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Sex disparities in cancer

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ABSTRACT

Sex is a key biological factor affecting the development of many cancer types. There are considerable differences between male and female subpopulations in terms of cancer incidence, prognosis and mortality. Recent studies have extensively characterized the sex-biased molecular changes in cancer patients. Further efforts should be made to develop sex-specific cancer prevention and therapeutic strategies.

1. Introduction

Sex is one of the most important factors affecting many biological processes and has a profound impact on the development and progression of various diseases, including cancer. Substantial evidence has shown considerable differences between male and female subpopulations in terms of cancer incidence, prognosis, mortality and treatment response. The reasons underlying these observed differences are complicated, but generally can be attributed to (i) external factors such as sex-biased social behaviors — smoking, alcohol consumption and delayed diagnosis, and (ii) internal factors, including sex chromosomes, hormone levels, and sex-biased molecular changes. Here, we review sex disparities in cancer incidence and mortality for common primary cancer types, then present the molecular differences between male and female patients, and discuss the related clinical implications.

1.1. Disparities in cancer incidence

According to the statistics of cancer epidemiology, the incidence of many primary malignant tumours is significantly different between males and females. These studies have systematically evaluated susceptibility to cancer by comparing the tumour incidence between males and females after adjusting for age. The noted differences have then served as a starting point to investigate the sex-related pathogenesis of certain cancer types.

In the United States, according to the newest data acquired from the Surveillance, Epidemiology, and End Results Program (SEER), in 2019, many primary malignant tumours showed disparity in incidence between males and females after age adjustment and delay adjustment, and the male-to-female cancer incidence ratio from high to low was as follows: cancers involving the oral cavity& pharynx (2.63) (pharynx alone, 4.32), esophagus (3.61), larynx (3.96), urinary bladder (3.37), liver & intrahepatic bile duct (2.40), gall bladder and biliary tract (0.91), anus (0.51), and thyroid (0.39) [1] (Fig. 1).

Some other cancer types also show differences in incidence between males and females. In the United States in 2019, the incidence of lung cancer was the second highest of all cancer types among both males and females [1]. Although a higher incidence of lung cancer occurs consistently among males than females in the general population, with a male-to-female ratio varying from 1.5 to 20, the incidence in females is increasing while that in males is dropping in many developed countries. This phenomenon may be partially attributed to the sex-specific differences in social and historical characteristics. Unlike lung cancer, females are more likely to develop thyroid cancer than males. Moreover, in recent years, there has been no significant change in the male-to-female incidence rate ratio for thyroid cancer, but the overall incidence continues to rise at a rate of > 5% per year [2]. This pattern may be related to the differential expression level of ERα/ERβ between males and females, along with greater attention to and treatment of thyroid nodules in the past few years. In the United States, Europe and

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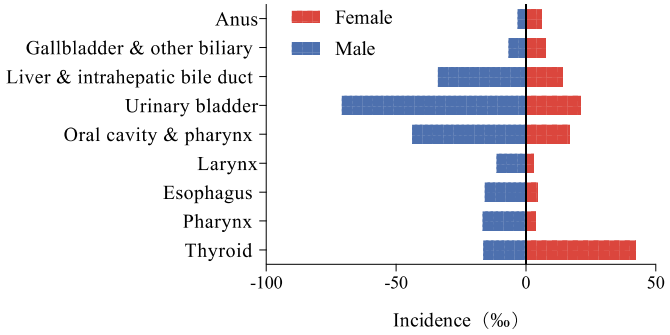

Fig. 1. Sex disparities in cancer incidence.

other developed countries, the overall incidence of colorectal cancer is declining; whereas in low-income countries, the overall incidence is rapidly rising [3]. The male-to-female incidence rate ratio of colorectal cancer is affected by age, anatomical location, ethnicity and other factors, suggesting that the sex differences in susceptibility to colorectal cancer are due to a combination of some genetic and molecular factors, metabolism, the regulatory environment and other factors. The incidence of esophageal cancer shows quite significant regional and ethnic differences, with males having a higher incidence rate than females [4]. Globally, the esophageal cancer incidence rate in males is 3–4 times higher than that in females. There is a slight male predominance in the incidence of primary brain and central nervous system tumours according to the latest report from the Central Brain Tumor Registry of the United States. This pattern applies to low-grade lesions as well as grade III and IV tumours [5].

