



Sex differences in the diagnosis, treatment and prognosis of cancer: the rationale for an individualised approach

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Received: 16 January 2023 / Accepted: 2 February 2023
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Abstract

Background Precision medicine in oncology aims to identify the most beneficial interventions based on a patient's individual features and disease. However, disparities exist when providing cancer care to patients based on an individual's sex.

Objective To discuss how sex differences impact the epidemiology, pathophysiology, clinical manifestations, disease progression, and response to treatment, with a focus on data from Spain.

Results Genetic and environmental factors (social or economic inequalities, power imbalances, and discrimination) that contribute to these differences adversely affect cancer patient health outcomes. Increased health professional awareness of sex differences is essential to the success of translational research and clinical oncological care.

Conclusions The Sociedad Española de Oncología Médica created a Task Force group to raise oncologists' awareness and to implement measures to address sex differences in cancer patient management in Spain. This is a necessary and fundamental step towards optimizing precision medicine that will benefit all individuals equally and equitably.

Keywords Cancer · Epidemiology · Sex · Female · Male · Treatment

Introduction

'Precision medicine' is defined as '*a healthcare approach with the primary aim of identifying which interventions are likely to be of most benefit to which patients based upon the features of the individual and their disease*' [1].

Careful consideration of sex differences is a fundamental step towards precision medicine that will promote equality and equity in healthcare [2].

The terms 'sex' and 'gender' are not interchangeable. 'Sex' refers to the biological differences between males and females, and encompasses sex organs, endogenous hormones and chromosomes [3]. 'Gender', however, is a sociocultural construction that encompasses the roles, norms and behaviours expected for males and females in society, which may or may not correspond to their sex [3, 4]. Each individual's health is determined by both their biological sex and gender expression [3] because access to healthcare and interactions with healthcare professionals can be influenced by sex and/or gender due to social or economic inequalities, power imbalances or discrimination [4, 5].

Oncology research has mainly focussed on the genomic profile of a cancer to personalise treatment, and current approaches to precision medicine in oncology generally do not include factors such as sex or gender in therapeutic decisions [6]. It is of increasing concern that sex and gender influence cancer susceptibility, progression, survival and response to different treatments; as such, there is growing recognition that a patient's sex and gender also need to

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be considered in the formulation of an optimal treatment approach [7].

There is evidence to suggest that women do not receive the same treatment for cancer as men [8, 9]. This is unsurprising because women have been historically excluded from clinical trials for various reasons, resulting in research and medical attention focussed on male physiology; indeed, the diagnosis, treatment, and prevention of disease originates from studies carried out mainly on male cells, male mice and men [10]. The Sociedad Española de Oncología Médica (SEOM) in Spain has created a Women's Task Force, named Oncogenyx, to analyse the impact of sex and gender on the diagnosis, treatment and outcomes of cancer patients. The aim is to improve the quality of care for cancer patients in Spain by implementing appropriate measures to address sex/gender disparities. One of the first initiatives of Oncogenyx was to carry out a survey among SEOM members to assess the awareness of Spanish oncologists with regard to sex differences in the diagnosis, treatment and prognosis of patients with cancer. Participation in the survey was not very high, which indicates the dire need to inform and educate oncologists on these sex differences. This article describes the rationale for the SEOM Task Force by discussing how sex

differences impact the diagnosis, treatment and outcomes of cancer, with a focus on data from Spain.

Sex differences in cancer incidence and mortality

Disparities occur in cancer incidence and mortality based on a patient's sex [11]. Although women in Europe tend to report worse general health than men, the probability of somatic tumour development is higher and the prognosis is worse in men (Fig. 1) [12]. Overall, the age-standardised incidence and mortality rates of patients with cancer are higher in men than in women, both globally [13] and in Spain [14, 15]. The major exceptions (excluding cancers specifically related to reproductive organs, such as breast cancer or prostate cancer) are thyroid and gallbladder cancer (Fig. 1), both of which occur at higher rates in women than in men [12–14].

