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REVIEW

Sexual dimorphism in solid and hematological malignancies

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Abstract

Cancer represents a leading cause of death with continuously increasing incidence worldwide. Many solid cancer types in non-reproductive organs are significantly more frequent and deadly in males compared to females. This sex-biased difference is also present in hematologic malignancies. In this review, we present an overview about sex differences in cancer with a focus on leukemia. We discuss mechanisms potentially underlying the observed sex-biased imbalance in cancer incidence and outcome including sex hormones, sex chromosomes, and immune responses. Besides affecting the pathobiology of cancers, sex differences can also influence drug responses, most notably those to immune checkpoint blockers. Therefore, sex should become a relevant factor in clinical trial design in order to avoid over- or under-treatment of one sex.

Keywords Sex difference · Sex hormones · Immune system · Leukemia

Introduction

Cancer represents a complex group of diseases with multifactorial causes and is a major disease burden worldwide. Each year, more than 14 million patients are diagnosed with cancer and more than 50% of these cancer patients die. Therefore, cancer is one of the leading causes of morbidity and mortality in the world. In many countries, cancer is the second most common cause of death after cardiovascular diseases. However, due to significant improvement in treatment and prevention of cardiovascular diseases, cancer has or will soon become the number one cause of death in many parts of the world. Currently, cancer is the leading cause of death among women aged 40 to 79 years and among men aged 45 to 79 years [1, 2]. Additionally, elderly people are more susceptible to cancer and population aging is a growing problem in many countries. Thus, cancer will become an even greater health burden worldwide with an almost doubling of cancer cases from 14.1 million in 2012 to predicted 24 million by 2035 [2–6].

It is surprising that considering the impact of cancer on human health, relatively few comprehensive analyses of sex differences in cancer risk and survival based on robust data sources were conducted. Moreover, even less functional data exist about the mechanisms how sex differences affect cancer pathobiology and therapy responses. In this review, we summarize what is known about sex differences in solid and hematologic malignancies with a special focus on immune responses.

Sex differences in solid cancer

It is widely known that men and women are similar in many aspects; however, important biological and behavioral differences exist between the two sexes. These differences affect manifestation, epidemiology, and pathophysiology of many widespread diseases [7].

Sex plays a crucial role in the incidence, prognosis, and mortality in the majority of cancers in all age groups [2, 8–10]. Data from different parts of the world have shown that men are both at increased risk and have a worse prognosis with a consistently poorer survival compared with women for most cancers [2, 11–15]. From the estimated 14.1 million cancer cases in 2012

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around the world, 7.4 million cases occurred in men and 6.7 million in women [6]. Altogether, sex is an important factor in cancer pathogenesis independently of geographic location and age. In both males and females, the incidence rate of cancer increases substantially with age; however, the lifetime probability of developing cancer is 44.9% in males and 38.1% in females. Furthermore, cancer incidence rates are about 20% higher in men than in women, and the mortality rates are about 40% higher in males. Interestingly, the probability to develop cancer is higher in males despite a shorter life expectancy [16]. The analysis of age- and sex-specific cancer incidence data, from Cancer Incidence in Five Continents provided by the International Agency of Research on Cancer (IARC), documented the universal nature of the sex disparity in cancer, showing that males had higher incidence rates consistently across geographical regions [11, 17].

In 2018, the most common cancers expected to occur in males are prostate, lung, and colorectal cancers, altogether accounting for 42% of all cases in men. In women, the three most common cancers are breast, lung, and colorectal cancers, which collectively represent 50% of all cases [3, 5, 18, 19]. The most common causes of cancer-related deaths are lung, prostate, and colorectal cancers in men and lung, breast, and colorectal cancers in women. These four different cancers account for 45% of all cancer deaths, with 25% due to lung cancer [2, 5, 17–19].

The quantitative differences in incidence and outcome between males and females vary by cancer type (Table 1). The disparity between males and females in terms of mortality is twofold higher compared to the incidence. This is most likely due to sex-biased differences in the frequency of certain cancer types [8, 18]. For instance, the largest male-to-female sex disparities are documented in cancer of the esophagus, larynx, and bladder, in which incidence and death rates are about fourfold higher in men. In melanoma, incidence rates are about 60% higher in men than in women and mortality is doubled compared to females [20]. Other common cancer types with a high male-to-female ratio are colorectal cancer, lung cancer, non-Hodgkin lymphoma, hepatocellular carcinoma (HCC), and Kaposi sarcoma [2, 19]. The only neoplasms with higher incidence rates in women compared to men are anal, gallbladder, and thyroid cancers [4, 15]. Notably, in thyroid cancer, incidence rates are threefold higher in women than in men, while mortality is equivalent. This might be caused by the fact that the less aggressive histologic subtypes of thyroid cancer are more common in women, whereas the more aggressive histologic subtypes have similar distribution between sexes [21].

