, the opposite was true. The variations found in this study could have several causes, but sex hormones could be one of them (Wakelee et al., 2006). Bevacizumab clearance-related factors could also affect bevacizumab toxicity and perhaps result in a lack of benefit. Males cleared 26 percent more quickly than females did. The more significant toxicity in women on the PCB arm may be due to slower female clearance. Data suggest that bevacizumab may have differing effects on OS among men and women with NSCLC. Bevacizumab is an active medication for treating NSCLC in female patients, and its inclusion did lead to appreciable gains in RR and PFS(Brahmer et al., 2011).

The more remarkable survival and toxicity observed in women may be explained by changes in medication metabolism that may result in more significant amounts of cytotoxic chemicals in females than in males. However, the complete explanation is likely to be more complex. Differences in DNA damage susceptibility might be one factor (Wakelee et al., 2006). Females are less capable of repairing DNA, which might support their higher risk of getting lung cancer (Hewer and Phillips, 1994; Mollerup et al., 1999; Spitz et al., 2003; Wei et al., 2000). DNA adducts have been created when active metabolic products that are not detoxified bond to the genome. Polymorphisms influence rates of detoxification. Due to their lower ability to repair their DNA, women may be more vulnerable to harmful and therapeutic outcomes of cancer treatment, especially when using platinum drugs which cause DNA adduct formation. In cisplatin-based cancer treatment, better results are obtained if the DNA repair is diminished. Thus, evidence that suggests a possible role for diminished DNA repair in increasing women's susceptibility to lung cancer may help to explain both the more significant toxicity reported in women and the improved survival rates were seen in 1594 patients who received platinum-based therapy. Estrogens have been associated with increased lung cancer cell growth and the formation or stabilization of DNA adducts, suggesting that hormonal factors may be a.

6.3. Small cell lung cancer

Having a female partner improves the prognosis of small-cell lung cancer. Despite evidence that women with other tumor forms suffer from increased treatment toxicity, there have not been many investigations of gender-related toxicity in SCLC. Most bronchogenic carcinomas, between 15 and 20 percent, are small-cell lung cancers (SCLC). According to demographic research, men are more often diagnosed with NSCLC than women, who are more likely to get SCLC. It's interesting to note that sex has been discovered to be a prognostic factor that is independent of lung cancer subtypes, with females having a greater survival rate than men. In particular, the female gender is related to a favorable prognosis for SCLC in univariate and multivariate analyses. Despite receiving the same number of chemotherapy cycles as men and having a better prognosis, women incur more chemotherapy-related toxicity than men when treating SCLC. This is probably the result of multiple factors.

6.4. Colon cancer

Using data from 34,640 patients, we verified that female patients with colon cancer consistently develop statistically and clinically higher toxicity from all currently used adjuvant chemotherapy, including those based on capecitabine and oxaliplatin. The severity of this effect is highest for patients with severe neutropenia and leukopenia, but it is present across most adverse events and regimens. Variability in the efficacy and toxicity results can be roughly divided into two categories. Pharmacokinetic variability reflects variations in drug exposure levels amongst populations, for instance, as a result of variations in metabolism or absorption. Contrarily, pharmacodynamic variability results from variations in a drug's biological effects among patients despite identical drug intake. However, it is known that a patient's sex can impact pharmacokinetics and pharmacodynamics in terms of drug disposition and drug sensitivity (Soldin and Mattison, 2009).

Additionally, the current chemotherapy dose does not contribute to the considerable individual variations regarding body composition in patients with comparable BSA. In females, 5-FU elimination is lower. The increased toxicity in females is explained by the decreased clearance of 5-FU. These findings support the idea that tailored fluoropyrimidine doses should be sex-specific. Since the pharmacokinetics of 5-FU is more accurately predicted by fat-free mass in addition to total body weight than traditional anthropometric measurements, gender variations in the composition of the body, especially the significantly more significant percentage of metabolically active, fat-free body mass in males (Wagner et al., 2019), might be significant too (Gusella et al., 2002). Most males who get a standard dose of 5-FU have "sub-therapeutic" plasma levels (Mueller et al., 2013). The mean 5-FU dose was more significant in men to reach "therapeutic" 5-FU levels. In the phase III PETACC-3 trial of FOLFIRI, 48.9% of female participants and 38.2% of male participants showed all-grade lethargy (Wagner et al., 2021). Anti-cancer drugs with sex differences in efficacy and toxicity were summarized in Table 1.

6.5. Mechanistic insights into anti-cancer drugs

6.5.1. 5-FU

Dihydropyrimidine Dehydrogenase activity decreased in females, and there is a 15% difference between male and female DPD activity. Reduced 5-FU degradation in females affects toxicity and therapeutic effectiveness. More frequently and severely than males, women encountered toxicities from 5-FU-based chemotherapy, such as stomatitis, leukopenia, alopecia, and diarrhea (Mader, 2007).

