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RESEARCH

Effect of sex on psychological distress and fatigue over time in a prospective cohort of cancer survivors

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Abstract

Background Studies indicate a higher level of distress in women than men with cancer, but whether this difference is retained over time is unknown. We studied the frequency and level of distress and fatigue during time according to gender in a cohort of cancer survivors.

Patients and methods In this prospective study, cancer survivors were invited to undergo a psychological session immediately before the medical visit. Distress was assessed by the distress thermometer, and fatigue was assessed by the ESAS-r scale. Patients underwent follow-up visits to assess changes over time.

Results A total of 305 patients and 568 visits were performed with a median follow-up of 15.8 months. At baseline, females, young age, and breast cancer patients had significantly higher distress. However, there was an increase in distress of 0.29 points every 6 months in males (95% CI, 0.09–0.50) versus no change in females (0.03 points, 95% CI, − 0.09–0.15; *p*-interaction = 0.01). The different behavior of cancer distress during time according to gender was more evident in subjects aged 68 or older due to increasing physical problems in men (*p*-interaction = 0.005). There was no change in fatigue with time according to sex.

Conclusions Women, younger age, and breast cancer patients had increased cancer distress at the initial visit. However, women tend to stabilize during follow-up, whereas men tend to worsen their distress, especially because of physical and emotional problems, suggesting different coping capabilities.

Trial registration The study is registered at ClinicalTrials.gov NCT05122052.

Implications for Cancer Survivors Interventions aimed at improving recognition of emotions related to disease experience in male cancer survivors appear necessary.

Keywords Psychological distress · Cancer survivors · Fatigue · Gender differences

Introduction

Distress and fatigue in cancer survivors are important factors affecting treatment compliance, efficacy, and quality of life. The prevalence of moderate or severe emotional distress in cancer patients ranges from 30 to 45% depending on the point of assessment [1, 2]. The National Comprehensive Cancer Network indicates that all cancer survivors should undergo a distress measurement as the sixth vital parameter to prevent more serious psychological disorders, including anxiety, depression, and coping disturbance [3]. There is evidence that distress can negatively impact quality of life and treatment compliance [4] and is associated with poorer clinical outcome in cancer patients [5, 6].

Implementing a screening distress program is important because evidence indicates that heightened distress often goes unrecognized by oncology professionals [7]. Moreover, distress in cancer survivors has been shown to be higher in females than males [8–10], but the behavior of distress over time has not been studied in prospective studies, nor is it known if there are differences related to gender. Importantly, gender role conflict and traditional masculine norms are important factors that can hamper adjustment in men with

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cancer [11]. In cancer survivors, it has been demonstrated that traditional and restrictive masculine and gender role conflict are related to greater physical and psychological problems in men [12, 13]. Gender role conflict may negatively influence the physical and psychological outcomes of men with cancer through compromised emotional approach coping [14]. These differences may have important therapeutic implications in terms of personalized psychological support as cancer progresses during individual trajectories.

In addition to distress, fatigue is often unrecognized by the physician and therefore underestimated, although it affects 30–40% of patients at the time of diagnosis and 80–90% of patients undergoing chemotherapy or radiotherapy and appears to be greater in women and in younger patients [15]. Given the impact of fatigue on quality of life and adherence to care, the ESMO guidelines indicate the need to implement, as part of the diagnostic assessment, a screening at regular intervals both during therapy and during the course of the disease to propose a personalized treatment [16].

The aim of the present study was to examine the effect of gender during time on psychological distress and fatigue in cancer survivors across a broad range of cancer types. Our hypothesis was that women report higher psychological distress and fatigue than men at the initial visit, but a reversed trend is observed during follow-up between men and women [17], possibly as a result of different coping capabilities.

Methods

Study design

This was a prospective, observational study aimed at assessing the effect of gender on cancer distress and fatigue during follow-up in a consecutive cohort of cancer patients seen by a team of two specialists, a psycho-oncologist (GR), and a medical oncologist (ADC), in a consecutive two-stage clinical session. The study was conducted in the ambulatory clinic of the Villa Serena Hospital, GVM group, an affiliated clinical center of the E.O. Ospedali Galliera, Genoa, Italy. The study was approved by the Ethical Committee of the Liguria Region, Genoa, Italy, and informed consent was obtained from each participant. The study is registered at ClinicalTrials.gov NCT05122052.