Overall, females have a lower risk and better prognosis than males in a wide range of cancer types unrelated to reproductive function. While it is obvious that cancer incidence rates reflect patterns of behavior and changes in medical practice, such as screening frequency, the underlying reasons for the survival disadvantage in males remain incompletely understood.

Table 1 Global incidence and deaths for solid cancers and hematological malignancies with the highest sex disparity in incidence

Cancer type	Incidence*		Mortality**	
	Men	Women	Men	Women
Solid cancers				
Larynx [a]	5.0	0.7	3.0	0.4
Bladder [a]	11.5	2.9	5.1	1.3
Esophagus [a]	10.2	3.4	9.9	3.0
Liver [a]	22.3	7.5	18.3	6.6
Nasopharynx [a]	2.0	0.7	1.4	0.4
Lung [a]	44.9	17.8	39.1	14.8
Stomach [a]	25.0	10.8	17.9	8.3
Gallbladder [b]	2.6	3.0	2.3	2.6
Thyroid [b]	2.2	4.4	0.6	0.7
Hematological malignancies				
Leukemia [a]	8.4	5.5	5.8	3.6
Acute myeloid leukemia [a]	1.8	1.2	1.6	1.0
Chronic myeloid leukemia [a]	0.6	0.4	0.4	0.3
Acute lymphocytic leukemia [a]	1.2	0.9	0.9	0.6
Chronic lymphocytic leukemia [a]	2.0	1.2	0.8	0.4
Non-Hodgkin lymphoma [a]	8.1	5.5	4.5	2.8

*The number of new cases per 100,000 people

**The number of deaths per 100,000 people

[a] Higher male/female ratio

[b] Higher female/male ratio

Mechanisms of sex differences in cancer

As mentioned before, the reasons for the increased cancer susceptibility in men are not well understood. In any case, possible causes for this phenomenon include differences in environmental exposures, lifestyle, endogenous hormones, sex chromosomes, epigenetics, and probably complex multidirectional interactions between these factors.

Reasons for the sex disparity in cancer can be mainly divided into environmental or acquired factors and intrinsic biological mechanisms. Initially, the observed higher cancer risk has been attributed to increased exposure of men to environmental carcinogens such as smoking, alcohol consumption, sunlight exposure, and occupational toxins [22–24]. It is evident that these are major cancer risk factors; however, sex-biased differences in them only offer partial explanation for the sex differences in cancer risk. Differences in environmental exposures between men and women are documented for some cancers with a sex disparity including lung, esophagus, larynx, liver [23], and melanoma [25]. However, this is not the case for many cancer types with a sex bias, where no external factors are known to be responsible for the sex disparity in cancer incidence and survival. Therefore, it is very likely that intrinsic sex-biased differences in hormones, genes, epigenetic

modifications, immune responses, and metabolism also have a strong influence on the sex-dimorphic differences in cancer risk and outcome besides the extrinsic factors [16, 26, 27].

Sex hormones

Sex hormones modulate gene expression and have an effect on the development of various cancers. Through their signaling pathways, they can affect multiple cancer-intrinsic and cancer-extrinsic mechanisms including proliferation, cell death, immune responses, oxidative stress, autophagy, and metabolism [8, 16, 28].

The interaction between cancer and non-steroid sex-related hormones, such as prolactin (PRL) [29–31], luteinizing hormone (LH) [32, 33], follicle-stimulating hormone (FSH) [34–36], and gonadotropin-releasing hormone (GnRH) [37, 38] has been studied for decades. These investigations showed a role of PRL in cancers arising from non-reproductive organs such as the liver, skin, or brain tissue [39–41]. However, the majority of publications indicated that these hormones are mainly promoting cancer of reproductive tissues including the prostate, ovary, and breast [29–39].

The largest body of literature exists about the effect of sex steroid hormones on cancer development in non-reproductive organs, indicating their relevance in sex-specific effects. The three major sex steroid hormone receptors are estrogen receptor alpha (ERα), estrogen receptor beta (ERβ), and androgen receptor (AR). They are activated by estrogen (17β-estradiol) and by androgens, including testosterone and dihydrotestosterone, respectively [42, 43]. Also, progesterone and its receptor are most likely involved in cancers of the non-reproductive organs including non-small cell lung cancer (NSCLC), colon and thyroid cancers [44–46].