In Spain, the incidence of lung cancer is lower in women than in men [16–18], but the difference between the sexes is becoming less marked as a result of changes in smoking habits in men and women [16, 17]. Consequently, the incidence of lung cancer has somewhat stabilised in men, while it continues to increase in women

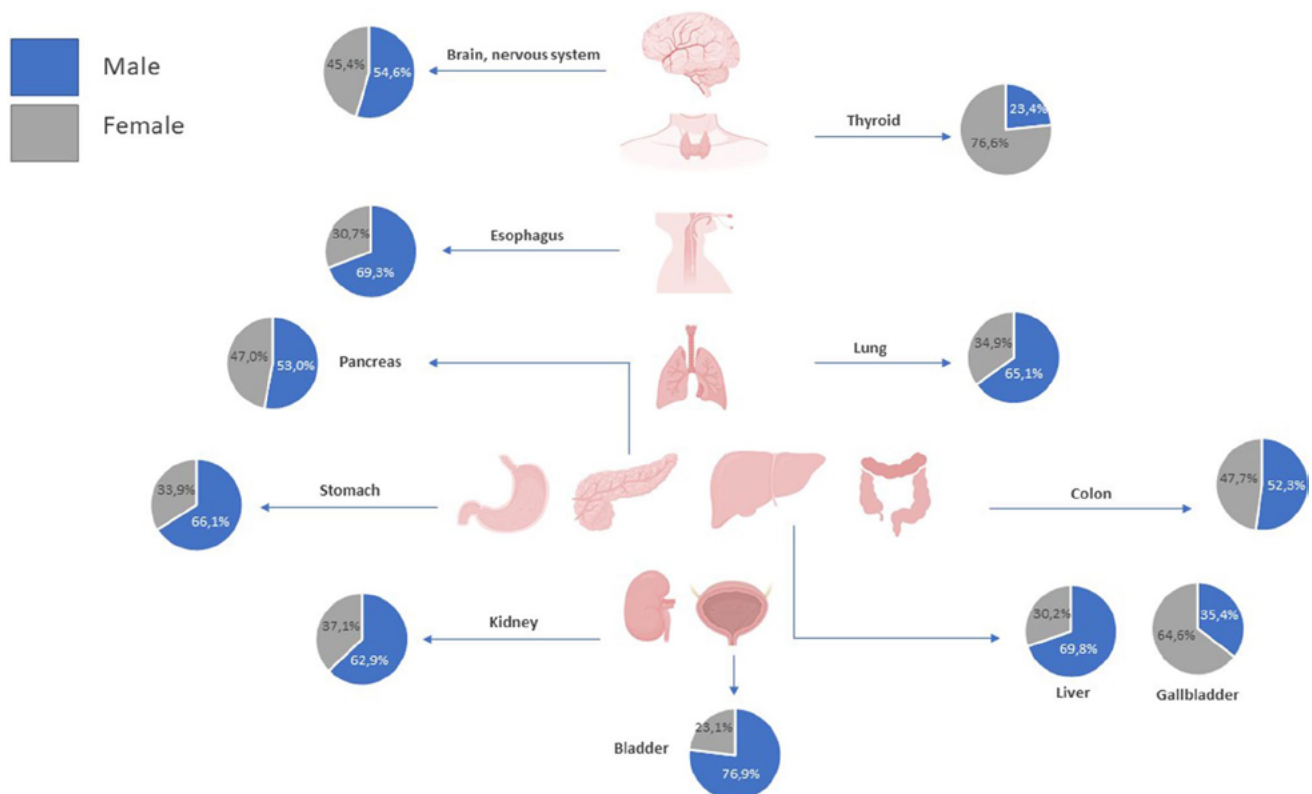


Fig. 1 Sexual dimorphism in the incidence of different cancer types unrelated to reproductive functions representing the percentages of new diagnosed cancer cases in 2020 among men and women. The

percentage values have been calculated using data retrieved from the Global Cancer Observatory GLOBOCAN 2020 [68]. The data have been extracted from Cardano M [12]. Created using Biorender

[16]. Spanish women also show lower age-adjusted rates of mortality compared with Spanish men across a range of cancers, including colorectal cancer [19, 20], cancer of the lip, oral cavity or pharynx [21], lung cancer [22–24], non-melanoma skin cancer [25], oesophageal cancer [26] and pancreatic cancer [27, 28].

With regard to sex-specific tumours, the leading causes of premature mortality among women and men are breast cancer and prostate cancer, respectively [29].

