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Regulation of Sex Hormone Receptors in Sexual Dimorphism of Human Cancers

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Abstract

Gender differences in the incidences of cancers have been found in almost all human cancers. However, the mechanisms that underlie gender disparities in most human cancer types have been under-investigated. Here, we provide a comprehensive overview of potential mechanisms underlying sexual dimorphism of each cancer regarding sex hormone signaling. Fully addressing the mechanisms of sexual dimorphism in human cancers will greatly benefit current development of precision medicine. Our discussions of potential mechanisms underlying sexual dimorphism in each cancer will be instructive for future cancer research on gender disparities.

Keywords

sexual dimorphism; cancer incidence; sex hormones; estrogen receptor; androgen receptor

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Authors' Contributions

Z.L. designed and wrote the manuscript. D.Z. and C.M. wrote and revised the manuscript. J.A.V. provided the Mayo Clinic Cancer Registry data. J.H.N., D.M.H, S.P.B, and S.A.M. revised the manuscript.

Statements of Conflicts of Interest

All authors declare no potential conflicts of interest.

Introduction

Sexual dimorphism is an important feature of human cancers but has been under-investigated and mostly neglected in clinical diagnosis and therapy. Our recent study showed that almost all human cancers showed significant differences between two genders (under paralleled review). Both genetic and environmental factors contribute to the initiation and progression of cancer in the form of germline genetic variations and defects, somatic mutations, and the inflammatory responses resulting from exposure to toxic chemicals, excessive alcohol consumption, and/or viral infection [1–3]. However, the mechanisms that underlie gender disparities in most human cancer types have been under-investigated. Sex hormones, i.e., estrogens in women and androgens in men, are the drivers of sexual dimorphism in general. Estrogen receptor-dependent estrogen signaling through three estrogen receptors, estrogen receptor alpha (ERα), estrogen receptor beta (ERβ), and G protein-coupled estrogen receptor (GPER1), and androgen receptor (AR) -dependent androgen signaling play the major roles in sexual dimorphism of human cancers. Here, we summarize previous studies and current progresses on sex hormone signaling in human cancers. The mechanisms of sexual dimorphism in human cancers have not been heavily investigated, except for some conclusive evidences in mice, e.g., sexual dimorphism of liver cancer is controlled by Foxa1/2-dependent ERα-mediated prevention and AR-mediated promotion on tumor growth in mice [4], which parallel well with the male-dominant liver cancer in humans. Here, we provide a comprehensive overview of potential regulatory mechanisms underlying sexual dimorphism of each cancer by focusing on sex hormone signaling and sex hormone receptor-dependent regulation. Our comprehensive overview about gender differences in cancer incidence and sex hormone regulation in cancer initiation and progression will provide a general guidance for the investigation of sexual dimorphism in human cancers and will be instructive and beneficial for cancer research and cancer diagnosis, prognosis, and therapy.

Summary of findings

I. The overview of gender differences in human cancers

According to sex-specific organs or development, we divide all cancer types into two groups: sex-dimorphic and sex-specific (or extremely sex-dimorphic with single sex-oriented, including male-specific and female-specific) cancers. In our recent study, we calculated the average incidence ratios between men and women for all human cancer the SEER data in 1970–2014 (under paralleled review). Among the 30 types of human cancers included in the SEER data (Fig. 1), 24 of them are sex-dimorphic and all have statistically significant incidence differences between men and women, two types are men-specific (prostate cancer and testicular cancer), and four types of cancers are women-specific (breast cancer, cancer of the cervix uteri, cancer of the corpus and uterus, NOS, and ovarian cancer). Although males have a rare occurrence of breast cancer [5, 6], we considered breast cancer as female-specific because mammary glands are barely developed in men. For all 24 sex-dimorphic cancers, 23 of them are male-dominant, and interestingly, only one cancer, thyroid cancer, is female-dominant.