Several studies exist showing that sex hormones contribute to differences in the cancer incidence between men and women. One of the most striking examples of increased cancer susceptibility of males versus females, due to steroid sex hormones is the HCC [2, 19, 28]. Estrogens inhibit the production of IL-6, which fosters progression of HCC. Consistently, IL-6 levels are higher in males leading to a higher risk for HCC development [47, 48]. In addition, male and female hormone receptors contribute to HCC in an antagonistic manner. AR stimulates, whereas ERα restrains proliferation of HCC cells by modulating anabolic metabolism of nucleotides and amino acids required for proliferation. The estrogen-dependent protection against HCC depends on the transcription factors Foxa1/2. The ablation of these transcription factors eliminates sex differences in mouse models by converting the tumor-suppressive role of estrogen into a tumor-promoting one [49, 50].

Several other cancer types including colon cancer, glioma, or melanoma exhibit higher incidence and aggressiveness in males and postmenopausal females compared with premenopausal females, supporting a protective role of estrogens also in these cancers [28]. One study indicates that estrogen decreases the production of secondary bile acid, which promotes development of malignant transformation in colonic epithelium [51, 52]. Consistently, estrogen hormone replacement therapy reduces the incidence of colorectal cancer in postmenopausal women, altogether further supporting the protective role of estrogens in this cancer [53]. Consistently, increased estrogen signaling leading to ERβ activation is a favorable prognostic marker, especially in colon cancer [54, 55].

In contrast to most other cancers, as described above, the incidence of thyroid cancer is significantly higher in females than in males [21]. One possible explanation could be an opposite role for sex steroid hormones in this context. Indeed, it was shown that AR expression in thyroid follicular cells reduces proliferation [56], while estrogen treatment induces proliferation and suppresses apoptosis [57].

Consistent with adult cancer, male children have overall higher incidence and mortality rates compared to female children [58]. There are only few exceptions to the male preponderance in childhood cancer including infant leukemia, thyroid cancer, melanoma, and alveolar soft part carcinoma. This finding that the male bias in cancer is also present in childhood is important because it suggests that other sex-related factors besides sex steroid hormones have an important influence on cancer.

Sex chromosomes and other genetic factors

Chromosomal aberrations can lead to increased cell proliferation. Often, these changes interfere with the normal cellular control mechanisms by disrupting proto-oncogenes and tumor suppressor genes and allowing additional alterations to occur in the genome. Cancer cells can gain multiple types of chromosomal aberrations during tumor progression, including rearrangements, deletions, and duplications of chromosomes. As a result, the genome becomes progressively unstable [59].

There are substantial genetic disparities between males and females contributing to differences in the incidence of a variety of cancers. The most substantial genetic difference between the two sexes is due to the X and Y chromosomes [8]. Interestingly, X chromosome-linked genes show variation in their expression among females. In female mammals, most genes on one X chromosome are silenced as a result of X chromosome inactivation. However, up to 25% of genes escape X-inactivation and are expressed by genes from both X chromosome resulting in increased gene dosage in women compared to men [60].

Such differential gene dosages are potential contributors to sexually dimorphic traits influencing cancer [61]. For example, one X-inactivation process involves transcriptional silencing and chromatin compaction promoted by long non-coding RNA X-inactive specific transcript (XIST) [62]. Some genes encoded on the X chromosome frequently escape XIST-mediated inactivation including the tumor suppressor gene UTX, which is involved in regulating the cell cycle progression from G1 to S phase [63]. In men, a UTX homolog termed UTY is present on the Y chromosome but its biologic activity is very low or absent. Therefore, UTY cannot compensate for UTX function leading to an altogether higher UTX gene dosage effect in females resulting in enhanced cancer suppression [64]. In addition, loss-of-function UTX mutations have also been found in renal carcinoma and esophageal squamous cell carcinoma, cancers that are more frequent in men than in women [65, 66]. This additional loss of UTX function would lead to a further increased susceptibility of males to these cancers.

There are also data suggesting lung cancer–promoting mechanisms in females. It has been reported that gastrin-releasing peptide (GRP), a bombesin-like peptide, is present in two actively transcribed alleles in women compared with men because of the presence of two X chromosomes. The GRP gene is located on chromosome Xp22, near a cluster of genes that escape X-inactivation, and this peptide is secreted by most lung tumor cells leading to increased cell proliferation in the lung [67].