Psychological session

Before the oncology visit, each patient was invited to undergo a psychological interview of 20–30 min. During the interview with a psycho-oncologist/psychotherapist of analytical background, the following aspects were addressed: (1) favor emotional expression identifying the most difficult issues to promote mechanisms of elaboration of living experiences; (2) offer a containment of intense emotions; (3) assess awareness of diagnosis and prognosis; (4) favor expression of fears regarding treatment expectancy; (5) favor the expression of difficulties regarding the inability to cope with prior commitments before the disease; (6) assess the family and friend network; and (7) improve the patient medic communication and relationship, if necessary. At the beginning of the psychological session, the distress thermometer [18] and ESAS-r scale [19] were compiled together with the demographic characteristics, including children, education, marital status, and occupation. With the patient's consent, all outstanding issues that were relevant to the therapeutic plan were discussed between the psychotherapist and the medical oncologist before the oncology visit together with delivery of the DT and ESAS-r scale results.

Distress thermometer

Since 1999, the National Comprehensive Cancer Network (NCCN) has recommended routine screening for distress in all cancer patients. The patient rates his/her level of distress over the past week. The distress thermometer (DT) was developed as a simple tool to effectively screen for symptoms of distress. The instrument is a self-reported tool using a single-item tool using a 0 (no distress) to 10 (extreme distress)–point Likert scale resembling a thermometer. Additionally, the patient is prompted to identify sources of distress using a 39-item supplemental list of potential sources of distress, including the following domains: emotional, physical, practical, family, and spiritual/religious problems. DT scores are categorized into three levels, 0–3, low, 4–6, moderate, 7–10, and severe, according to the National Comprehensive Cancer Network 2013 [20]. The DT has demonstrated adequate reliability and has been translated and validated into numerous languages, including Italian [21]. The tool is easy to administer and empowers the clinician to facilitate appropriate psychosocial support and referrals.

ESAS-r fatigue

The Edmonton Symptom Assessment System (ESAS) represents one of the first symptom batteries in palliative care and has since been validated by multiple groups, translated into over 20 languages, and adopted in both clinical practice and research to support symptom assessment in many centers worldwide [19]. A revised ESAS numeric rating scale (ESAS-r) consisting of 9 core symptoms (pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, feeling of well-being, shortness of breath) and an optional 10^{th} symptom has more recently been developed. Specifically, ESAS-r stated the time frame of symptom assessment as "now," added brief explanations for tiredness ("lack of energy"),

drowsiness ("feeling sleepy"), depression ("feeling sad"), and anxiety ("feeling nervous") and well-being ("how you feel overall"), changed "appetite" to "lack of appetite", adjusted the order of symptoms, removed the horizontal line over the numbers and shaded alternate items in gray for readability, and suggested constipation as the tenth item.

Medical oncology visit

The chief medical oncologist of the Department of Medical Oncology performed all medical visits to determine, confirm, or change the treatment plan according to disease status. Every patient had an electronic medical record where all host, tumor, and treatment characteristics are listed. This record is linked to the hospital via a central computer server that controls and provides information to other computers in a network and allows downloading instrumental imaging and diagnostic tests.

Sample size and statistical methods

Our hypothesis was that men had lower cancer distress than women at baseline but a worsening relative to women during follow-up. A sample size of 300 evaluable subjects with at least one-third men was estimated to allow us to detect a significant sex-by-time interaction on cancer distress with 80% power and 5% two-way alpha significance. Descriptive statistics included the mean, standard deviation, median, and 25th and 75th percentiles for continuous variables; in the case of categorical factors, absolute and relative frequencies were used. Chi-square or Fisher's exact, Kruskal–Wallis, or *t*-tests were used to compare categorical and continuous factors, respectively. The longitudinal analysis for distress, ESAS-r, and the mean number of problems was done by using a mixed model adjusted for baseline covariates as fixed effects and including intercept and slope (time) as random effects. All effects are shown with the related 95% confidence intervals. The analysis was performed with STATA (version 14, StataCorp, College Station, TX, USA).

Results

The study population consisted of 391 patients seen between March 1, 2016, and December 31, 2020. However, for 86 patients, some baseline demographic or clinical information was missing, leaving 305 patients and 568 visits fully assessable for the study. On average, a mean ± SD of 1.9 ± 1.2 visits per patient was conducted with a median follow-up of 15.8 months and a mean interval between the two visits of 10.5 ± 7.9 months. The participant flow diagram is depicted in supplementary Fig. 1.