1.2. Disparities in cancer mortality

For a few decades, analyses of the statistics of cancer epidemiology have shown that a patient's sex affects his/her prognosis for a variety of primary malignant tumours. Compared to female patients, male patients are generally associated with higher mortality and worse survival times. Across different cancer types, the male-to-female mortality rate ratios show greater disparities but the differences in patient survival times between males and females are less significant [6]. In 2019, according to the SEER database, the male-to-female mortality rate ratio of primary cancer types in the United States was 1.17 [1].

U.S. mortality rates are higher for males than females with the most common cancer types [6]. In 2019, the male-to-female cancer mortality rate ratio was as follows, listed from high to low: cancers involving the esophagus (3.77), larynx (3.56), oral cavity & pharynx (2.45) (pharynx alone, 2.99), urinary bladder (2.38), liver & intrahepatic bile duct (1.88), thyroid (0.79), gallbladder & other biliary tract (0.61), and anus (0.61) [1] (Fig. 2).

Lung cancer seems to have the highest mortality rate among both males and females in the United States [1]. As with lung cancer incidence, the associated mortality shows a similar pattern in that the male-to-female mortality rate ratio has gradually decreased: lung cancer mortality is decreasing among males, while it continues to increase among females. There is a noteworthy difference in esophageal cancer mortality between males and females, and the male-to-female mortality rate ratio is much higher than that incidence ratio, which may be because sex is an independent prognostic factor in esophageal cancer, with females who have this disease experiencing longer survival times than males [7]. The urinary bladder mortality rate in the United States is 2–3 times higher among male patients; but female patients have worse outcomes. This may be due to various factors, including sex differences in hormones, metabolic enzyme activity, and delayed diagnosis in females [8]. Liver cancer also shows great disparity in mortality rates between male and female patients, with a male-to-female ratio of 1.50 in 2016. One reason may be that androgen receptors enhance the replication ability of the virus, and the receptor–virus interaction triggers the expression of genes that are associated with liver cancer [9].

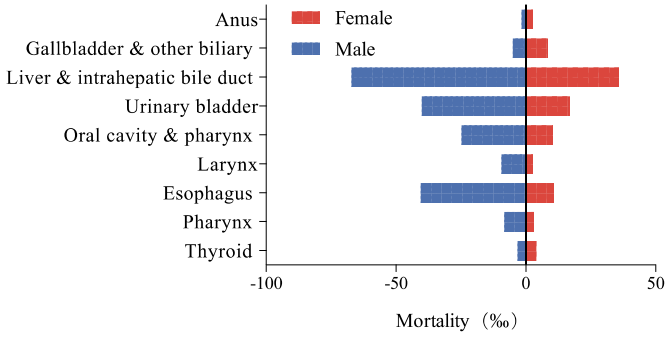

Fig. 2. Sex disparities in cancer mortality.

1.3. Disparities at the molecular level

Although extensive efforts have been made to characterise the sex-biased patterns of cancer epidemiology, the molecular causes underlying such sex disparities remain still largely unknown. Over the last decade, studies have pinpointed the individual molecular changes related to sex bias in cancer. These studies can be generally classified into three groups. (i) Germline variants: these studies usually compare the germline DNA of cancer patients to that of healthy people (controls) to identify the SNPs associated with conferring risk or protection among one sex. A large body of literature has accumulated on this topic. (ii) Gene expression: these studies employ microarrays or RNA-seq to compare the sex-biased gene expression patterns between male and female patients. Sex chromosome genes have been a particular focus. (iii) Somatic alterations: these studies identify the sex-biased features of somatic alterations (e.g., copy number gain/loss or somatic mutations) between male and female patients. We recently used molecular data from The Cancer Genome Atlas (TCGA) to perform a comprehensive analysis of the molecular differences between male and female patients across various cancer types [10]. Our analysis employed multi-dimensional molecular data, including somatic mutations, somatic copy number alterations, DNA methylation, and the expression of mRNA, miRNA, and proteins. Combining the signals from various data, our study revealed two groups of cancer types: the “weak sex effect” group, which contains limited numbers of sex-biased genes; and the “strong sex effect” group, which contains much more extensive sex-biased gene signatures. Importantly, the cancer types in the strong sex effect group show more sex-biased incidence and mortality rate ratios than those in the weak sex effect group, suggesting a considerable contribution of genetic disparities to the bias observed in cancer epidemiology. Below, we summarise several gene-based biological themes related to sex differences.