The X chromosome contains the largest number of immune-related genes of the whole human genome. Therefore, X chromosome-linked immune regulatory genes, which are differentially expressed between males and females could potentially contribute to sexual dimorphisms in immune responses important for cancer surveillance. However, in this field, more research is required to elucidate which of the X chromosome-encoded immunoregulatory genes contribute to sex bias in anticancer immune responses. There are several X-linked microRNAs (miRNAs), which can influence the sex-specific expression of immune-related genes. For example, miR-98, miR-188-3p, miR-421, and miR-503, which can influence T cell receptor signaling among other functions, were some of the genes with higher expression in women compared to men [28, 68]. Interestingly, the X chromosome is also generally enriched in genes encoding miRNAs, with an almost twofold higher density compared to autosomes. Among these are several miRNAs with pro-oncogenic functions, such as miR-222 and miR-223 in gastric cancer [28, 69] and others with a positive prognostic association including miR-20b and miR-361 for oropharyngeal carcinoma [28, 69]. However, altogether, the function of most X chromosome-linked miRNAs remains unclear.

Besides X chromosome-related genes, alterations of the Y chromosome are frequent in cancer development. Recent studies demonstrate that loss of the Y chromosome is associated with various male-biased diseases, including some cancers. Loss of the entire Y chromosome has been reported not only in prostate cancer but also in pancreatic [70], colorectal [71], and bladder cancers [72], all of which have a male prevalence. The same effect has been observed with short-arm deletions of the Y chromosome [28, 73]. This suggests a protective effect of Y chromosome genes against cancer.

In contrast, the three Y chromosome genes SRY, RBMY, and TSPY have the potential of promoting cancer development, which may be mediated, by inducing an increase of X-linked AR expression or activity. Chromosomal amplification of a region adjacent to SRY has been found in male patients with HCC, possibly contributing to the higher incidence in males, due to increased AR expression promoting HCC proliferation. Vice versa, SRY ablation can impair HCC development, which further corroborates the tumor-promoting role of SRY [74]. RBMY and TSPY both of which can enhance AR expression are aberrantly activated in male HCC [75]. Interestingly, its homolog TSPY on the X chromosome, TSPX, can be tumor suppressive by acting as a co-activator of AR and AR variants, which promote certain tumor types (please see above) [76].

An interesting phenomenon that has been described in colorectal cancer is the “feminization” of male cancer cells. A subset of colorectal carcinoma male patients (46%) exhibited a feminization phenomenon in the form of gains of X chromosomes (or an arm of X) and/or losses of the Y chromosome. Feminization of cancer cells was significantly associated with microsatellite stabilization and wild-type B-Raf proto-oncogene (BRAF) gene status, a proto-oncogene with a negative prognostic impact in colorectal and other cancers if mutated [77].

Other genetic mechanisms besides sex chromosomes were found to be associated mechanisms with sex differences in cancer. For example, the lower incidence of bladder cancer in women has been correlated with the sulfotransferase 1A1 (SULT1A1) histidine (His) genotype. It was reported that this genetic polymorphism of SULT1A1 significantly decreased the risk of bladder cancer exclusively in women [78]. However, the underlying mechanisms are currently unknown and warrant functional studies.

In non-small cell lung cancer (NSCLC), which is one of the most common cancers [3], it has been observed that tumors in women are different compared to those in men because of differential gene expression between female and male patients. For instance, some protective genes encoding carcinogen-metabolizing enzymes like CYP1A1 (aryl hydrocarbon hydroxylase) or GSTM (glutathione *S*-transferase Mu 1) are significantly higher expressed in female compared to male smokers [79]. However, the data are only correlative at this point and further study is required to better understand the functional consequences of the different CYP1A1 and GSTM

levels in females versus males and whether they have a protective effect in tobacco-induced carcinogenesis.

P53 is an important tumor suppressor gene controlling cell cycle progression, DNA integrity and survival of cells exposed to DNA damaging agents [80]. Similarly to the effect observed for gastrin-releasing peptide receptor (GRPR), a higher frequency of G to T transversion was found in the p53 gene in lung tumors of women leading to a higher frequency of p53 inactivation [81]. This mutation is an early critical event in lung carcinogenesis and resistance to therapies; thus, a higher frequency of p53 loss is a disadvantage in females [80].

Mutations in important lung cancer driver genes have been found more frequently in NSCLC tumors from women compared to men resulting in a constitutive activation of downstream pro-proliferative pathways [82]. Similarly, mutations in the oncogene Kirsten rat sarcoma virus (KRAS) are more frequent in females compared to males [83, 84]. While historically more men than women have died from lung cancer as a result of higher numbers of male smokers, non-smoking women may be more susceptible to develop lung cancer compared to non-smoking men [79, 85]. This notion is further corroborated by the fact that also other driver alterations including epidermal growth factor receptor (EGFR) [86], BRAF [87], anaplastic lymphoma kinase (ALK) [88], or ROS proto-oncogene 1 (ROS1) [89] are more common in female never- or light smokers.