The associations between patient and tumor characteristics and distress or fatigue at baseline are described in Table 1. There was a significant association between distress and fatigue (Spearman correlation $r = 37.8$, $p < 0.001$). At baseline, women and younger patients were significantly more distressed than men or older patients. Retired people were less distressed and had a lower incidence of severe fatigue than employees. Additionally, women with breast cancer were more distressed than patients with other tumor sites. There was no association between distress and education, tumor stage (early versus advanced), line of treatment (adjuvant for early stage vs first line vs additional lines for metastatic disease), or presence of an active treatment. Likewise, there was no association between fatigue and sex, age, marital status, tumor site, stage, line of treatment, or current active treatment.

The effect of the different variables on distress and fatigue during time is shown in a multivariate analysis in Table 2. There was a different behavior of cancer distress in men versus women over time, consisting of an increase in distress in men and no change in women during follow-up (p-interaction = 0.028). The mean trajectories for distress score during follow-up according to patient gender are illustrated in Fig. 1, where panel a shows the individual trajectories and the raw mean evolution by gender, whereas panel 1b illustrates the mean behaviors according to the adjusted statistical model for males and females. At baseline, men had significantly lower distress than women (− 1.25; 95% CI = − 1.95, − 0.55; $p = 0.001$). However, there was a significant effect modification on psychological distress by gender over time, with a mean increase in distress of 0.29 points every 6 months in males (95% CI = 0.09, 0.50) and no change in females (0.03 points, 95% CI = − 0.09, 0.15, p-interaction = 0.01). A further subgroup analysis according to age suggested that the effect modification of gender on distress during time was not generalized but limited to subjects aged 68 or older. Indeed, the time by gender interaction term was not significant in subjects aged 67 or younger ($p = 0.612$), whereas the mean and 95% CI increment of distress was 0.36 (95% CI = 0.13, 0.60) points every 6 months in males and 0.02 (− 0.21, 0.26) in females among subjects aged 68 or older (p-interaction = 0.045). Noticeably, the apparent increase in distress in women after 24 months shown in panel 1a must be taken with caution given a lower number of observations after the first year.

Regarding other factors, a trend toward a higher level of distress over time was observed in divorced/separated or single patients ($p = 0.058$) and in patients with locally advanced or metastatic cancer ($p = 0.078$). Moreover, lower levels of distress were observed in patients with prostate or genitourinary cancers versus other tumor sites ($p = 0.048$).

Regarding the factors affecting fatigue during follow-up, housewives and office workers as well as patients with

Table 1 Patient and tumor characteristics according to distress thermometer and ESAS-r fatigue score

