EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

AWARENESS AND INTEREST OF ONCOLOGY PROFESSIONALS IN SEX AND GENDER DIFFERENCES IN CANCER RISK AND OUTCOME - ANALYSIS OF AN ESMO GENDER MEDICINE TASK FORCE SURVEY

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SUMMARY

Investigating sex and gender differences is critical to improving the outcomes of both male and female cancer patients. The European Society for Medical Oncology (ESMO) Gender Medicine Task Force assessed the awareness of sex and gender differences and interest in education and training among oncology professionals.

The Task Force conducted an online, anonymous survey in November 2022 to assess the awareness of the ESMO Gender Medicine Task Force's presence, knowledge of sex and gender differences in disease risk and outcomes, and interest in education and training on this topic.

Responses from 506 participants from 83 countries were analysed. Of these, 55.3% were women, 58.7% were from Europe, and 61.9% were working at a university hospital. 63% and 61.7% had previously heard about the concept of studying sex and gender differences in oncology and the ESMO Gender Medicine Task Force, respectively. Most participants knew that the body composition, especially fat free body mass, is sex and age-dependent (85.6%), drug dosing based on body surface area does not consider sex differences (61.7%), distribution of molecular subtypes of different tumour types is sex-related (59.3%), men are at greater risk for most cancer types (53.6%) and that clinical trials often report only the primary endpoint according to the sex of the patient but not secondary endpoints (52.8%). Fewer participants knew that sex hormones are important for the development of non-sex related cancer types (45.6%), anticancer therapies are in general more toxic for women (38.5%), and that the sex of the donor and the receiver affects the outcome after allogeneic stem cell transplantation (23.7%). Only 19.7% already studied sex and gender differences in their field, and 84.2% indicated that they would like more education on sex and gender differences in oncology. Overall, the level of agreement with the statements was comparable between men and women.

INTRODUCTION

Sex and gender affect disease susceptibility, clinical presentation, treatment response, and outcome. Yet, as biological sex and sociocultural gender are broadly debated in society and medicine, sex- and gender-based disparities are still inadequately addressed or not at all.

Globally, while men are more prone to most cancer types, across various treatment settings, women present a significantly higher risk for severe toxicity for different anticancer drugs, including cytotoxic agents, targeted therapies, and immune checkpoint inhibitors [1][2]. Various sex (biology) and gender (sociocultural) related factors possibly contribute to these differences [3][4]. Additionally, traditional drug dosing in oncology (fixed doses or according to the body surface area) does not consider sex differences in body composition, which influences drug metabolism and clearance [5,6]. In clinical trials, in general, only the primary outcome is reported according to sex. Even if any differences between men and women are found, they are usually

disregarded given that the trials are not designed and do not have the statistical power to assess potential sex differences [4] [7]. Therefore, together with the inadequate representation of female participants in cancer clinical trials [8] and their lack of power to do meaningful subgroup analyses of all endpoints according to sex [9], the true magnitude and clinical relevance of sex differences in anticancer drug effects remain insufficiently investigated.

ESMO has realized that the investigation of sex and gender differences is critical to improving the outcome of both women and men with cancer and has, therefore, launched the ESMO Gender Medicine Task Force in 2019 [10]. The missions of this Task Force are to "raise awareness of the presence of potential sex differences in biology and treatment outcomes of non-sex related cancers and the impact of gender on access, quality of life and long-term consequences of anticancer therapy." It is currently not known to what extent oncology professionals are aware of potential sex and gender differences in cancer biology and treatment effects, whether they are interested in education and training on this subject, and whether they are considering and investigating sex and gender differences in their area of expertise. To address this knowledge gap, we surveyed oncology professionals in November 2022.

METHODS

Survey population and design

The survey, designed by the ESMO Gender Medicine Task Force, was hosted on the Qualtrics platform (open from 23 November to 30 November 2022), it was made available on the ESMO website, through ESMO membership emails, and promoted through social media. Participation was voluntary and anonymous. The ESMO Executive Board approved the project. No ethics committee approval was required.

Survey instrument. The survey collected data including participant demographics and career-related questions such as specialization, work experience, workplace, and clinical fields of work. We asked about awareness of the study of sex and gender differences in oncology and the presence of the ESMO Gender Medicine Task Force. In addition to eight statements on sex and gender differences in disease risk and outcomes, we assessed whether participants would like more education on sex and gender differences and whether they already study this topic in their field. We used a five-point Likert-type scale to measure the participant's level of agreement with the statements.

Statistical analyses

SPSS V.26.0/V.27.0 and GraphPad Prism V9.0 were used for statistical analyses.

We used medians and interquartile ranges to describe the distribution of skewed continuous variables and reported proportions for categorical variables. We reported descriptive statistics for the sample overall and sex-stratified.