6.5.2. Paclitaxel

According to a study, female patients with solid tumors eliminate paclitaxel 20% less quickly than male patients. Compared to males (1.74 mmol/l), the peripheral compartments of females (0.83 mmol/l) are saturated at lower plasma concentrations. However, males eliminate paclitaxel more quickly (0.5 h) than females (1 h). DNA repair was lower in females than in males, which may account for sex-related disparities. After delivering the cytotoxic anti-cancer treatment, the weaker DNA

Table 1
Anti-cancer drugs with sex differences in efficacy and toxicity.

Drug	Sex differences		
	Parameter	Male	Female
5-fluorouracil	Clearance	Higher	Lower
	Toxicity	Less frequent	higher toxicity (including stomatitis, leukopenia, alopecia and diarrhea) frequently
Paclitaxel	Elimination	Higher	Lower
	Distribution	Peripheral compartment of males is saturated at higher plasma concentrations levels	Peripheral compartment of females is saturated at lower plasma concentrations levels
	Severe leukopenia	Mild leukopenia	Experienced severe leukopenia
	Progression-free survival	Shorter	Longer
Doxorubicin	Clearance	Higher	Lower
	Risk of early cardiotoxicity (Childhood leukemia)	Higher	Lower
Cisplatin	Toxicities	Mild	Higher toxicities including vomiting and nausea
	Heat latency and motor nerve conduction in rates	Prolonged heat latency and slower motor nerve conduction	Normal heat latency and motor nerve conduction
	IC-50	Lower	Higher
Bevacizumab	Clearance	Higher	Lower
	Hypertension and neutropenia	Severe	Mild
	Abdominal pain	Higher	Lower
Rituximab	Clearance	Higher	Lower
	Half-life of Elimination	Higher	Lower
	Treatment and outcomes	Less prominent	More prominent
	Progression-free survival in diffuse large B-cell lymphoma and follicular lymphoma	Worsen	Less or mild

repair ability may damage tumor cells in female patients and affect their prolonged progression-free survival (Yamamoto et al., 2008).

6.5.3. Doxorubicin

Doxorubicin is predicted to produce free radicals in a different way that damages cancer cells' DNA and membranes. Male patients with normal liver function had considerably higher doxorubicin clearance (59 l/h/m2) than female patients with breast cancer or lymphoma (27 l/h/m2). The toxicity of doxorubicin may be increased in women due to independent risk factors such as cardiac problems. Compared to boys, females with pediatric leukemia who were exposed to doxorubicin had a higher chance of developing early cardiotoxicity. P-glycoprotein, a drug transporter that expels numerous foreign compounds from cells, is produced by the multidrug resistance protein one gene. Males express P-glycoprotein at a 2-fold higher level than females do. Doxorubicin accumulates and causes cardiotoxicity in females when the p-glycoprotein expression decreases (Mitry and Edwards, 2016).

6.5.4. Cisplatin

Patients who receive cisplatin-based therapy are significantly more likely to have toxicities such as nausea and vomiting in women than in men. Physiological factors such as different body composition and metabolic activity may be what is causing the sex-dependent difference. Male-derived cell lines showed more sensitivity to cisplatin than female-derived cell lines in the Yoruban community, which was made up of people of African heritage. Male-derived cell lines have a lower half-maximal inhibitory concentration (IC50) than female-derived cell lines (Huang et al., 2007).

6.5.5. Bevacizumab

A monoclonal antibody called bevacizumab suppresses vascular endothelial growth factor and prevents tumour angiogenesis. Bevacizumab clearance was reported to be 26% higher in male solid tumour patients than in female patients, which is related to the fact that men have more muscle mass than women. Non-small cell lung cancer patients who had bevacizumab chemotherapy experienced more severe hypertension, neutropenia, and stomach pain than male patients.

6.5.6. Rituximab

Rituximab is a monoclonal antibody targeting the B cell surface protein CD20. Male patients with diffuse large cell lymphoma (DLBCL) had a higher clearance of rituximab (8.21 ml/h) than female patients (12.68 ml/h), and their elimination half-life is also longer. Better treatment outcomes were more noticeable in females than in males in the DLBCL treatment with rituximab. Only DLBCL patients who are treated with rituximab and are male GSTT1 deletion may be associated with a poor prognosis. Additionally, in both DLBCL and follicular lymphoma, male patients receiving rituximab treatment had a lower PFS than female patients (Müller et al., 2012).