		Overall = 305 *N* (%)	Distress				ESAS–fatigue			
			Low	Moderate	Severe	*p* value	Low	Moderate	Severe	*p* value
			112 (36.7%)	119 (39.0%)	74 (24.3%)		158 (51.8%)	118 (38.7%)	29 (9.5%)	
Sex	F	199 (65.3)	58 (29.2)	80 (40.2)	61 (30.6)	< 0.00	96 (48.2)	82 (41.2)	21 (10.6)	0.223
	M	106 (34.7)	54 (50.9)	39 (36.8)	13 (12.3)		62 (58.5)	36 (34.0)	8 (7.5)	
Age, years	≤67	159 (52.1)	50 (31.5)	61 (38.4)	48 (30.2)	0.025	83 (52.2)	61 (38.4)	15 (9.4)	0.985
	≥68	146 (47.9)	62 (42.5)	58 (39.7)	26 (17.8)		75 (51.4)	57 (39.0)	14 (9.6)	
Education	Primary/middle school	108 (35.4)	34 (31.5)	47 (43.5)	27 (25.0)	0.642	49 (45.4)	46 (42.6)	13 (12.0)	0.468
	High school	118 (38.7)	45 (38.1)	45 (38.1)	28 (23.7)		64 (54.2)	43 (36.4)	11 (9.3)	
	Degree	79 (25.9)	33 (41.8)	27 (34.2)	19 (24.1)		45 (57.0)	29 (36.7)	5 (6.3)	
Marital status	Spouse/cohabitee	219 (71.8)	89 (40.6)	83 (37.9)	47 (21.5)	0.149	116 (53.0)	86 (39.3)	17 (7.7)	0.420
	Vidow	36 (11.8)	12 (33.3)	16 (44.4)	8 (22.2)		16 (44.4)	15 (41.7)	5 (13.9)	
	Divorced/separated	26 (8.5)	5 (19.2)	10 (38.5)	11 (42.3)		16 (61.5)	7 (26.9)	3 (11.5)	
	Single	24 (7.9)	6 (25.0)	10 (41.7)	8 (33.3)		10 (41.7)	10 (41.7)	4 (16.6)	
Occupation	Retiree	155 (50.8)	65 (41.9)	66 (42.6)	24 (15.5)	0.024	92 (59.4)	51 (32.9)	12 (7.7)	0.029
	Office worker	68 (22.3)	19 (27.9)	26 (38.2)	23 (33.8)		31 (45.6)	26 (38.2)	11 (16.2)	
	Housewife	38 (12.5)	10 (26.3)	15 (39.5)	13 (34.2)		11 (29.0)	23 (60.5)	4 (10.5)	
	Other	24 (7.9)	8 (33.3)	7 (29.2)	9 (37.5)		13 (54.2)	10 (41.6)	1 (4.2)	
	Self-employed	20 (6.6)	10 (50.0)	5 (25.0)	5 (25.0)		11 (55.0)	8 (40.0)	1 (5.0)	
Tumor site	Breast	111 (36.4)	32 (28.8)	44 (39.6)	35 (31.5)	0.064	52 (46.8)	51 (46.0)	8 (7.2)	0.465
	Prostate, genitourinary	96 (31.5)	43 (44.8)	34 (35.4)	19 (19.8)		49 (51.0)	36 (37.5)	11 (11.5)	
	Digestive organs, peritoneum	65 (21.3)	29 (44.6)	24 (36.9)	12 (18.5)		39 (60.0)	19 (29.2)	7 (10.8)	
	Other (lung, eye melanoma)	33 (10.8)	8 (24.2)	17 (51.5)	8 (24.2)		18 (54.5)	12 (36.4)	3 (9.1)	
Stage	Local	185 (60.7)	69 (37.3)	73 (39.5)	43 (23.2)	0.880	96 (51.9)	73 (39.5)	16 (8.6)	0.791
	Locally advanced/metastatic	120 (39.3)	43 (35.8)	46 (38.3)	31 (25.8)		62 (51.7)	45 (37.5)	13 (10.8)	
Line of treatment	Adjuvant/neoadiuvant	175 (57.4)	60 (34.3)	73 (41.7)	42 (24.0)	0.609	89 (50.9)	70 (40.0)	16 (9.1)	0.463
	First line	87 (28.5)	37 (42.5)	31 (35.6)	19 (21.8)		46 (52.9)	35 (40.2)	6 (6.9)	
	2nd+	43 (14.1)	15 (34.9)	15 (34.9)	13 (30.2)		23 (53.5)	13 (30.2)	7 (16.3)	
Chemo or radiotherapy	No	150 (49.2)	58 (38.7)	58 (38.7)	34 (22.7)	0.732	71 (47.3)	64 (42.7)	15 (10.0)	0.296
	Yes	155 (50.8)	54 (34.8)	61 (39.4)	40 (25.8)		87 (56.1)	54 (34.8)	14 (9.0)	