Immune-related genes. TNFRSF8 (CD30), CD52 and PDCD1 (PD-1) represent immune checkpoints that are more frequently lost in males, which may contribute to sex-biased clinical responses to immunotherapy. In childhood acute lymphoblastic leukaemia (ALL), genetic changes identified with sex bias are mostly related to the immune system. Several polymorphisms in major histocompatibility complex DR beta 4 (HLA-DRB4: rs2395185) and interferon regulatory factor 4 (IRF4: rs12203592) show risk that is only related to boys [11,12]. All of these genes are crucial to the immune system through their role in presenting the peptides derived from extracellular proteins. Markers in the interferon gamma gene (IFNG: rs2069727), heat shock 70 kDa protein 1B (HSPA1B: rs1061581) and human hemochromatosis (HFE: rs807212) confer protective effects to boys only [13–15]. In contrast, the HLA class II histocompatibility antigen, DR alpha chain (HLA-DRA: rs3135388), and human leukocyte antigen C (HLA-C: rs9264942) show risk and protective factors that relate to only girls with this disease. In

nasopharyngeal cancer, an immune-related gene called MICA shows disparities between male and female patients, and the frequency of MICA*A9, *A5.1 and MICA/HCP5 deletions greatly increases in male patients [16,17]. GG/GC genotypes in the pre-miR-146a gene are associated with a significantly increased risk of cancer in males, and this microRNA plays a regulatory role in some immune pathways. Further, our pan-cancer analysis of gene expression in tumour samples identifies a few immune-related pathways associated with sex bias across cancer types, including allograft rejection, IL2 and STAT5 signalling, IL6, JAK, and STAT3 signalling, inflammatory responses, interferon alpha response, interferon gamma response, and TNF-a signalling and complement [10].

Metabolism-related genes. In childhood ALL, some polymorphisms in cytochrome P450 1A2 (CYP1A2) have protective effects for girls, while those in NAT1 and NAT2 are risk factors for boys only [18]. In acute myeloblastic and lymphoblastic leukaemia, the deletion of glutathione S-transferase theta-1 (GSTT1) confers a greater risk to only male patients [19]. As for lung cancer, polymorphism in both the vascular endothelial growth factor (VEGF) and family 1, subfamily A, polypeptide 1 (CYP1A1) of cytochrome P450 are associated with disease risk in male patients [20,21]; while methylene tetrahydrofolate reductase (MTHFR) has both risk and protective associations with only female patients [22]. In contrast, polymorphisms in glutathione S-transferase Mu 1(GSTM1) are associated with a greater disease risk in females [23]. CYP1A1 plays an important role in lung DNA adduct formation and supports a higher susceptibility to lung cancer among females. In colorectal cancer, the SNPs in GSTM1 and GSTM3 have greater association with male patients, and the rs35996865 G variant allele in ROCK1 occurs more frequently in male patients [24,25]. However, APOE, NAT2 and ABCB1 all have greater association with female patients who have colorectal cancer. In pancreatic cancer, the NAT1 genotype is associated with risk for male patients only [26]. In bladder cancer, ERCC2 Lys751Gln is associated with greater risk for male patients, while SULT1A1 (rs9282861) is associated with protection for female patients [27,28]. In lung adenocarcinoma, the epidermal growth factor receptor (EGFR) is a major therapeutic target, and our TCGA analysis shows a higher mutation frequency in female patients, which may contribute to a higher response rate to targeted therapy in female patients. Furthermore, in this disease, metabolism-related STK11 (LKB1) and DMD show significant sex-biased mutation rates. STK11 is more frequently mutated in male patients than in female patients, while DMD mutations are more common in female patients [10]. In liver hepatocellular carcinoma, mutations of CTNNB1, which is related to various metabolic pathways, are more common in male patients. Across the cancer types we surveyed, clear cell kidney carcinoma and papillary kidney carcinoma contain the highest number of clinically actionable genes associated with a sex bias. The signature of papillary kidney carcinoma includes FBXW7, FGFR1, RET, and TSC2; and the signature of clear cell kidney carcinoma includes FGFR3, AKT, TSC2, and KIT. In clear cell kidney carcinoma, the amplicon 3q26 containing PI3KCA occurs more frequently in female patients, and PI3KCA activation has been reported to predict sensitivity to PI3K/AKT/mTOR inhibitors; whereas deletions of 1p36.23 (harboring *MTOR*) and 10q23.31 (harboring PTEN) are more prevalent in male patients [10].