Epigenetics

Environmental and lifestyle factors can have a sex-specific influence on the epigenome. Furthermore, sex hormones can influence DNA methylation and chromatin conformation [90, 91]. In postmenopausal women treated with estrogen replacement, a higher methylation of long interspace nuclear element (LINE) was observed probably resulting in higher genomic stability because hypomethylation of LINE is associated with genomic instability [92].

Overall, DNA methylation and chromatin remodeling represent important mechanisms for X chromosome inactivation, and therefore, these processes have an important influence on sex differences caused by escape from X-inactivation. This does not only affect the X chromosome because it was shown that growth hormone (GH) signaling induces a sex-biased effect on chromatin remodeling via FoxA and STAT5 in males but not in females [93, 94]. Altogether, chromatin states are a major determinant of sex-biased chromatin accessibility and gene expression.

In addition, quantitative profiling of DNA methylation of a small panel of genes including ESR1, MTHFR, CALCA, and MGMT showed that males have substantially higher methylation levels [95]. Consistently, males exhibit substantially higher methylation levels of the RASSF1A promoter, one of the most frequent epigenetic inactivation event detected in NSCLC and small cell lung cancer (SCLC) types leading to lower activity of this important tumor suppressor [96, 97]. There are currently few reports implicating epigenetic changes in the sex disparity in cancer susceptibility, but the future epigenetic epidemiology studies are likely to test these possibilities [16, 91, 96, 98].

Immune system

There are substantial sex-biased differences in infection and autoimmunity suggesting that the immune system differs between men and women [99]. Men are more prone to infections and cancer, which could be explained by inferior immune surveillance mechanisms compared to women. Immune surveillance is a major defense mechanism against cancer and infectious diseases. Sexual dimorphisms in innate and adaptive immune responses were shown to contribute to differences in cancer outcome and responses to therapies in males versus females [8, 16]. This sex-bias in anti-cancer immune responses is due to different mechanisms: the expression of sex chromosome-linked genes, the effects of the sex hormones, and sex-specific environmental factors [100].

Sex steroid hormones exert their biological effects through hormone receptors expressed by different types of immune cells. Hormone receptor signaling can affect immune responses differentially in males and females, which can contribute to the sex-biased incidence rates of cancer [16, 99]. Literature indicates that ERs are present in B and T lymphocytes, neutrophils, macrophages, natural killer (NK) cells, mast cells, and dendritic cells (DC) [101–104]. ARs are expressed in macrophages, mast cells, and T and immature B lymphocytes [104, 105]. Therefore, sex hormones can influence the development and function of multiple immune cell populations, shaping innate and adoptive immune responses. Generally, adult females mount stronger innate and adaptive immune responses than males, usually resulting in faster clearance of pathogens [99, 106]. Interestingly, male infants can produce higher inflammatory responses than female infants; however, after puberty, inflammatory responses are consistently higher in females than in males, suggesting an important role of sex hormones in the sex bias of immune responses [99].

One important effect of the female sex hormone estrogen is that it promotes immune responses while the male sex hormone testosterone acts immunosuppressive. Estrogens enhance immune responses by increasing the following mechanisms: antibody-mediated responses to exogenous antigens, T cell cytotoxicity, activation of antigen-presenting cells, and secretion of pro-immune cytokines and chemokines [107]. Estrogens promote the anti-tumoral pro-inflammatory functions of macrophages in a dose-dependent manner by promoting the secretion of pro-inflammatory cytokines such as IL-12 and IL-1β [107]. In addition, they promote proliferation of macrophages. Estrogen can also inhibit immunosuppressive

neutrophils and increase DC differentiation and activation [103]. Furthermore, estrogens increase NK cytotoxicity and the production of pro-inflammatory cytokines including IL-1, IL-6, and TNFα. They also promote B cell development and humoral immune responses by increasing the levels of IgG and IgM. As a consequence, females elicit stronger humoral immune responses compared to males [16, 99, 104, 108].

In contrast, studies indicate that androgens can diminish immune responses by decreasing antibody production, T cell proliferation, and major histocompatibility complex class II (MHC II) antigen expression by antigen-presenting cells. Males have higher NK cell frequencies than females, but androgens decrease their cytotoxicity and stimulate the production of the immunosuppressive cytokine IL-10. In addition, the phagocytic activity of neutrophils and macrophages is lower in males than in females. Antigen-presenting cells (APCs) from males are less efficient at presenting peptides [16, 99, 108, 109]. In concordance, females show a higher CD4:CD8 ratio with a higher absolute CD4 cell count and a higher fraction of activated $CD4^+$ T cells compared to men.