II. Sex-dimorphic cancers

Next, we summarize the incidence data and potential mechanisms of sexual dimorphism in ten human cancer types with higher incidence ratios of at least 2-fold.

a) Kaposi Sarcoma—Kaposi sarcoma is a vascular neoplasm with nodular lesions on mucous membranes, skin, and connective tissues like bone, blood vessels, lymph nodes, and muscle with aberrant differentiation, inflammation, proliferation, and angiogenesis [7, 8]. Four types of clinical variations of Kaposi sarcoma have been identified, including classic (sporadic), endemic (African), epidemic (AIDS-associated), and iatrogenic (post-transplant) sarcoma [9, 10]. Classic Kaposi sarcoma was found in older men of European origin and caused by the Kaposi Sarcoma-associated herpesvirus (KSHV) [9, 11]. Kaposi sarcoma is rarely found in immuno-competent people, but the incidence of Kaposi sarcoma dramatically increases in homosexual and bisexual AIDS patients due to immunodeficiency, and about 15% to 20% AIDS patients develop Kaposi sarcoma [11, 12].

According to the SEER data, we found that the averaged incidence ratio of Kaposi sarcoma between men and women was 27.29 in USA during 1975–2014 (Fig. 1), which is the highest incidence ratio of sexual dimorphism in all types of human cancers. A recent study showed that the case ratio of the classic Kaposi sarcoma between men and women was 10.0 and the case ratio of the AIDS-associated Kaposi sarcoma was 3.0 among 105 Chinese patients [13]. Interestingly, in the highly HIV-infected regions, such as south and west Africa, the incidence of Kaposi sarcoma was much less sex-dimorphic compared to the SEER data [14–19].

Kaposi sarcoma is thus more common in males due to a higher incidence of AIDS in homosexual males in the western world, but apart from this, it remains a male-dominant cancer in humans worldwide. However, this sexual dimorphism has been understudied. A few studies showed that HIV-positive patients with Kaposi sarcoma had significantly higher levels of serum androgens than HIV-positive patients without Kaposi sarcoma and HIV-negative men, and proposed that excess amount of androgen might stimulate the function of suppressor T-cells [20–22].

b) Cancer of the larynx—Cancer of the larynx or laryngeal cancer arises in the throat, and cigarette smoking is one of the strongest environmental risk factors of laryngeal tumorigenesis [23–25]. This cancer includes three subtypes based on locations: glottis, supraglottis, and subglottis, with most larynx cancers being of the glottis subtype.

According to the SEER data, the average incidence ratio between men and women was about 5.18 in 1975–2014 and the second highest sexual dimorphism of all human cancers in the SEER data (Fig. 1).

Mechanisms underlying sex dimorphism of laryngeal cancer has been moderately investigated. The regulations of sex hormone signaling in the proliferation of laryngeal cancer cells of squamous cell carcinoma are controversial; e.g., estrogen promoted the cell proliferation of through GPER1 or possibly ERα36 (a short isoform of ERα) but suppressed the cell proliferation through ERβ, but these differential regulations were also at a cell line-

dependent manner [26–30]; although this cancer is more common in males, androgen was reported to inhibit the growth of laryngeal cancer cells [31]; thus, anti-androgen therapy had failed for patients with laryngeal tumors [32], though whether androgen receptors were expressed or involved in laryngeal tumorigenesis was still unclear [33–35].

c) Mesothelioma—Malignant mesothelioma is an aggressive neoplasm arising from mesothelial cells, and most mesothelioma locate at the pleural and peritoneal cavities, the pericardium, or the tunica vaginalis [36]. The incidence of mesothelioma has been increasing worldwide in recent decades and was peaked during the 1980s and 1990s [37]. Most (90%) malignant pleural mesothelioma might be related to prior asbestos exposure [38]. Mesothelioma was barely diagnosed before the age of 49; and mesothelioma patients died at a mean age of 70 years old [39].

The SEER data show that the average sex-dimorphic incidence ratio of mesothelioma between men and women was 4.70 (Fig. 1). Similar high sex-dimorphic incidence ratios of mesothelioma have also been reported in other countries and areas, including South Africa, Japan, France, Taiwan, Italy and Australia [40–48]. Thus, mesothelioma is a male-dominant cancer in humans.