P values refer to Fisher's exact test or Chi-squared for frequencies

Table 2 Longitudinal analysis for distress and ESAS fatigue

		Distress			ESAS–fatigue		
		Beta	95%CI	*p* value	Beta	95%CI	*p* value
Sex	M vs F	−1.25	−1.95, −0.55	<0.001	−0.22	−0.88, 0.44	0.510
Months of follow-up		0.00	−0.02, 0.02	0.650	0.01	−0.01, 0.03	0.255
Month by sex interaction		0.04	0.00, 0.08	0.028	−0.01	−0.05, 0.03	0.598
Age, years	≥68 vs ≤67	−0.34	−1.03, 0.36	0.342	0.16	−0.51, 0.84	0.631
Education	High vs middle/primary school	−0.06	−0.71, 0.59	0.597	−0.54	−1.15, 0.06	0.059
	Degree vs middle/primary school	−0.35	−1.09, 0.38		−0.79	−1.47, −0.11	
Marital status	Widow vs spouse/cohabitee	−0.31	−1.17, 0.56	0.058	0.59	−0.21, 1.39	0.202
	Divorced/separated vs spouse/cohabitee	1.06	0.06, 2.06		0.21	−0.70, 1.12	
	Single vs spouse/cohabitee	0.85	−0.15, 1.85		0.84	−0.10, 1.79	
Occupation	Office worker vs retiree	0.46	−0.38, 1.30	0.814	0.96	0.15, 1.77	0.034
	Housewife vs retiree	0.45	−0.45, 1.35		1.09	0.23, 1.95	
	Other vs retiree	0.30	−0.85, 1.45		−0.25	−1.32, 0.82	
	Self-employed vs retiree	0.18	0.99, 1.36		0.47	−0.69, 1.63	
Tumor site	Prostate or genito-urinary vs breast	−0.45	−1.14, 0.24	0.048	0.05	−0.59, 0.69	0.995
	Digestive organs, peritoneum vs breast	0.11	−0.66, 0.88		−0.04	−0.77, 0.69	
	Others (lung or eye) vs breast	0.90	−0.11, 1.92		0.04	−0.90, 0.98	
Stage	Locally advanced/metastatic vs local	0.77	−0.09, 1.63	0.078	0.49	−0.33, 1.32	0.242
Line of treatment	First vs adjuvant/neoadjuvant	−0.68	−1.53, 0.18	0.264	−0.05	−0.86, 0.77	0.994
	2nd + vs adjuvant/neoadjuvant	−0.31	−1.42, 0.79		−0.05	−1.09, 1.00	
CT/RT	Yes vs no	0.22	−0.37, 0.81	0.469	−0.02	−0.57, 0.53	0.946

The two model are referred to two different mixed model with all covariates shown in the table, random intercept (patient), and random slope (time); 2nd +, second line foreward

a lower level of education had a higher level of fatigue ($p = 0.034$ and $p = 0.059$) (Table 2). The behavior of the fatigue score over time according to gender is illustrated in supplementary Fig. 2. There was no significant difference at baseline ($p = 0.510$, panel 2a), nor was there an effect modification during such time according to gender (p-interaction = 0.598, panel 2b).

The effect modification by gender on cancer distress over time was reflected in the number of problems composing the DT (Fig. 2). At baseline, men had significantly fewer distress-related problems than women overall ($p = 0.010$) and in the emotional domain ($p = 0.01$), whereas during follow-up, there was a reversed trend with an increase in distress in men and a trend toward a decrease or a plateau in women (time by gender interaction $p = 0.010$). Specifically, men had increasing physical problems, whereas women improved over time (p-interaction = 0.005). A similar pattern was noted for emotional problems, although the interaction term was not statistically significant because of the smaller number of items contributing to this domain ($p = 0.147$). We found no evidence that worse patients stayed longer in the study. In fact, patients with a more advanced stage showed a trend toward a shorter follow-up ($p = 0.115$), and patients on chemotherapy at baseline had a significantly shorter follow-up ($p = 0.027$). Neither distress nor fatigue at baseline influenced the follow-up duration ($p = 0.435$ and $p = 0.895$, respectively).

Discussion

Gender as a social process implies an ongoing socialization of feminine and masculine norms, roles, relationships, and expectations since men and women are culturally conditioned to perceive and respond differently to life events, such as illness [22]. Our findings indicate that gender has a different impact on cancer distress over time from both the psychological and physical points of view. Younger age, female sex, and breast cancer were associated with a higher level of distress at baseline compared with older age, male sex, and other tumor sites at their initial cancer history. Moreover, retired people have lower distress and fatigue than employees who most likely feel they cannot cope with work commitments at a time when they have less physical and psychological abilities following the illness [23, 24]. Stage was associated with a trend toward a shorter follow-up due to disease worsening. Moreover, a higher stage was associated with a tendency toward higher distress in the longitudinal analysis over time ($p = 0.078$). Breast cancer patients had a trend toward higher distress at baseline ($p = 0.068$) and