DNA damage, repair and p53 pathway. Sex differences also exist in genes related to DNA damage and repair. Higher methylation levels, which can be related to gene silencing, and chromatid breaks following exposure to gamma rays are both more common among males. Although there is a higher level of DNA damage in males, the capacity of DNA repair in females is lower [29]. Generally, there are higher recombination rates in the germ cells of females, except at the telomeres of chromosomes, where recombination rates are higher in males [30]. In acute myeloblastic and lymphoblastic leukaemia, a SNP in NAD(P)H dehydrogenase (quinone 1) (rs1800566) can make p53 more stable by preventing it from degrading. Furthermore, NQO1 has a greater risk connection for male patients only [31]. The mouse double minute 2 homolog (MDM2: SNP309), which antagonises p53, accelerates the age at diagnosis for females in a variety of cancers, including diffuse large B-cell lymphoma, soft tissue sarcoma, childhood ALL, and colorectal cancer [32].

Genes in sex chromosomes. Since males and females have different copies of sex chromosomes (i.e., X chromosome and Y chromosome), genes on these chromosomes are expected to be involved in the sex bias in cancer. Indeed, we found that the most common genes with sex-biased expression across cancer types are significantly enriched in the X chromosome [10]. Furthermore, some genes on the X chromosome that can escape from X-inactivation, and thus "escape from X-inactivation tumour suppressor" (EXITS), thereby protect females from a "single-hit" functional loss. A recent pan-cancer analysis revealed male-biased mutations in these genes, suggesting a notable contribution of EXITS genes in females to reduced cancer incidence among that subpopulation [33].

The X-inactive specific transcript (XIST), which is an RNA gene on the X chromosome of placental mammals that acts as a major effector of the X inactivation process, has been shown to interact with BRCA1. Males and females with XIST show different characteristics of susceptibility to cancer. Although the significance of XIST in females remains unknown, males with XIST have increased risk of developing lung cancer, non-Hodgkins lymphoma, and testicular tumours; whereas their risk of prostate cancer appears to be reduced.

1.4. Clinical implications and future directions

Sex-biased molecular signatures may have significant clinical implications. First, for the risk-associated SNPs identified, it is essential to use independent patient cohorts to validate their effects in a more rigorous way. Then, based on the markers that are rigorously validated, sex-specific cancer prevention strategies should be developed. Since the effects of single SNPs are small, it will be more effective to build multiple-marker risk assessment models. Second, for genes with sex-biased expression patterns, it is important to elucidate whether the pattern is specific to tumour tissues or also holds true in normal tissues. This knowledge will be helpful when developing expression-based biomarkers or tumour subtypes. Indeed, many proposed prognostic genes may simply recapitulate the association of sex with clinical outcomes, which may not confer independent prognostic power. Further, it is important to elucidate the difference among the molecular markers with sex-biased expression, the sex-specific markers correlated with cancer phenotype, and the ones underlying the sex-specific cancer mechanisms. Third, our recent study demonstrated that > 50% of clinically actionable genes show sex-biased molecular signatures [10]. Thus, sex should be explicitly considered when applying targeted therapies for these genes. Fourth, for drug development, sex-specific early-stage clinical trials may be more effective for the target genes that have a sex-biased signature since the sample size in these trials is usually small. Last, but not least, more efforts should be made to identify sex-specific molecular markers for immunotherapy.

2. Conclusions

The statistical analyses of cancer epidemiology over decades have well documented the sex disparities in cancer incidence, prognosis and mortality. Many studies, especially those recent genomic profiling studies, have further pinpointed the molecular changes related to sex in cancer, but their mechanistic insights remain to be seen. Further efforts should be made to elucidate the relative contributions of various factors (both internal and external factors) to the sex disparities and develop sex-specific prevention, diagnostic and therapeutic strategies.

Conflicts of interest

The authors declare no conflict of interest related to this work.

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