The most commonly etiology for mesothelioma is the exposure to asbestos, which may explain the higher incidence rate in men de to male-dominant occupations, such as mining [49–52]. However, this cannot explain the consistent gender differences of mesothelioma in non-mining men and women. Investigations on the mechanism of sexual dimorphism of mesothelioma has been mainly focused on ERβ, e.g., estrogen signaling inhibited the growth of malignant mesothelioma cells through ERβ [53–56]; ERβ expression in human pleural mesothelioma cells was regulated by histone demethylase KDM6B under either normoxic or hypoxic conditions [57], indicating ERβ-mediated sexual dimorphism in mesothelioma is independent of environmental factors, such as mining; further, GPER1 activated the chemotaxis and migration of mesothelioma [58]; and ERα and AR expressed in the tumors of peritoneal mesothelioma but how they regulate the tumorigenesis were unclear [59].

d) Urinary Bladder Cancer—Urinary bladder cancer is the fifth most common malignancy in industrialized countries [60], arises from the epithelial cells of the urinary bladder, and includes two major histological types: urothelial carcinoma (> 90%) and squamous cell carcinoma (3–5%) [61]. Cigarette smoking, occupational exposures to infected waters, and chronic bladder inflammation are risk factors for urinary bladder cancer [62–64]. From the SEER data, we found that the average sex-dimorphic incidence ratio of urinary bladder cancer was 3.96 and this ratio was well maintained throughout the years in 1975–2014 (Fig. 1).

The mechanisms underlying sexual dimorphism of urinary bladder cancer have been actively investigated and are highly dependent on sex hormone signaling. Although estrogen was found to promote the growth of urothelial bladder cancer cells through both ERα and ERβ [65, 66], both estrogen therapy and anti-estrogen therapy prevented or suppressed the tumorigenesis of urothelial bladder cancer [67–69]. Also, following an antibody validation study, the expression of ERβ in the bladder or bladder cancer cells is debated [70].

Conversely, GPER1-mediated estrogen signaling inhibited the proliferation of urinary bladder cancer cells [71]. AR-mediated androgen signaling promoted the growth and metastasis of urothelial bladder cancer cells whereas androgen deprivation therapy and AR ablation or inhibition suppressed the tumorigenesis of urothelial bladder cancer [72–78]. Thus, the role of estrogen or androgen signaling, which both promote cell growth in the male-dominant sexual dimorphism in urothelial bladder cancer requires further investigation.

e) Esophageal Cancer—Cancer of the esophagus or esophageal cancer arises from the food pipe between throat and stomach. Esophageal cancer has two major subtypes: esophageal adenocarcinoma and esophageal squamous cell carcinoma [79]. Cigarette smoking, alcohol consumption, and poor oral health are risk factors for esophageal cancer [80]. Based on SEER data, the average sex-dimorphic incidence ratio of esophageal cancer was about 3.66 in 1975–2014 (Fig. 1).

Sex hormone signaling diverges between the two major subtypes of esophageal cancers. In esophageal adenocarcinoma, AR-dependent androgen signaling suppressed cell proliferation [81] whereas estrogen signaling (through both ERα and ERβ) promoted the cell growth [82, 83]. In contrast, in esophageal squamous cell carcinoma, AR-dependent androgen signaling promoted the cell growth and migration [84–86] whereas whether estrogen signaling suppressed the cell growth through ERα or ERβ was under the debate [85, 87–91]. These studies have been mainly conducted in human esophageal cancer cell lines.

f) Liver cancer—Liver cancer includes hepatocellular carcinoma (HCC) and cholangiocarcinoma. Liver cancer is closely linked to chronic liver diseases including chronic Hepatitis virus infections, exposure to aflatoxin and alcohol, and diabetes and the metabolic syndrome [92–95]. The average sex-dimorphic incidence ratio of liver cancer was 2.69 in the SEER data (Fig. 1).