7. Radiation therapy

In order to further individualize radiation therapy, it is proposed to take the genomic makeup of healthy cells into account. Radiotherapy should examine the biological and genetic makeup of normal tissue and tumors in contrast to systemic treatment methods (Andreassen et al., 2002). Although the total dosage largely determines the magnitude of this effect, the dose received by each portion of irradiated normal tissue and the volume of such tissue, ionizing radiation's effect on normal tissue, serves as a dose-limiting factor. According to how long after treatment is given, average tissue damage is classified as either acute toxicity (occurring shortly after treatment or within a few months). Radiation toxicity is affected by secondary determinants of damage, including host-related variables, comorbid disorders such as diabetes, collagen vascular diseases, nutritional state, age, and time from last surgery (Bentzen, 2006; Bentzen and Overgaard, 1994; Shires et al., 1995; Ugoretz, 2002).

According to the topic, there were 1.12–1.87 times as many radiation-sensitive genes in female donors than in men, suggesting that females could be more sensitive to radiation (Li et al., 2019). In the control group, females always had greater gene levels. The levels of the ATM, TGF-b1, SOD2, XRCC1, and XRCC3 genes changed over time after radiotherapy as the weeks went by. Particularly in male rats, higher toxicity was linked to collapse, and there was a correlation that may be considered statistically significant between the expression and the variable of ATM, SOD2, and XRCC1 and collapse in male rats. Even while male rats' ATM gene expression was originally lesser and tended to rise following radiation, the rise could not stop the emergence of a high rate of collapse. Our findings that gender was a substantial risk factor for radiation-induced lung damage were validated by experimental and clinical findings. TGF-b1 has been linked to radiation-induced pneumonia in patients with lung cancer who underwent treatment with three-dimensional conformal radiation therapy. In light of this, male patients can be administered drugs that boost ATM and TGF-b1 gene expression prior to radiotherapy to lessen lung toxicity induced by radiation (Cosar et al., 2022).

8. Conclusion

Men and women may respond differently to certain drugs regarding pharmacokinetics and pharmacodynamics. Because of this, it is indispensable to have an understanding of the gender differences in the way the body metabolizes drugs since these differences have the potential to impact both the safety and efficacy of medications. Prior to the treatment of women, doctors and the pharmaceutical industry need to create specific therapeutic goals for the pharmaceuticals that will be used. This will help to reduce the number of therapeutic adverse events that occur. It is necessary to decide whether the treatment should be evaluated based on clinical signs and symptoms or on the results of laboratory tests, whether the drug's toxicity will be evaluated based on clinical or laboratory assessment, and what factors will determine the appropriate treatment duration. In addition, one has to be familiar with and comprehend the fundamentals of clinical pharmacology, absorption, disposition, metabolism, and elimination as they relate to the medicine that will be used. In particular, the physician who is writing the prescription ought to have an understanding of the relationship between the drug dose, the drug concentration, and the desired biological effect at the site of action; the mechanism of action of the drug; and the impact of the chosen drug on the patient's signs, symptoms of adverse effects, and laboratory testing. Since the majority of the data on sex differences are typically collected through post hoc analysis, the conclusions that can be reached as a result are restricted. In the era of precision medicine, a patient's biological sex and gender need to be considered for treatment decisions. As such, the representation of women needs to be increased in clinical trials, and trials should be designed to allow meaningful subgroup analysis by sex for both drug response and drug toxicity.

Personalized medicine allows clinical oncologists, pharmacologists, and pharmacists to provide an accurate way of treating patients that are based on their unique traits, such as their genetic profile. Personalized medicine is critical in oncology, where there is more focus on prevention and surgical and chemoradiotherapy treatments can cause short-term side effects and have long-term effects on how the body works. Based on each person's pharmacokinetics and pharmacodynamics, there is evidence that men and women respond differently to anti-cancer drugs in terms of how well they work and how dangerous they are. There is evidence that sex affects how cancer works, how it looks, responds to treatment, and spreads. Sex is one of the most critical factors in figuring out how well chemotherapy will work and how harmful it will be, and it can also improve the person's pharmacogenomics in making personalized therapy. Future research should be planned with a primary focus on this subject to achieve a deeper comprehension of the fundamental processes behind disparities between the sexes. It will be easier to establish the extent to which these variances will have ramifications for clinical management if we get access to more detailed data.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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No data was used for the research described in the article.

References

Andreassen, C.N., Alsner, J., Overgaard, J., 2002. Does variability in normal tissue reactions after radiotherapy have a genetic basis - where and how to look for it? Radiother. Oncol. 64 (2). https://doi.org/10.1016/S0167-8140(02)00154-8.

Antohe, M., Nedelcu, R.I., Nichita, L., Popp, C.G., Cioplea, M., Brinzea, A., Hodorogea, A., Calinescu, A., Balaban, M., Ion, D.A., Diaconu, C., Bleotu, C., Pirici, D., Zurac, S.A., Turcu, G., 2019. Tumor infiltrating lymphocytes: the regulator of melanoma evolution (Review). Oncol. Lett. 17 (5). https://doi.org/10.3892/ol.2019.9940.