Sex hormones can also influence different sets of T-helper cells (Th) with important roles in adaptive immunity including Th1 cells generating $CD8^+$ T cell-mediated type 1 responses and Th2 cells promoting humoral responses. It was demonstrated that estrogen and progesterone enhance type 2 and suppress type 1 responses in females, whereas testosterone suppresses type 2 responses and shows an inconsistent pattern for type 1 responses in males [108, 110].

Taken together, these studies illustrate that sex steroids are potent regulators of immune responses, which can contribute to the sex-specific incidence rates and outcomes in cancer. Based on the findings described above, one would hypothesize that the advantage for females could be caused by enhanced anti-cancer antibody dependent cell-mediated cytotoxicity (ADCC) due to increased humoral responses and antigen-production. In addition, increased activity and cytotoxicity of NK cells could contribute to the favorable outcome in females. However, currently, these are hypotheses because no data exist on the influence of sex on anti-cancer immune responses. Therefore, mechanistic studies are necessary to dissect sex-biased effects in anti-tumor immune responses.

Other factors

Autophagy represents an important mechanism capable to prevent cancer occurrence and progression [111]. Several studies refer to a role of autophagy in sex-specific tumor models. One example in human cancer is that monoallelic deletions of *beclin 1* are more prevalent in females. This could lead to higher cancer susceptibility because targeted mutant mice with heterozygous disruption of *beclin 1* show decreased autophagy. They are more prone to the development of spontaneous tumors including lymphomas, lung carcinomas, hepatocellular carcinomas, and mammary precancerous lesions [112]. However, the underlying molecular mechanisms especially with respect to whether they occur in humans are poorly defined.

Metabolism also has an important impact on cancer development and progression. Reduced ERα signaling and aromatase deficiency lead to compromised conversion of androgens to estrogens, which is associated with increased obesity, a risk factor for cancer development [113]. Oxidative stress is a crucial factor promoting cancer progression and therapy resistance due to induction of genetic instability and hypoxia-induced reactive oxygen species (ROS) [114]. It is known that males express lower amounts of anti-oxidant enzymes, resulting in more oxidative stress compared to females [115]. Similarly, exposure to ultraviolet light has a more detrimental effect in males due to enhanced immunosuppression in the skin leading to a higher susceptibility for skin cancer.

The higher incidence of thyroid and gallbladder tumors in women, mentioned above, are most likely due to a higher prevalence of benign thyroid disease and gallbladder stones, which are known to be risk factors for these cancers [116].

Sex differences in efficacy and toxicity of chemotherapy

The outcome of advanced-stage cancer patients depends to a great extent on their capability to tolerate and respond to treatment. Therefore, sex-biased differences in efficacy and toxicity of chemotherapies can contribute to differences in outcome between sexes. Indeed, sex-related differences at the genetic and molecular levels can affect responses to chemotherapies [8]. It is very likely that sex differences in drug pharmacokinetics and pharmacodynamics play a role in drug efficacy. For instance, gastrointestinal motility has been shown to be affected by sex hormones leading to a slower transit time in females than in males, which can lead to differences in uptake of oral drugs [117].

Literature suggests that women are more prone to develop side effects than men due to lower clearance of anti-cancer drugs from the circulation, which is mostly due to sex differences in drug metabolism [8, 108]. For instance, women develop stomatitis, alopecia, and diarrhea after treatment with 5-FU more frequently than men due to a lower activity of dihydropyrimidine dehydrogenase (DPD) [118]. In addition, female patients have a 20% lower clearance of paclitaxel compared to men leading to higher frequencies of leukopenia in women [8, 119]. Similarly, bevacizumab is cleared less efficiently from the circulation of females leading to more severe hypertension and neutropenia after treatment in women [120]. In addition, chemotherapy-induced nausea is more frequent in females due to a lower activity of anti-emetic drugs [8, 121].