RESULTS

Participants demographics

A total of 506 participants from 83 countries responded to the survey invitation and completed the survey. The personal and professional demographic characteristics of the participants are outlined in Table 1. Overall, 55.3% of the participants were women, 52.9% were ≤ 40 years of age, and 67.8% had specialized in medical oncology.

Most participants (28.9%) had 5-10 years of experience working in oncology, 93% were ESMO members (93%) and were working in Europe (58.7%). About half of the participants (52.0%) had worked in basic cancer research, and the majority worked at a university hospital (61.9%). Most participants treated breast cancers (57.9%), followed by colorectal (56.3%) and lung cancer (49.4%).

Awareness of study of sex and gender differences in oncology and ESMO Gender Medicine Task Force

Most participants (63%) had heard previously about the concept of studying sex and gender differences in oncology, while 25.9% had not heard about it or were unsure (11.1%). Similarly, most participants (61.7%) had heard about the ESMO Gender Medicine Task Force compared to 32.6% who had not.

Knowledge of sex and gender differences in oncology

We assessed the level of agreement on eight statements about sex and gender differences (Figure 1). About half of the participants (53.6%) agreed that men were at greater risk for most cancer types, 24.1% disagreed, and 22.3% did neither agree nor disagree. The statement that anticancer therapies are, in general, more toxic for women was agreed on by 38.5% while 30.3% participants disagreed. A significant proportion of the respondent neither agreed not disagreed (31.2%). Most participants (59.3%) agreed that the distribution of molecular subtypes of different tumour types is sex-related, while 15.4% disagreed. Few participants knew that the sex of the donor and the receiver affected the outcome after allogeneic stem cell transplantation, with 23.7% agreeing, 24.1% disagreeing with this statement and 52.2% neither agreeing nor disagreeing. That sex hormones are important for the development of non-sex-related cancer types was agreed upon by 45.6% of the participants, while 27.1% disagreed. Most participants (61.7%) disagreed with the statement that drug dosing based on body surface area takes sex differences into account, while 25.1% agreed. The vast majority (85.6%) agreed that the body composition, especially fat-free body mass, is sex and age-dependent, compared to only 5.9% who disagreed. Regarding clinical trials often reporting only the primary endpoint according to the patient's sex but not secondary endpoints, 52.8% agreed with this statement, compared to 19.1% who disagreed.

Interest in education and research on sex and gender differences in oncology

84.2% of the participants indicated they would like more education on sex and gender differences in oncology. Only 19.7% indicated that they already studied sex and gender differences in their field, while 55.9% did not.

Overall, the level of agreement with the statements was comparable between men and women.

DISCUSSION

Our survey indicates that most ESMO members are knowledgeable about the presence of the ESMO Gender Medicine Task Force and sex and gender differences in body composition, the sex-related distribution of molecular tumour subtypes, the greater cancer risk of men, the absence of sex-dependent drug dosing and the lack of reporting of secondary trial endpoints by sex.

However, there is a significant knowledge gap regarding the impact of sex hormones on the development of non-sex-related cancers, the higher risk of treatment toxicity for female patients, and the effect of donor and receiver sex on allogeneic stem cell transplantation outcomes. For several statements, a significant proportion of the participants chose to neither agree nor disagree, suggesting insecurity and lack of information on the topic.

The investigation of sex as a determinant of cancer susceptibility and prognosis has accelerated over the last decade. For various cancer types, sex differences in the distribution of histological and molecular subtypes are well documented [11] [12][13]. One of the most prominent examples is non-small cell lung cancer with

enrichment of EGFR-altered or KRASG12C mutant subtypes among never-smoker women, suggesting sex differences in susceptibility to tobacco-related carcinogens [14]. There is an increasing body of evidence showing an effect of androgen and oestrogen signalling in various non-sex-dependent cancers, including lung, bladder, and liver cancer and melanoma [15][16]. A large retrospective study analysing over 50,000 patients treated with allogeneic haematopoietic stem cell (HSC) transplantation found that male patients matched with female donors had worse outcomes than any other patient/donor combination. Male patients engrafted with female donor HSCs experienced more graft-versus-host disease (GvHD) and transplant-related mortality, highlighting the importance of donor and receiver sex for HSC function [17].

Despite the increased risk of clinical and haematological toxicity among women, sex-based drug dosing strategies are currently not available. Various structural barriers in drug dosing, clinical trial conduct, reporting of endpoints, and drug development and approval mechanisms hamper the integration of sex and gender aspects in treatment decisions [18]. The current dosing strategies are, therefore, inaccurate and lead to higher blood drug concentrations and toxicity in female patients compared to male ones for several anti-cancer therapies. The establishment of novel treatment approaches requires awareness of the potential sex effects at all levels of drug development, including compound discovery at preclinical experiments. An extensive survey among academic cancer researchers has revealed that although most participants were aware of the concept of studying sex differences in cancer biology, they disagreed that investigating sex differences in every aspect of cancer research and in all non-sex related cancer types was essential [19].