Bentzen, S.M., 2006. Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. Nat. Rev. Cancer 6 (Issue 9). https://doi.org/10.1038/nrc1950.

Bentzen, S.M., Overgaard, J., 1994. Patient-to-patient variability in the expression of radiation-induced normal tissue injury. Semin. Radiat. Oncol. 4 (2). https://doi.org/10.1016/S1053-4296(05)80034-7.

Bolufer, P., Collado, M., Barragán, E., Cervera, J., Calasanz, M.J., Colomer, D., Roman-Gómez, J., Sanz, M.A., 2007. The potential effect of gender in combination with common genetic polymorphisms of drug-metabolizing enzymes on the risk of developing acute leukemia. Haematologica 92 (3). https://doi.org/10.3324/haematol.10752.

Bond, G.L., Hu, W., Bond, E.E., Robins, H., Lutzker, S.G., Arva, N.C., Bargonetti, J., Bartel, F., Taubert, H., Wuerl, P., Onel, K., Yip, L., Hwang, S.J., Strong, L.C., Lozano, G., Levine, A.J., 2004. A single nucleotide polymorphism in the MDM2 promoter attenuates the p53 tumor suppressor pathway and accelerates tumor formation in humans. Cell 119 (5). https://doi.org/10.1016/j.cell.2004.11.022.

Brahmer, J.R., Dahlberg, S.E., Gray, R.J., Schiller, J.H., Perry, M.C., Sandler, A., Johnson, D.H., 2011. Sex differences in outcome with bevacizumab therapy: analysis of patients with advanced-stage non-small cell lung cancer treated with or without bevacizumab in combination with paclitaxel and carboplatin in the eastern cooperative oncology group trial 4599. J. Thorac. Oncol. 6 (1). https://doi.org/10.1097/JTO.0b013e3181fa8efd.

Cancer Over Time. from. https://gco.iarc.fr/overtime/en/dataviz/bars?sexes=1_2&sort_by=value2. (Accessed 6 December 2022).

Capone, I., Marchetti, P., Ascierto, P.A., Malorni, W., Gabriele, L., 2018. Sexual Dimorphism of Immune Responses: a new perspective in cancer immunotherapy. Front. Immunol. 9 (MAR). https://doi.org/10.3389/fimmu.2018.00552.

Cappuzzo, F., Ciuleanu, T., Stelmakh, L., Cicenas, S., Szczésna, A., Juhász, E., Esteban, E., Molinier, O., Brugger, W., Melezínek, I., Klingelschmitt, G., Klughammer, B., Giaccone, G., 2010. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol. 11 (6). https://doi.org/10.1016/S1470-2045(10)70112-1.

Cosar, R., Ozen, A., Tastekin, E., Sut, N., Cakina, S., Demir, S., Parlar, S., Nurlu, D., Kavuzlu, Y., Koçak, Z., 2022. Does gender difference effect radiation-induced lung toxicity? An experimental study by genetic and histopathological predictors. Radiat. Res. 197 (3). https://doi.org/10.1667/RADE-21-00075.1.

Crocetti, E., Mallone, S., Robsahm, T.E., Gavin, A., Agius, D., Ardanaz, E., Lopez, M.D.C., Innos, K., Minicozzi, P., Borgognoni, L., Pierannunzio, D., Eisemann, N., 2015. Survival of patients with skin melanoma in Europe increases further: results of the EUROCARE-5 study. Eur. J. Cancer 51 (15). https://doi.org/10.1016/j.ejca.2015.07.039.

Davidson, M., Wagner, A.D., Kouvelakis, K., Nanji, H., Starling, N., Chau, I., Watkins, D., Rao, S., Peckitt, C., Cunningham, D., 2019. Influence of sex on chemotherapy efficacy and toxicity in oesophagogastric cancer: a pooled analysis of four randomised trials. Eur. J. Cancer 121. https://doi.org/10.1016/j.ejca.2019.08.010.

Do, T.N., Ucisik-Akkaya, E., Davis, C.F., Morrison, B.A., Dorak, M.T., 2010. An intronic polymorphism of IRF4 gene influences gene transcription in vitro and shows a risk association with childhood acute lymphoblastic leukemia in males. Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 1802 (2). https://doi.org/10.1016/j.bbadis.2009.10.015.

Duma, N., Abdel-Ghani, A., Yadav, S., Hoversten, K.P., Reed, C.T., Sitek, A.N., Enninga, E.A.L., Paludo, J., Aguilera, J.V., Leventakos, K., Lou, Y., Kottschade, L.A., Dong, H., Mansfield, A.S., Manochakian, R., Adjei, A.A., Dronca, R.S., 2019. Sex differences in tolerability to anti-programmed cell death protein 1 therapy in patients with metastatic melanoma and non-small cell lung cancer: are we all equal? Oncol. 24 (11). https://doi.org/10.1634/theoncologist.2019-0094.