Besides chemotherapy, targeted therapies including immune checkpoint blockers (ICB) are increasingly used to treat patients. Program cell death protein (ligand) 1 (PD-(L)1) inhibitors block the interaction between the PD-1 receptor expressed by cytotoxic T cells and PDL-1, which is aberrantly expressed by cancer cells and suppresses T cell responses. Thus, this blockade of this immune checkpoint leads to increased anti-tumor T cell responses. Anti-PD-(L)1 antibodies can induce durable anti-tumor responses, including stabilization of the disease and partial or complete remissions, as observed in a fraction of patients with advanced cancers including NSCLC, melanoma, non-Hodgkin lymphoma, and bladder, head and neck, and renal cell cancers [122]. In addition, blockade of cytotoxic T lymphocyte antigen 4 (CTLA-4) can increase T cell priming in lymphatic organs and anti-CTLA4 antibodies are in routine clinical use in melanoma. Interestingly, some studies suggest that sex can influence the response to cancer immunotherapy. One recent meta-analysis of randomized controlled trials with anti-PD(L)1 and anti-CTLA-4 antibodies suggests a significant survival advantage for males compared to females (HR 0.72 in male patients vs. 0.86 in female patients, $p = 0.0019$) [123]. This overall difference between a favorable outcome for males versus females upon immune checkpoint blockade was also corroborated in another meta-analysis [124]. The underlying mechanistic reasons for the discrepant outcome between males and females are currently not well understood. More research is needed in order to develop a better understanding on whether pharmacokinetic or differences in the strength of the anti-tumor immune responses upon ICB are different between males and females. However, these findings underline the necessity to adapt the design of clinical trials for the detection of sex differences in treatment efficacy.

Sex differences in hematological malignancies/leukemia

Hematological malignancies comprise a group of cancers affecting the blood, bone marrow, lymph, and lymphatic system, among which are the leukemias. Leukemia is caused by an overproduction of aberrant white blood cells. There are four main types of leukemia: acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), and acute myeloid leukemia (AML) [125]. Leukemia is among the ten most frequent cancers in incidence and mortality causing approximately 4% of deaths from all cancers worldwide [19]. Sex disparity is similar in leukemia compared to solid cancer. Altogether, males have a higher incidence and mortality of leukemia with incidence rates of 17.6 and 10.8 per 100.000 man/woman per year, respectively. The mortality rate is 5% higher in males compared with females during the first 5 years after diagnosis (mortality rates of 9.0 vs. 5.0 per 100.000 man/woman per year respectively) [3, 9, 10, 126].

As for most cancer types, the incidence of leukemia increases with age. However, cancer is the second most common cause of death among children aged 1 to 14 years and leukemias account for 29% of all childhood cancers [2]. As mentioned above, generally, male children have a similar disadvantage compared to adults in cancer incidence and outcome. Infant leukemia, occurring between birth and 2 years, represents one exception with female infants having a higher incidence [16]. During childhood, estrogen and androgen levels are very low and not much different between males and females suggesting prenatal programming of gene expression as a possible explanation for the female bias in infant leukemia [127].

In ALL, no significant differences are present between the sexes in the age group under 10 years, in which ALL predominates over other leukemias, while a marked male excess of cases emerges after puberty and in older age groups [16]. In adult ALL, sex-biased differences become evident, with incidence rates of 1.9 and 1.6 per 100.000 man/woman and mortality ratios of 0.5 and 0.4 per 100.000 man/woman [128].

In AML, the published studies are more contradictory. Depending on the age group and cohort analyzed, some studies showed a sex-biased difference with a disadvantage in males concerning incidence and mortality [128] while no significant differences between sexes have been reported in other publications [129, 130]. It was described that females showed a substantially increased survival benefit compared to their male counterparts in patients diagnosed between the age of 15 and 24 years and thereafter but not before puberty, which points to a function of sex hormones in mediating these effects [2, 19, 129].

With regard to lymphoma, non-Hodgkin lymphoma (NHL) shows a stable male excess in all age groups during childhood and adolescent periods, as well as in adults. Interestingly, Hodgkin lymphoma (HL) shows an age-dependent variation between sexes. The overall incidence of HL in children is greater in females than in males, but the sex distribution is age dependent, with the striking male-to-female ratio in HL before puberty when the disease is rare, which is reversing to a higher female-to-male ratio in adolescents when HL becomes more common [131].

CML and CLL are extremely rare during childhood. Similarly to the previously described leukemias, during adulthood CML and CLL display male excess regarding incidence (in CML the ratios are 2.4 vs. 1.4, in CLL 6.4 and 3.3 per 100.000 man/woman, respectively) and mortality (in CML, the ratios are 0.4 vs. 0.2, in CLL 1.9 and 0.8 per 100.000 man/woman, respectively) ratios [2, 132, 133].