Liver cancer is one of the mostly investigated cancers regarding sexual dimorphism because it is conserved in both rodents and humans [96–106]. Gender differences in the liver cancer were firstly discovered in mice in 1930s [96–98]. Later studies elucidated that ERα-mediated estrogen signaling and AR-mediated androgen signaling play the major and opposite roles in hepatic tumorigenesis, i.e., estrogen signaling prevented whereas androgen signaling promoted tumor growth in females and males, respectively [96–99, 107–112]. Although neither ERβ nor GPER1 is expressed in normal liver and liver tumors from rodents and humans, one recent study showed that global but not liver-specific ablation of Gper1 accelerated hepatocarcinogenesis [113]. Two recent studies have made great contributions on the molecular mechanisms underlying sexual dimorphism of liver cancer. Naugler *et al* found that MyD88-dependent IL-6 production promoted chemically induced hepatocarcinogenesis in male mice, while estrogen-mediated inhibition of IL-6 production contributed to the reduction of hepatic tumorigenesis in female mice [99]. However, employing IL-6 antagonists or estrogen and its analogs to treat HCC has brought controversial results [104, 114, 115]. Li *et al* found that both of the ERα-mediated protection and AR-mediated facilitation of hepatic tumorigenesis in mice depended on Foxa1/2, while deficiency of Foxa1 and Foxa2 in the mouse liver would reverse the protective role of ERα and the detrimental role of AR for HCC [4]; and genetic variants that

affected the binding of FOXA2 and ERα were associated with the increased incidence of HCC in patients [4]. Recent clinical studies showed the promising evidence that estrogen supplements reduced the risk of HCC in women and increased the survival of female HCC patients [116, 117]. Thus, detailing the sex hormone signaling targets may help developing effective target therapy for HCC.

g) Cancer of oral cavity and pharynx—Cancer of the oral cavity and pharynx is mostly oral squamous cell carcinoma (OSCC), which arises from the squamous cell lining of the mouth and throat. Aging, alcohol abuse, and tobacco are risk factors for OSCC. The average sex-dimorphic incidence ratio for this group of cancers has been at a steady level around 2.59 in the SEER 1975–2014 data (Fig. 1).

It is interesting that both estrogen and androgen signaling promote the growth of OSCC cells. ERα, ERβ, GPER1, and AR were all expressed in OSCC tissues and their expression levels were possibly related to the pathological grades or malignancy of tumors [118–124]. Estrogen signaling promoted the growth of OSCC cells through ERα, ERβ, and GPER1 [122, 124–126]. AR-dependent androgen signaling promoted the growth of OSCC cells [121].

h) Stomach Cancer—Stomach cancer or gastric cancer is a malignant tumor arising from the lining of stomach. Infection by the *Helicobacter pylori* accounts for more than 60% of cases, and smoking, diet, and obesity are other risk factors [127–130]. About 90–95% of gastric cancer is gastric adenocarcinoma, which includes histological subtypes: diffuse and intestinal [131]. There was no significant difference in the incidence of the diffuse subtype between men and women [132–134], thus the intestinal subtype accounted for sexual dimorphism in gastric cancer. The average sex-dimorphic incidence ratio for gastric cancer was around 2.0 in the SEER data (Fig. 1).

The regulation of estrogen signaling in the growth of gastric cancer cells is still confusing due to limited evidence, i.e., ERα-mediated estrogen signaling promoted cell growth whereas. For example, estrogen signaling, through ERα or a splicing variant of ERα, promoted the growth of gastric cancer cells [135, 136] whereas ERβ-mediated estrogen signaling inhibited the growth of gastric cancer cells [137] and genetic variants in the *ESR2* gene were highly associated with survival in patients with locally advanced gastric cancer [138]. AR-mediated androgen signaling promoted the growth and metastasis of gastric cancer cells [139].

i) Cancer of the Kidney and Renal Pelvis—Kidney or renal cancer originates from kidney and the lining of renal pelvis, and includes four major subtypes: renal cell carcinoma (about 85%), transitional cell carcinoma, Wilms tumors, and renal sarcoma [140]. Smoking, obesity and hypertension have been estimated to account for nearly half of cases [141, 142]. The average sex-dimorphic incidence ratio was stable around 2 in the SEER data (Fig. 1). Similar male dominance of kidney cancer was also observed in Denmark (1.67), Europe (2.0), and Korea (2.5) [143–146].