Foell, J., Hewes, B., 2007. T cell costimulatory and inhibitory receptors as therapeutic targets for inducing anti-tumor immunity. Curr. Cancer Drug Targets 7 (1). https://doi.org/10.2174/156800907780006841.

Gill, S., Loprinzi, C.L., Sargent, D.J., Thomé, S.D., Alberts, S.R., Haller, D.G., Benedetti, J., Francini, G., Shepherd, L.E., Seitz, J.F., Labianca, R., Chen, W., Cha, S.S., Heldebrant, M.P., Goldberg, R.M., 2004. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? J. Clin. Oncol. 22 (10). https://doi.org/10.1200/JCO.2004.09.059.

Global Cancer Observatory. (n.d.-a). Retrieved December 6, 2022, from https://gco.iarc.fr/.

Global Cancer Observatory. (n.d.-b). Retrieved December 6, 2022, from https://gco.iarc.fr/.

Gusella, M., Crepaldi, G., Barile, C., Bononi, A., Menon, D., Toso, S., Scapoli, D., Stievano, L., Ferrazzi, E., Grigoletto, F., Ferrari, M., Padrini, R., 2006. Pharmacokinetic and demographic markers of 5-fluorouracil toxicity in 181 patients on adjuvant therapy for colorectal cancer. Ann. Oncol. 17 (11). https://doi.org/10.1093/annonc/mdl284.

Gusella, M., Toso, S., Ferrazzi, E., Ferrari, M., Padrini, R., 2002. Relationships between body composition parameters and fluorouracil pharmacokinetics. Br. J. Clin. Pharmacol. 54 (2). https://doi.org/10.1046/j.1365-2125.2002.01598.x.

Hewer, A., Phillips, D.H., 1994. Different susceptibility to smoking-induced DNA damage among male and female lung cancer patients. Cancer Res. 54 (22). https://doi.org/10.1016/0169-5002(95)98701-b.

Hoensch, H., Morgenstern, I., Petereit, G., Siepmann, M., Peters, W.H.M., Roelofs, H.M.J., Kirch, W., 2002. Influence of clinical factors, diet, and drugs on the human upper gastrointestinal glutathione system. Gut 50 (2). https://doi.org/10.1136/gut.50.2.235.

Huang, R.S., Kistner, E.O., Bleibel, W.K., Shukla, S.J., Dolan, M.E., 2007. Effect of population and gender on chemotherapeutic agent-induced cytotoxicity. Mol. Cancer Therapeut. 6 (1). https://doi.org/10.1158/1535-7163.MCT-06-0591.

Jacobs, J.F.M., Nierkens, S., Figdor, C.G., de Vries, I.J.M., Adema, G.J., 2012. Regulatory T cells in melanoma: the final hurdle towards effective immunotherapy? Lancet Oncol. 13 (Issue 1). https://doi.org/10.1016/S1470-2045(11)70155-3.

Joerger, M., Huitema, A.D.R., van den Bongard, D.H.J.G., Schellens, J.H.M., Beijnen, J.H., 2006. Quantitative effect of gender, age, liver function, and body size on the population pharmacokinetics of paclitaxel in patients with solid tumors. Clin. Cancer Res. 12 (7 I). https://doi.org/10.1158/1078-0432.CCR-05-2069.

Khamly, K.K., Thursfield, V.J., Fay, M., Desai, J., Toner, G.C., Choong, P.F.M., Ngan, S.Y.K., Powell, G.J., Thomas, D.M., 2009. Gender-specific activity of chemotherapy correlates with outcomes in chemosensitive cancers of young adulthood. Int. J. Cancer 125 (2). https://doi.org/10.1002/ijc.24376.

Kim, H.I., Lim, H., Moon, A., 2018. Sex differences in cancer: epidemiology, genetics and therapy. In Biomolecules and Therapeutics 26. https://doi.org/10.4062/biomolther.2018.103, 4.

Kim, S.E., Paik, H.Y., Yoon, H., Lee, J.E., Kim, N., Sung, M.K., 2015. Sex- and gender-specific disparities in colorectal cancer risk. World J. Gastroenterol. 21 (17). https://doi.org/10.3748/wjg.v21.i17.5167.

Klimm, B., Reineke, T., Haverkamp, H., Behringer, K., Eich, H.T., Josting, A., Pfistner, B., Diehl, V., Engert, A., 2005. Role of hematotoxicity and sex in patients with Hodgkin's lymphoma: an analysis from the German Hodgkin Study Group. J. Clin. Oncol. 23 (31). https://doi.org/10.1200/JCO.2005.205.60.

Kovats, S., 2015. Estrogen receptors regulate innate immune cells and signaling pathways. Cell. Immunol. 294 (2). https://doi.org/10.1016/j.cellimm.2015.01.018.