Several hypotheses to explain reasons for the male preponderance of leukemia and NHL have been proposed. For

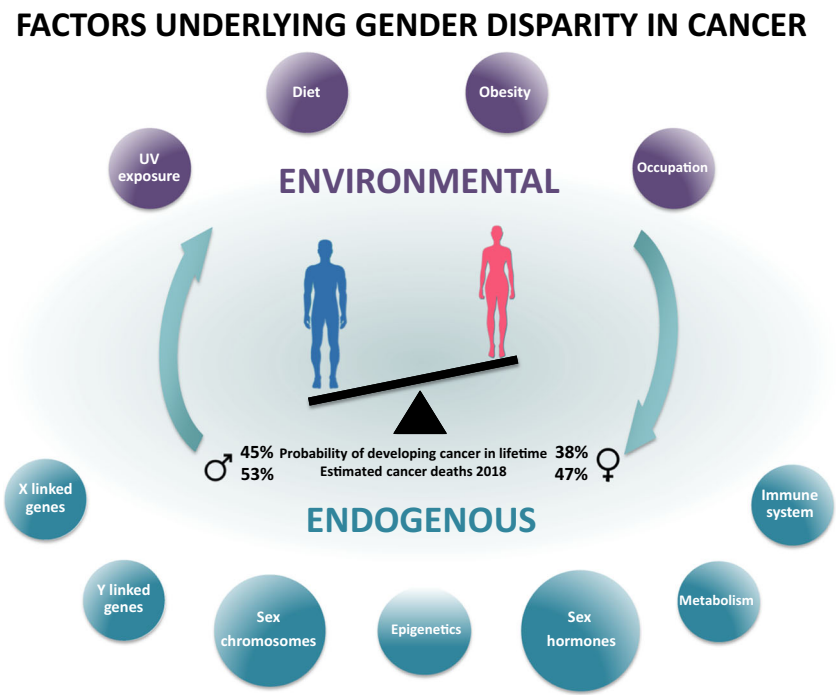

Fig. 1 Endogenous and environmental factors contributing to sexual dimorphism in cancer

instance, the increased incidence rate of leukemias in men has been attributed to occupational exposures including organic solvents. However, there has been no conclusive documentation of any occupational hazard, which would lead to the sex disparity observed in hematologic malignancies [128]. Therefore, it is rather likely that the similar mechanisms as described above in solid cancer contribute to the sex disparities in leukemia and lymphoma.

Again, the steroid sex hormones represent important factors influencing sex bias in leukemia and lymphoma. ALL is more likely to occur in men, which can be due to the lower estrogen levels compared to females. Estrogen inhibits nuclear factor kappa β (NF-κβ), which regulates the transcription of interferon regulatory factor 4 (IRF4). IRF4 is involved in the differentiation of B and T cells and is overexpressed in B cell malignancies including lymphoma as a result of NF-κB hyperactivation. IRF4 polymorphisms are associated with the incidence of ALL and are more frequent in men. It has been reported that IRF4 polymorphisms are associated with higher susceptibility in men to CLL and NHL, too [134]. Thus, a combination of intronic polymorphism of IRF4 and lack of estrogen might predispose men to leukemia and lymphoma [134]. Thus, the protective effect of estrogens in solid tumors extends to hematological malignancies, especially ALL and NHL [8, 28].

Another explanation for the sex difference in hematologic malignancies is attributed to sex chromosome-related mechanisms. Acquired loss of chromosome Y or chromosome X is more frequently observed in elderly male patients with blood cancer compared to females. The presence of these abnormalities suggests a higher genetic instability of leukemia cells in males which can contribute to the progression of the leukemia [135].

Genetic polymorphisms can also contribute to the sex-biased incidence of hematologic malignancies. It was reported that male patients with ALL had a higher incidence of a deletion in the glutathione *S*-methyltransferase T1 (GSTT1) gene compared to females. This deletion results in the abrogation of enzymatic activity leading to inefficient detoxification of a wide range of potential environmental carcinogens [136]. Similarly, a polymorphism resulting in the substitution of C to T in NAD(P)H:quinone oxidoreductase 1 (NQO1), an enzyme that catalyzes free radical detoxification, was associated with a higher incidence of ALL and AML only in males, but not in females [136].

Altogether, substantially less is known about the underlying reasons of sex disparity in hematologic malignancies. However, similar to the mechanisms described in solid cancer, genetic and steroid sex hormone-induced effects were shown to contribute to sex-biased effects in leukemia and lymphoma.

Conclusions

Sex has a significant influence on incidence, mortality, and treatment responses in cancer. Male sex is consistently associated with increased risk and higher excess mortality for most cancer types; however, the underlying reasons are not entirely understood. Several endogenous and environmental factors can contribute to the sex disparity in cancer epidemiology (Fig. 1). Due to the high impact of cancer for global health, further research is needed in order to better dissect

mechanisms of sex bias in cancer. In addition, sex-specific differences in treatment outcome, especially after immune checkpoint blockade warrant adaptation in clinical trial protocols, with determination of pharmacokinetics in males versus females and with separate randomization groups between males and females.

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