Potential reasons for sex differences

Cancer occurs as a result of a complex interplay between genetic and environmental factors, which differs between the sexes.

Genetic factors

The Cancer Genome Atlas (TCGA) analysed the molecular profiles of a range of cancers in males and females and identified those with strong or weak sex-related differences (Table 1) [30]. The tumour mutational burden tends to be lower in females than males in various cancers [31, 32]; this may affect the antigenicity of the tumour and therefore the efficacy of immune checkpoint inhibitor (ICI) therapy [33]. In addition, the X and Y chromosomes themselves may play a role in determining cancer biology [11, 34]. Tumour suppressor genes may be present on the inactive X chromosome (Xi) in females, and genes called ‘escape from typical X-inactivation tumour suppressors’ (EXITS) can confer protection against cancer in females that is not present in males [34]. Similarly, men may develop extreme downregulation or loss of Y chromosome expression, which increases their risk of cancer through the loss of tumour suppressor genes on the Y chromosome [35]. There is also evidence of differences between the sexes in response to genotoxic stress and activation of DNA damage repair pathways, with women

expressing higher levels of DNA repair genes and acquiring fewer somatic mutations over a lifetime, than men [12].

Environmental factors

Socioeconomic inequity can impact on cancer occurrence and diagnosis in a number of ways, by affecting lifestyle behaviours, diet, smoking, alcohol consumption, awareness of risks, exposure to environmental pollutants and access to healthcare [36]. In Spain, social inequity has been associated with an increased risk of cancer incidence and mortality in both sexes, but the effect of socioeconomic deprivation on this risk varies between sexes and between cancer types [37, 38]. While inequalities between the sexes is not as marked in Spain as it is in some other countries, women still lag behind men in work opportunities, pay and educational attainment, and are still required to undertake more of the domestic, child-rearing and caregiving activities [29], with all the socioeconomic and lifestyle impacts these differences may confer.

Sex differences in the pathophysiology of cancer

Biological sex is first and foremost a genetic modifier of disease pathophysiology, clinical presentation and response to treatment [2]. Sex hormones have different effects on the tumour microenvironment (TME), affecting the function of cancer-associated fibroblasts, the remodelling of the extracellular matrix, angiogenesis and possibly lymphangiogenesis [39]. Across a range of cancers, strong sex-related differences in the TME have been noted in relation to the profile of infiltrating immune cells, immune checkpoint gene expression and functional pathways [32, 40]. Moreover, the sex-related patterns of immune features differ by cancer type (e.g. between lung cancer and melanoma) [41]. Sex-related differences in cancer pathophysiology may explain why there are often differences between men and women in the predominant histological subtype or the stage of cancer at presentation [42, 43]. For example, in Spain, women with lung cancer present with more advanced disease compared with men [44, 45] and are less likely than men to have squamous cell carcinoma [45].

Impact of sex differences on diagnosis and treatment

Although sex disparity in cancer incidence, aggressiveness and disease prognosis has been observed for a variety of cancers, relatively little is known and evaluated about the impact of sex on diagnosis and clinical disease management. A study in the US showed that women with pancreatic cancer had a longer time between symptom onset and diagnosis, and from diagnosis to surgery, compared

Table 1 Cancers showing strong or weak sex-related molecular differences [30], based on somatic mutations, somatic copy number alterations, DNA methylation, mRNA expression, micro-RNA expression and protein expression

Weak sex-related differences	Strong sex-related differences
Lower grade brain glioma	Thyroid carcinoma
Glioblastoma multiforme	Head and neck squamous cell carcinoma
Colon adenocarcinoma	Lung squamous cell carcinoma
Rectal carcinoma	Lung adenocarcinoma
Acute myeloid leukaemia	Hepatocellular carcinoma
	Bladder urothelial carcinoma
	Papillary renal cell carcinoma
	Clear cell renal cell carcinoma

with male patients [46]. Data from Spain show that there are sex-related differences in the time between screening or symptoms and diagnosis of rectal cancer, and that this form of cancer is suspected and confirmed earlier in men than it is in women [9]. As a result, women are more likely than men to be diagnosed later with disseminated disease [9]. An Italian study found that although greater adherence to colorectal screening programmes were by women, the sensitivity of screening was higher for men than women (80.1% vs 74.8%) [47]. Similarly, other inequalities may exist, such as a later diagnosis of, although rare, breast cancer in males [48].