The mechanisms underlying sexual dimorphism of kidney cancer have been less studied. The evidence of estrogen signaling in the growth of kidney cancer cells is limited, e.g., *ESR1* polymorphism was associated with the risk of kidney cancer [147]; GPER1 promoted the growth and metastasis of kidney cancer cells [148]; and AR-mediated androgen signaling promoted the growth of kidney cancer cells [149, 150].

j) Thyroid Cancer—Thyroid cancer is the most common and major lethal endocrine malignancy [151], and includes two major subtypes: papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) [152, 153]. Thyroid cancer is the only female-dominant sex-dimorphic cancer in humans with an average sex-dimorphic incidence ratio of −2.56 in the SEER data (Fig. 1).

Sexual dimorphism of thyroid cancer has been heavily investigated. ERα, ERβ, GPER1, and AR were expressed at various levels in thyroid tumor tissues [70, 154–160]. Interestingly, both estrogen signaling and androgen signaling promoted the growth of thyroid cancer cells [155, 161, 162]. Estrogen signaling through all three estrogen receptors, ERα, ERβ, and GPER1, promoted the growth and metastasis of thyroid cancer cells [155, 163–167] and ERα expression was increased in thyroid tumors compared to controls [154, 168, 169]. Recently, estrogen was shown to promote the growth of thyroid cancer stem cells in vitro and in mouse xenografts provided an additional explanation for the cause of female-dominant sexual dimorphism in thyroid cancer [170].

Discussions

1. Sex hormone signaling in sexual dimorphism of human cancers

Sexual dimorphism in human cancer susceptibility has been observed for almost a century. However, the mechanism underlying the incidence divergence between the two genders is still elusive for most cancer types. Accumulated evidences demonstrated that sex hormone receptor-mediated signaling plays the essential roles in the sexual dimorphism of human cancer incidence during the initiation, progression, metastasis, and prognosis of human cancers. Generally, three types of estrogen receptors, ERα, ERβ, and GPER1, and AR are involved in sex dimorphic regulation of human cancers at different manners. We summarize all studies that addressed sexual dimorphism of human cancers regarding sex hormone signaling and the involvement of sex hormone receptors in Table 1. However, only a few cancers have been carefully investigated for this regard, such as liver cancer. For most of other cancers, sexual dimorphism has been barely or incompletely addressed. Interestingly, sex hormone signaling or sex hormone receptor-mediated signaling does not always regulate the progression of human cancers in the same direction or plays opposite roles in two types of cancers or even in the same type of cancer; e.g., ERα-mediated estrogen signaling promotes the tumor growth of breast cancer, cancer of the cervix uteri, cancer of the corpus and uterus, and ovarian cancer, but it prevents the tumor growth of liver cancer; estrogen signaling through ERα and ERβ plays opposite roles in the same cancer, such as stomach cancer and ovarian cancer. Estrogen receptor-mediated estrogen signaling shows great tissue or cancer specificity, such as ERα in liver cancer, ERβ in mesothelioma cancer, and GPER1 in kidney cancer. Additionally, other co-regulators or epigenetic factors may be involved in

the process of these identical or opposite regulations of sex hormone receptors. Some cancers have more complicated sex hormone signaling, e.g., all sex hormone receptors, ERα, ERβ, and GPER1, and AR have shown to regulate the tumorigenesis of urinary bladder cancer, oral cancer, and thyroid cancer (Table 1). Another interesting aspect in sexual dimorphism of human cancers was not discussed in this article but deserves more attention, i.e., men dominated in the cancer incidence but female cancer patients had more advanced diseases and worse survival than men. Thus, we are far away from complete understanding the mechanisms underlying sexual dimorphism of human cancers and fully elucidating the contributions of sex hormone signaling and sex hormone receptors to sexual dimorphism in each cancer type will require tremendous efforts and investigations.