Laffont, S., Seillet, C., Guéry, J.C., 2017. Estrogen receptor-dependent regulation of dendritic cell development and function. Front. Immunol. 8. https://doi.org/10.3389/fimmu.2017.00108. Issue FEB.

Lee, M.L., Chen, G.G., Vlantis, A.C., Tse, G.M.K., Leung, B.C.H., van Hasselt, C.A., 2005. Induction of thyroid papillary carcinoma cell proliferation by estrogen is associated with an altered expression of Bcl-xL. Cancer J. 11 (2). https://doi.org/10.1097/00130404-200503000-00006.

Li, S., Lu, X., Feng, J. bin, Tian, M., Wang, J., Chen, H., Chen, D.Q., Liu, Q.J., 2019. Developing gender-specific gene expression biodosimetry using a panel of radiation-responsive genes for determining radiation dose in human peripheral blood. Radiat. Res. 192 (4). https://doi.org/10.1667/RR15355.1.

Liu, K.A., Dipietro Mager, N.A., 2016. Women's involvement in clinical trials: historical perspective and future implications. Pharm. Pract. 14 (1). https://doi.org/10.18549/PHARMPRACT.2016.01.708.

Luo, Q., O'Connell, D.L., Yu, X.Q., Kahn, C., Caruana, M., Pesola, F., Sasieni, P., Grogan, P.B., Aranda, S., Cabasag, C.J., Soerjomataram, I., Steinberg, J., Canfell, K., 2022. Cancer incidence and mortality in Australia from 2020 to 2044 and an exploratory analysis of the potential effect of treatment delays during the COVID-19 pandemic: a statistical modelling study. Lancet Public Health 7 (6), e537–e548. https://doi.org/10.1016/S2468-2667(22)00090-1.

Mader, R.M., 2007. The potential of gender-specific tumor pharmacology. Pharmacogenomics 8 (3). https://doi.org/10.2217/14622416.8.3.271.

Marosi, C., 2006. Gender aspects of treatment and drug related toxicity in medical oncology. In: Wiener Medizinische Wochenschrift, vol. 156. https://doi.org/10.1007/s10354-006-0347-9. Issues 19–20).

Mitry, M.A., Edwards, J.G., 2016. Doxorubicin induced heart failure: phenotype and molecular mechanisms. In: IJC Heart and Vasculature, vol. 10. https://doi.org/10.1016/j.ijcha.2015.11.004.

Mollerup, S., Ryberg, D., Hewer, A., Phillips, D.H., Haugen, A., 1999. Sex differences in lung CYP1A1 expression and DNA adduct levels among lung cancer patients. Cancer Res. 59 (14).

Morgan, E., Arnold, M., Camargo, M.C., Gini, A., Kunzmann, A.T., Matsuda, T., Meheus, F., Verhoeven, R.H.A., Vignat, J., Laversanne, M., Ferlay, J., Soerjomataram, I., 2022. The current and future incidence and mortality of gastric cancer in 185 countries, 2020–40: a population-based modelling study. EClinicalMedicine 47, 101404. https://doi.org/10.1016/J.ECLINM.2022.101404.

Mueller, F., Büchel, B., Köberle, D., Schürch, S., Pfister, B., Krähenbühl, S., Froehlich, T.K., Largiader, C.R., Joerger, M., 2013. Gender-specific elimination of continuous-infusional 5-fluorouracil in patients with gastrointestinal malignancies: results from a prospective population pharmacokinetic study. Cancer Chemother. Pharmacol. 71 (2). https://doi.org/10.1007/s00280-012-2018-4.

Müller, C., Murawski, N., Wiesen, M.H.J., Held, G., Poeschel, V., Zeynalova, S., Wenger, M., Nickenig, C., Peter, N., Lengfelder, E., Metzner, B., Rixecker, T., Zwick, C., Pfreundschuh, M., Reiser, M., 2012. The role of sex and weight on rituximab clearance and serum elimination half-life in elderly patients with DLBCL. Blood 119 (14). https://doi.org/10.1182/blood-2011-09-380949.

Nipp, R.D., Greer, J.A., El-Jawahri, A., Traeger, L., Gallagher, E.R., Park, E.R., Jackson, V.A., Pirl, W.F., Temel, J.S., 2016. Age and gender moderate the impact of early palliative care in metastatic non-small cell lung cancer. Oncol. 21 (1). https://doi.org/10.1634/theoncologist.2015-0232.

Ortona, E., Pierdominici, M., Rider, V., 2019. Editorial: sex hormones and gender differences in immune responses. Front. Immunol. 10 (MAY), 1076. https://doi.org/10.3389/FIMMU.2019.01076/BIBTEX.