Most participants (84%) in our study wish for more education and training on the subject, suggesting awareness of a subjective lack of knowledge. Notably, the awareness of man and women professionals is similar. These results are comparable with a recent survey among Swiss oncologists and haematologists, where a significant proportion of the participants responded incorrectly to statements on the relevance of sex and gender in cancer research and clinical practice [20]. However, in contrast to ESMO members, in the Swiss cohort, more women, compared to men, wished sex and gender integrated into continuing education (85% vs. 61%) and research (90% vs. 69%) [20].

Our study has some limitations. Our study's participants still constitute only approximately 2% of the overall ESMO membership base. Participants were mainly medical oncologists who were established in their careers, with the majority based in Europe. Thus, these findings may not necessarily be representative of the views and knowledge of the medical and care personnel implicated in the care of cancer patients. Our study methodology involved optional online surveys associated with the risk of participant self-selection bias. Nevertheless, this remains the optimal methodology for accessing a wider audience.

Our survey revealed that oncology professionals are very interested in more training and education about the potential clinical implications of sex and gender differences in disease risk and outcome, thereby confirming the relevance of the work of the Gender Medicine Task Force for the Society.

Table 1. Participant characteristics

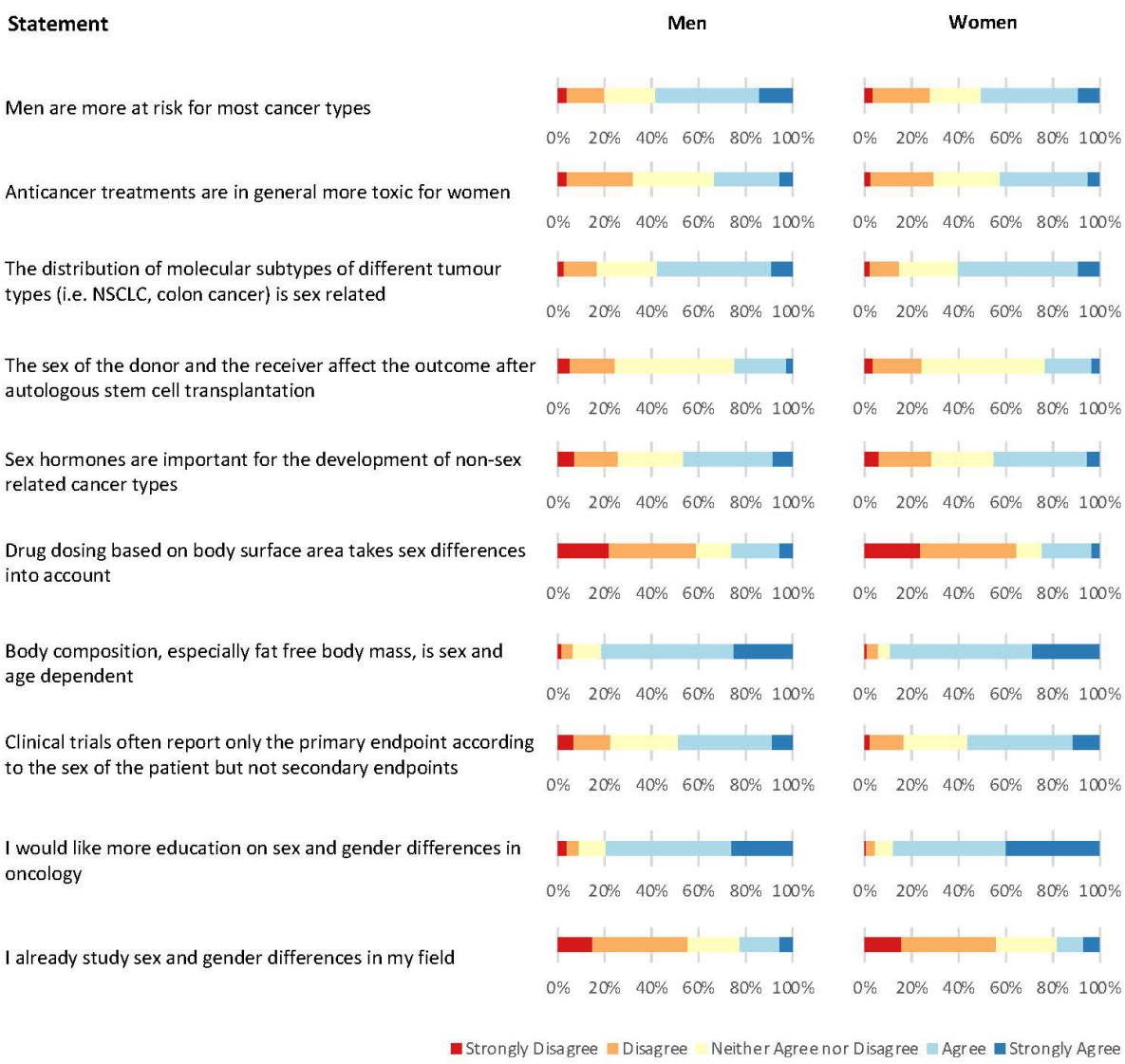
	All		Women		Men	
	N	%	N	%	N	%
N	506	100%	280	55.3%	220	43.5%
Age (years) n=506*						
21-40	268	53.0%	173	61.8%	93	42.3%
41 or older	238	47.0%	107	38.2%	127	57.7%
Specialty**						
Medical oncology	343	67.8%	197	70.4%	142	64.5%
Haemato-oncology	25	4.9%	6	2.1%	18	8.2%
Clinical oncology	54	10.7%	25	8.9%	29	13.2%
Radio-oncology	35	6.9%	15	5.4%	20	9.1%
Surgery	29	5.7%	16	5.7%	12	5.5%
Other	47	9.3%	28	10.0%	19	8.6%
Geographical region						