2. Key challenges and future perspectives

A key challenge in deciphering the mechanisms of sexual dimorphism in human cancers is the various expression levels of sex hormone receptors in different stages of tumorigenesis (mostly silenced in advanced stages of tumors), such as liver cancer and breast cancer, which may result from sexual dimorphism in organogenesis as we observed recently in the liver [171]. Additionally, antibodies used for measuring sex hormone receptors varied in quality and some of them led to errors, such as recent evidence for anti-ERβ antibodies [70] and previous evidence of upper non-specific bands from anti-ERα antibodies (HC-20 from Santa Cruz Bio). To improve the quality for the studies of sexual dimorphism in human cancers, genetic assays using tissue-specific knockout mouse models of sex hormone receptors and using human cancer cells with CRISPR/Cas9-mediated manipulations of sex hormone receptor expression will provide more solid and direct answers for this topic. Moreover, whether or how risk factors could or could not affect sexual dimorphism of human cancer is still unclear, i.e., non-mining men still had higher incidence of mesothelioma than non-mining women [49–52], smoking men had higher incidence of lung cancer than smoking women whereas non-smoking women had higher incidence of lung cancer than non-smoking men [172], and male-dominant HIV infection did not show similar degrees of male-dominant incidence in Kaposi Sarcoma [14–19]. More importantly, there are many big questions that remain to be answered in the sexual dimorphism of human cancers; e.g., why up to three estrogen receptors are required for regulation in a single cancer? Why males dominate almost all sex-dimorphic cancers? How the only female-dominant thyroid cancer is so different from other cancers? How aging control sex hormone levels or regulate sex hormone signaling in sex-dimorphic or sex-specific cancers? Is there a general principle or mechanism of sexual dimorphism in human cancers? Last but not the least, what are the roles of X and Y chromosomes play in sexual dimorphism of human cancers? Sex is one of the most obvious features or variables in human beings or mammals. Fully understanding the mechanisms underlying sexual dimorphism in normal humans would facilitate better understanding of sexual dimorphism in human cancers; and this would be essential for developing gender-specific biomarkers or treatment for cancer patients, which would be a critical first step of gender-specific precision medicine towards genuine personalized precision medicine.

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Abbreviations:

(SEER)	Surveillance, Epidemiology, and End Results Program
(ERα)	estrogen receptor alpha
(ERβ)	estrogen receptor beta
(GPER1)	G protein-coupled estrogen receptor
(AR)	androgen receptor

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Highlights

- Sex differences in the incidences of cancers have been found in almost all human cancers.
- A comprehensive overview of potential mechanisms underlying sexual dimorphism of each cancer regarding sex hormone signaling.
- Fully addressing the mechanisms of sexual dimorphism in human cancers will greatly benefit current development of precision medicine.
- Our discussions of potential mechanisms underlying sexual dimorphism in each cancer will be instructive for future cancer research on sexual dimorphism.