Pirker, R., Pereira, J.R., Szczesna, A., von Pawel, J., Krzakowski, M., Ramlau, R., Vynnychenko, I., Park, K., Yu, C.T., Ganul, V., Roh, J.K., Bajetta, E., O'Byrne, K., de Marinis, F., Eberhardt, W., Goddemeier, T., Emig, M., Gatzemeier, U., 2009. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 373 (9674). https://doi.org/10.1016/S0140-6736(09)60569-9.

Pirker, R., Pereira, J.R., von Pawel, J., Krzakowski, M., Ramlau, R., Park, K., de Marinis, F., Eberhardt, W.E.E., Paz-Ares, L., Störkel, S., Schumacher, K.M., von Heydebreck, A., Celik, I., O'Byrne, K.J., 2012. EGFR expression as a predictor of survival for first-line chemotherapy plus cetuximab in patients with advanced non-small-cell lung cancer: analysis of data from the phase 3 FLEX study. Lancet Oncol. 13 (1). https://doi.org/10.1016/S1470-2045(11)70318-7.

Ray Dorsey, E., Elbaz, A., Nichols, E., Abd-Allah, F., Abdelalim, A., Adsuar, J.C., Ansha, M.G., Brayne, C., Choi, J.Y.J., Collado-Mateo, D., Dahodwala, N., Do, H.P., Edessa, D., Endres, M., Fereshtehnejad, S.M., Foreman, K.J., Gankpe, F.G., Gupta, R., Hankey, G.J., et al., 2018. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 17 (11). https://doi.org/10.1016/S1474-4422(18)30295-3.

Regulations, Guidance, and Reports related to Women's Health. Fda (n.d.). https://www.fda.gov/science-research/womens-health-research/regulations-guidance-and-reports-related-womens-health. (Accessed 6 December 2022).

Rubin, J.B., Lagas, J.S., Broestl, L., Sponagel, J., Rockwell, N., Rhee, G., Rosen, S.F., Chen, S., Klein, R.S., Imoukhuede, P., Luo, J., 2020. Sex differences in cancer mechanisms. Biol. Sex Differ. 11. https://doi.org/10.1186/s13293-020-00291-x. Issue 1.

Shires, R., Lane, N.J., Inman, C.B.E., Lockwood, A.P.M., 1995. Microtubule systems associated with the septate junctions of the gill cells of four gammarid amphipods. Tissue Cell 27 (1). https://doi.org/10.1016/S0040-8166(95)80003-4.

Siegel, R.L., Miller, K.D., Jemal, A., 2016. Cancer statistics, 2016. CA A Cancer J. Clin. 66 (1). https://doi.org/10.3322/caac.21332.

Siegel, R.L., Miller, K.D., Jemal, A., 2017. Cancer statistics, 2017. CA A Cancer J. Clin. 67 (1). https://doi.org/10.3322/caac.21387.

Singh, S., Parulekar, W., Murray, N., Feld, R., Evans, W.K., Tu, D., Shepherd, F.A., 2005. Influence of sex on toxicity and treatment outcome in small-cell lung cancer. J. Clin. Oncol. 23 (4). https://doi.org/10.1200/JCO.2005.03.171.

Socié, G., Mary, J.Y., Esperou, H., Robert, D.V., Aractingi, S., Ribaud, P., Devergie, A., Toubert, M.E., Boudou, P., Cathelinau, B., Gluckman, E., Vexiau, P., 2001. Health and functional status of adult recipients 1 year after allogeneic haematopoietic stem cell transplantation. Br. J. Haematol. 113 (1). https://doi.org/10.1046/j.1365-2141.2001.02678.x.

Soldin, O.P., Mattison, D.R., 2009. Sex differences in pharmacokinetics and pharmacodynamics. Clin. Pharmacokinet. 48 (Issue 3). https://doi.org/10.2165/00003088-200948030-00001.

Spitz, M.R., Wei, Q., Dong, Q., Amos, C.I., Wu, X., 2003. Genetic susceptibility to lung cancer: the role of DNA damage and repair. Cancer Epidemiol. Biomark. Prev. 12 (8).

Stupp, R., Mason, W.P., van den Bent, M.J., Weller, M., Fisher, B., Taphoorn, M.J.B., Belanger, K., Brandes, A.A., Marosi, C., Bogdahn, U., Curschmann, J., Janzer, R.C., Ludwin, S.K., Gorlia, T., Allgeier, A., Lacombe, D., Cairncross, J.G., Eisenhauer, E., Mirimanoff, R.O., 2005. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N. Engl. J. Med. 352 (10). https://doi.org/10.1056/nejmoa043330.

Tevfik Dorak, M., Karpuzoglu, E., 2012. Gender differences in cancer susceptibility: an inadequately addressed issue. Front. Genet. 3 (NOV). https://doi.org/10.3389/fgene.2012.00268.