The impact of sex differences on screening and diagnosis of cancer emphasises the importance of understanding the influences of sex differences across the cancer care continuum [8]. As diagnostic modalities become more automated in future, it is important to ensure that computer-assisted diagnostic tools using artificial intelligence (AI) do not introduce a sex bias in diagnoses, particularly if the AI training was based on an unequal number of images from males and females [49].

Awareness of sex differences across the cancer care continuum also extends to patient mental health: evidence from Spain indicates that women with cancer experience more anxiety than their male counterparts [50], highlighting the need to consider sex disparities in the management of the mental health of patients with cancer.

Sex differences in the pharmacology of anticancer drugs

Most anticancer agents are administered at standard dosages according to body weight or body surface area, which may vary considerably between men and women [51]. Body surface area has been identified as an inaccurate method to calculate chemotherapy doses; the associated risk of underdosing was recognised over a decade ago [51]. Intrinsic sex-based differences in body weight, plasma volume, gastric emptying time, plasma protein levels, cytochrome P450 (CYP450) activity, drug transporter function and excretion activity influence the four major factors that contribute to pharmacokinetic variability in individuals (bioavailability, distribution, metabolism and elimination) [52]. For example, women have a larger distribution volume of lipophilic drugs, whereas men have a larger distribution volume of water-soluble drugs [52]. Men typically tend to have increased activity of CYP1A2, CYP2D6 and CYP2E1 enzymes, resulting in increased metabolism of their corresponding drug substrates, while women show higher CYP3A4 activity, which is integral in metabolising the majority of drugs [52]. These sex disparities affect the pharmacokinetic profile of a large number of

anticancer drugs and are responsible for 20% overexposure in women [53].

Impact of sex differences on response to treatment

Sex differences in metabolism and immune response may contribute to differential responses to treatment between men and women. As described above, women are less likely than men to respond to ICI therapy in a number of cancer types including non-small cell lung cancer [54] and melanoma [55], although this is not a universal finding [56]. In addition, male and female patients with similar genomic profiles may have a different response to treatment, and genomic biomarkers may be predictive in one sex but not the other. For example, in melanoma patients, the presence of *CFH*, *DGKG* or *PPP6C* mutations was predictive of a better response to ICI therapy in males but not in females [57]. These gene mutations were also significant predictors of response in the overall group [57], so unless researchers are aware of the potential for sex differences in predictive biomarkers, they may mistakenly believe that a biomarker that is predictive in men is also predictive in women (or vice versa).

Impact of sex differences on cancer treatment outcomes

Sex differences in response to treatment contribute to different cancer outcomes between men and women. This has been shown in Spain where the female sex is associated with improved survival across a range of cancers [58], including oropharyngeal cancer (despite a similar rate of recurrence) [59] and bladder cancer [60]. In contrast, a US study reported a significantly higher 90-day mortality rate in women compared with men, despite similar use of optimal treatments for muscle-invasive bladder cancer in both sexes [61]. However, women in Spain have higher rates of temporary or permanent cancer-related disability compared with men [62], indicating that while men may die more readily from cancer, the burden of cancer among survivors is greater among females.

Impact of sex differences on treatment safety and tolerability

A number of large-scale studies have shown that women are more likely to experience adverse events (AEs) during cancer treatment than men [63, 64]. Among 34,640 patients in the Adjuvant Colon Cancer End Points (ACCENT) database, the only AE that occurred significantly more often in men was transaminitis during treatment with capecitabine plus oxaliplatin [64]. In contrast, women experienced neutropenia, leukopenia, nausea and vomiting significantly more

often than men, irrespective of the chemotherapy regimen they received [64]. Further, according to an analysis of data from clinical trials by the South Western Oncology Group Network, the risk of women developing severe AEs was 34% higher than men, specifically in the treatment domains of chemotherapy (74% vs 68%), immunotherapy (57% vs 49%) and targeted therapy (50% vs 45%) [63].