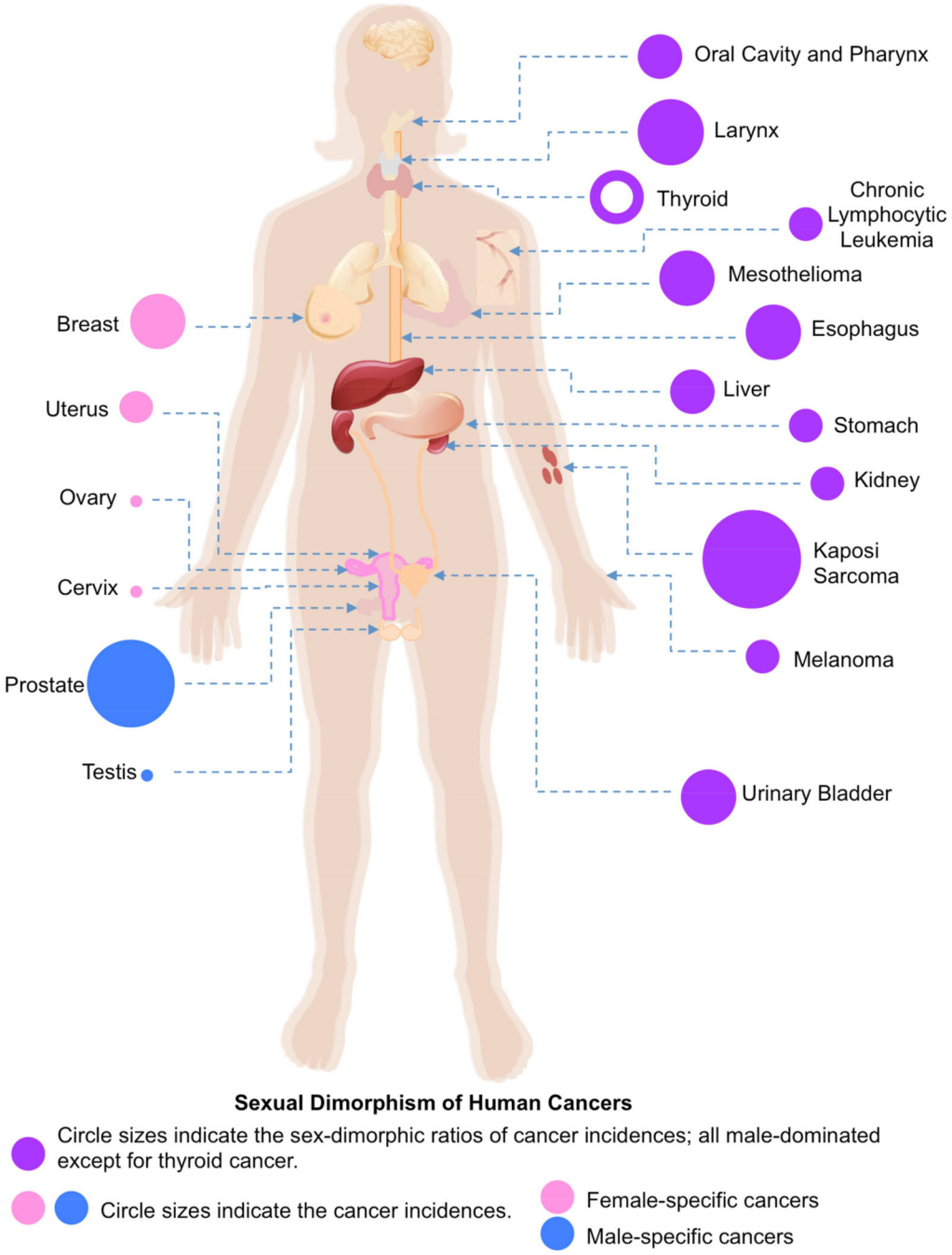

Figure 1.

TABLE 1.

Summary of Sex Hormone Signaling Studies in Human Cancers

	Cancer Type	Estrogen	ERα	ERβ	GPER1	AR	Androgen
1	Kaposi Sarcoma	–	–	–	–	–	↑?
2	Cancer of the Larynx	↑↓?	↑?	↓	↑	↑?	↓
3	Mesothelioma	↑↓?	?	↓	↑?	?	?
4	Urinary Bladder Cancer	↑↓	↑	↑	↓	↑	↑
5	Esophageal Cancer	↑↓	↑↓	↑↓	–	↑↓	↑↓
6	Liver Cancer	↓	↓	–	–	↑	↑
7	Oral Cavity and Pharynx	↑	↑	↑	↑	↑	↑
8	Stomach Cancer	↑↓	↑	↓	–	↑	↑
9	Cancer of the Kidney and Renal Pelvis	–	–	–	↑	↑	↑
10	Thyroid Cancer	↑	↑	↑	↑	↑	↑
11	Breast Cancer	↑	↑	↓?	↑?	↑	↑
12	Cancer of the Cervix Uteri	↑↓?	↑?	–	↓	–	↑
13	Cancer of the Corpus and Uterus, NOS	↑↓?	↑	↓?	↑	↓	↓
14	Ovarian Cancer	↑↓	↑	↓	↑↓?	↑	↑?
15	Prostate Cancer	↑↓?	↑?	↓?	↓	↑	↑
16	Testis Cancer	↑↓?	?	↓	↑	↓	↓

↑, Sex hormone signaling promotes tumorigenesis in human cancers.

↓, Sex hormone signaling suppresses tumorigenesis in human cancers.

↑↓, Controversial functions of sex hormone signaling in human cancers.

–, Sex hormone signaling in human cancers has not been investigated.

?, uncertain results