Europe	297	58.7%	176	62.9%	118	53.6%
Asia	118	23.3%	58	20.7%	59	26.8%
North America	30	5.9%	13	4.6%	15	6.8%
South America	33	6.5%	18	6.4%	15	6.8%
Africa	18	3.6%	8	2.9%	10	4.5%
Oceania	19	3.8%	7	2.5%	3	1.4%
Work experience						
Less than 5 years	109	21.5%	76	27.1%	32	14.5%
5 - 10 years	146	28.9%	84	30.0%	61	27.7%
11 - 15 years	87	17.2%	45	16.1%	41	18.6%
16 - 20 years	45	8.9%	28	10.0%	16	7.3%
21 - 25 years	44	8.7%	21	7.5%	22	10.0%
Over 25 years	75	14.8%	26	9.2%	48	21.8%
Types of cancer treated/studied **						
Brain	128	25.3%	73	26.1%	54	24.5%
Head and neck	178	35.2%	89	31.8%	86	39.1%
Thyroid gland	102	20.2%	53	18.9%	48	21.8%
Lung	250	49.4%	136	48.6%	112	50.9%
Liver	194	38.3%	103	36.8%	89	40.5%
Testis	146	28.9%	75	26.8%	69	31.4%
Prostate	205	40.5%	100	35.7%	103	46.8%
Skin Non-melanoma	103	20.4%	55	19.6%	45	20.5%
Skin Melanoma	167	33.0%	92	32.9%	72	32.7%
Bladder	179	35.4%	90	32.1%	87	39.5%
Kidney	178	35.2%	87	31.1%	88	40.0%
Pancreas	223	44.1%	123	43.9%	98	44.5%
Breast	293	57.9%	161	57.5%	129	58.6%
Gynaecological (endometrium, cervix, ovarian)	209	41.3%	119	42.5%	87	39.5%
Gastroeosopheal	244	48.2%	134	47.9%	108	49.1%
Colorectal	285	56.3%	147	52.5%	134	60.9%
Lymphoma	111	21.9%	54	19.3%	56	25.5%
Leukaemia	52	10.3%	21	7.5%	30	13.6%
Other	49	9.7%	28	10.0%	19	8.6%
Experience with basic cancer research						
Yes	263	52.0%	141	50.4%	119	54.1%
No	243	48.0%	139	49.6%	101	45.9%
Work setting						
University Hospital	313	61.9%	177	63.2%	131	59.5%
State hospital	118	23.3%	69	24.6%	47	21.4%
Private hospital	90	17.8%	43	15.4%	47	21.4%
Practice	35	6.9%	12	4.3%	23	10.5%
Research lab	29	5.7%	13	4.6%	16	7.3%
Other	16	3.2%	11	3.9%	5	2.3%
Having heard about sex and gender in oncology						

Yes	319	63.0%	178	63.6%	138	62.7%
No	131	25.9%	73	26.1%	56	25.5%
Not sure	56	11.1%	29	10.4%	26	11.8%

* 6 participants did not indicate their gender, they are included in the analysis of all patients, but not the analyses by gender

**non-exclusive category

Figure 1. Agreement on Statements about Sex and Gender Differences



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