Topalian, S.L., Drake, C.G., Pardoll, D.M., 2012. Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity. Curr. Opin. Immunol. 24 (Issue 2). https://doi.org/10.1016/j.coi.2011.12.009.

Torre, L.A., Siegel, R.L., Ward, E.M., Jemal, A., 2016. Global cancer incidence and mortality rates and trends - an update. Cancer Epidemiol. Biomark. Prev. 25 (Issue 1). https://doi.org/10.1158/1055-9965.EPI-15-0578.

Ugoretz, R., 2002. Oxford textbook of oncology. JAMA, J. Am. Med. Assoc. 287 (24). https://doi.org/10.1001/jama.287.24.3266.

Wagner, A.D., Grothey, A., Andre, T., Dixon, J.G., Wolmark, N., Haller, D.G., Allegra, C.J., de Gramont, A., Vancutsem, E., Alberts, S.R., George, T.J., O'Connell, M.J., Twelves, C., Taieb, J., Saltz, L.B., Blanke, C.D., Francini, E., Kerr, R., Yothers, G., et al., 2021. Sex and adverse events of adjuvant chemotherapy in colon cancer: an analysis of 34 640 patients in the ACCENT database. J. Natl. Cancer Inst. 113 (4). https://doi.org/10.1093/jnci/djaa124.

Wagner, A.D., Oertelt-Prigione, S., Adjei, A., Buclin, T., Cristina, V., Csajka, C., Coukos, G., Dafni, U., Dotto, G.P., Ducreux, M., Fellay, J., Haanen, J., Hocquelet, A., Klinge, I., Lemmens, V., Letsch, A., Mauer, M., Moehler, M., Peters, S., Özdemir, B.C., 2019. Gender medicine and oncology: report and consensus of an ESMO workshop. Ann. Oncol. 30 (Issue 12). https://doi.org/10.1093/annonc/mdz414.

Wakelee, H.A., Wang, W., Schiller, J.H., Langer, C.J., Sandler, A.B., Belani, C.P., Johnson, D.H., 2006. Survival differences by sex for patients with advanced non-small cell lung cancer on Eastern Cooperative Oncology Group trial 1594. J. Thorac. Oncol. 1 (5). https://doi.org/10.1097/01243894-200606000-00011.

Wei, Q., Cheng, L., Amos, C.I., Wang, L.E., Guo, Z., Hong, W.K., Spitz, M.R., 2000. Repair of tobacco carcinogen-induced DNA adducts and lung cancer risk: a molecular epidemiologic study. J. Natl. Cancer Inst. 92 (21). https://doi.org/10.1093/jnci/92.21.1764.

Wilson, M.A., Buetow, K.H., 2020. Novel mechanisms of cancer emerge when accounting for sex as a biological variable. Cancer Res. 80 (1). https://doi.org/10.1158/0008-5472.CAN-19-2634.

Woitowich, N.C., Beery, A.K., Woodruff, T.K., 2020. A 10-year follow-up study of sex inclusion in the biological sciences. Elife 9. https://doi.org/10.7554/eLife.56344.

Wu, Y.L., Lee, J.S., Thongprasert, S., Yu, C.J., Zhang, L., Ladrera, G., Srimuninnimit, V., Sriuranpong, V., Sandoval-Tan, J., Zhu, Y., Liao, M., Zhou, C., Pan, H., Lee, V., Chen, Y.M., Sun, Y., Margono, B., Fuerte, F., Chang, G.C., et al., 2013. Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial. Lancet Oncol. 14 (8). https://doi.org/10.1016/S1470-2045(13)70254-7.

Xi, Y., Xu, P., 2021. Global colorectal cancer burden in 2020 and projections to 2040. Transl. Oncol. 14 (10), 101174. https://doi.org/10.1016/J.TRANON.2021.101174.

Yamamoto, H., Sekine, I., Yamada, K., Nokihara, H., Yamamoto, N., Kunitoh, H., Ohe, Y., Tamura, T., 2008. Gender differences in treatment outcomes among patients with non-small cell lung cancer given a combination of carboplatin and paclitaxel. Oncology 75 (3–4). https://doi.org/10.1159/000159268.

Zheng, L., Wang, Y., Schabath, M.B., Grossman, H.B., Wu, X., 2003. Sulfotransferase 1A1 (SULT1A1) polymorphism and bladder cancer risk: a case-control study. Cancer Lett. 202 (1). https://doi.org/10.1016/j.canlet.2003.08.007.

Zhou, C., Wu, Y.L., Chen, G., Feng, J., Liu, X.Q., Wang, C., Zhang, S., Wang, J., Zhou, S., Ren, S., Lu, S., Zhang, L., Hu, C., Hu, C., Luo, Y., Chen, L., Ye, M., Huang, J., Zhi, X., et al., 2011. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 12 (8). https://doi.org/10.1016/S1470-2045(11)70184-X.