Sex disparities in clinical research

Historically, biomedical research has focussed on male physiology, at all levels: basic, preclinical and clinical [65]. Biomedical research in some medical specialities, such as cardiology, already reflects the importance of sex differences as modulators of disease biology [53]. However, in oncology, the importance of these difference is underestimated. For example, there is evidence that women are under-represented in clinical trials of treatments for many different types of cancer. As a result, drugs are being approved based on research that was conducted principally in men [66], with the results of this research, including drug toxicity or efficacy, extrapolated to all patients, assuming similar biological behaviour. There is a risk that negative results of clinical studies conducted mainly in men may lead to a discontinuation of drug development for treatments that may be effective and well tolerated in women [65]. Moreover, female researchers are under-represented in oncology publications [67].

Conclusion

There is growing evidence that sex differences influence cancer prevention, susceptibility, progression, survival and response to different treatments. The impact of biological sex on the aetiology of cancer has not been fully elucidated, but there is clear evidence that the disease is not the same in men and women. Sex differences in cancer biology and treatment deserve more attention and systematic research that is equally representative of women and men. Interventional clinical trials evaluating sex-specific dosing regimens are needed to improve the balance between efficacy and toxicity of anticancer drugs. Clinicians' increased awareness of sex differences in the epidemiology, pathophysiology, clinical manifestations, psychological effects, disease progression and response to treatment is essential to the success of oncological care and translational science. The SEOM has created a Task Force group to address sex differences in cancer biology and treatment, and to raise awareness of these differences among oncology professionals. The SEOM considers that the inclusion of a sex perspective is a necessary

and fundamental step towards precision medicine that will benefit all individuals equally and equitably.

Acknowledgements We would like to thank Catherine Rees, who wrote the outline of this manuscript on behalf of Springer Healthcare Communications, and Niresheene Ramchundar, PhD, of Springer Healthcare Communications who wrote the first draft of the manuscript. We thank Organon for their unrestricted support.

Author contributions RV designed the manuscript, performed the literature search and data analysis, drafted and critically revised the final article, and approved the final version. OJV performed the literature search and data analysis, critically revised the final article, and approved the final version. MJSA performed the literature search and data analysis, critically revised the final article, and approved the final version. FAP performed the literature search and data analysis, drafted and critically revised the final article, and approved the final version. AGA performed the literature search and data analysis, drafted and critically revised the final article, and approved the final version.

Funding The medical writing assistance was funded by Organon, who did not influence any aspect of the study design, data collection, analysis or interpretation, or the decision to submit the manuscript for publication.

Data availability The data generated or analysed are included in this article.

Declarations

Conflict of interest Ruth Vera has received honoraria from or acted in an advisory role for Roche, Sanofi, MSD, Merck, Eisai, Novartis, Pierre Fabre, Lilly, BAXTER, and ABBOTT, funding for educational or research programmes from Roche, Lilly and MSD, as well as payment of travel/accommodation expenses from Roche, Merck, Sanofi, Pierre Fabre, and MSD. Oscar Juan-Vidal has received honoraria from or acted in an advisory role for Boehringer Ingelheim, Bristol-Myers Squibb, Merck Sharp & Dohme, Roche/Genentech, AstraZeneca, Pfizer, Eli Lilly, AbbVie, and Takeda, and has received travel/accommodation expenses from Takeda and AstraZeneca. María José Safont Aguilera has received honoraria from or acted in an advisory role for Amgen, Merck, Servier, and Pierre Fabre, and travel/accommodation expenses from Amgen, Merck and Servier. Francisco Ayala de la Peña has received honoraria from or acted in an advisory role for AstraZeneca, Celgene, Eisai, Novartis, Roche, Pfizer, Pierre Fabre, Lilly, Sanofi, Seagen, and Daichi-Sankyo, funding for educational or research programmes from Celgene, Roche, and MSD, and travel/accommodation expenses from Roche, Pfizer, Celgene, Eisai, Pfizer, Pierre Fabre, and MSD. Aránzazu González del Alba has received research funding from Astellas, travel grants from Astellas, Jansen, Sanofi, BMS, Roche, Pfizer, MSD and Ipsen and honoraria for speaker engagements, advisory boards and continuous medical education from Janssen, Astellas, Sanofi, Bayer, Roche, Ipsen, BMS, MSD, Pfizer, Eusa Pharma, Eisai, Novartis, AAA and AstraZeneca.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

Consent to participate Not applicable.

Consent to publish Not applicable.

Code availability Not applicable.

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