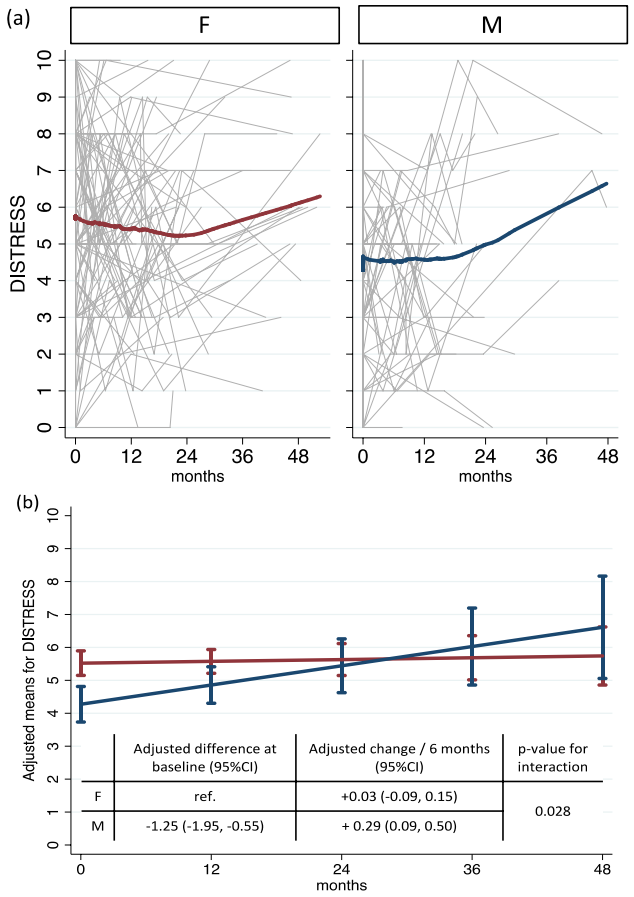

Fig. 1 Longitudinal analysis of distress according to gender. a Observed distress values for each patient according to gender. The line represents the locally weighted regression curve. Please take into account the significant loss of observations after 24 months when interpreting the apparent increase in distress in both gender groups. b Mean trend for predicted values of distress according to gender adjusted for age, education, marital status, tumor site, stage, line of treatment, and use of chemotherapy at baseline

higher distress during follow-up ($p = 0.048$) compared to other disease sites.

Our findings are consistent with previous studies conducted among various patient [25, 26] and healthy populations [27]. The difference in the distress level between men and women at the initial visit could depend on two complementary factors. The first is linked to a greater ease of women in recognizing and expressing their emotions, speaking of themselves, and capturing life situations in terms of interpersonal relations [28]. The second explanation can be linked to the greater attention paid to psychological discomfort in women with cancer. For instance, breast cancer research is well supported, and thus, the capacity of women to express discomfort and their strategies for adapting to the disease has been a subject of many studies, whereas cancer distress may be unrecognized in men and elderly patients [29].

Our main study objective was to evaluate the effect of gender on cancer distress throughout time in a prospective cohort of cancer survivors assessed by a team of two specialists, a psycho-oncologist, and a medical oncologist, in a real-time, sequential session, thus favoring emotional expression and facilitating patient-medic communication and reducing interobserver variability. Our findings show that while distress remains unchanged or even decreases in women with time, especially at the emotional level, there is a significant increase in distress in men, which is mainly associated with an increase in physical symptoms and emotional problems. Conversely, fatigue remains stable over time in both men and women. These results seem to be in line with previous findings that showed that women have a greater ease of recognizing and expressing emotions, abilities from which they receive greater benefit in terms of satisfaction in life, self-esteem, and minor anxiety [30]. We hypothesize that men are less able to make use of emotional expression as a coping strategy. Men tend to build their identity on control, strength, and problem solving and may have more difficulty accepting the loss of control and adapt to a situation of greater dependence [31]. Men also have a greater difficulty admitting feeling vulnerable and seeking help from doctors [32]. The difficulty in recognizing and expressing their emotions derives from cultural aspects and social expectations that have their roots in primary relationships. For example, the mother, in communicating with her child, recognizes and shares many more emotions with her daughter than her son, expecting the girl to be more emotional [33]. In line with this reasoning, the suicide rate is much higher in men than in women [34] despite a higher rate of depression and suicide attempts in women [35]. In addition, requests for euthanasia and physician-assisted suicide in cancer patients are significantly more frequent in men than in women [36].

Therefore, women seem better to adapt to the "role of patients" [37] and over time tolerate physical symptoms better and seem to become resilient to the loss of self-esteem and difficulty. The fact that men initially have less distress than women is supposedly due to the implementation of negative mechanisms and the lack of tools to adapt to the disease over time.

On the other hand, studies [38] have found that cancer-related masculine threat was significantly associated with decreased emotional processing, which ultimately explained the effect of cancer-related masculine threat on poor physical outcomes. Gender role conflict was also found to explain distress in men with prostate cancer [14]. Our study population of men was mainly composed of prostate cancer. Overall, these data suggest that gender role conflict and emotional approach coping, with the tendency for men to inhibit emotional expression, may lead to negative cancer-related physical and psychological events. Our hypotheses need to be addressed in a future study, including studies

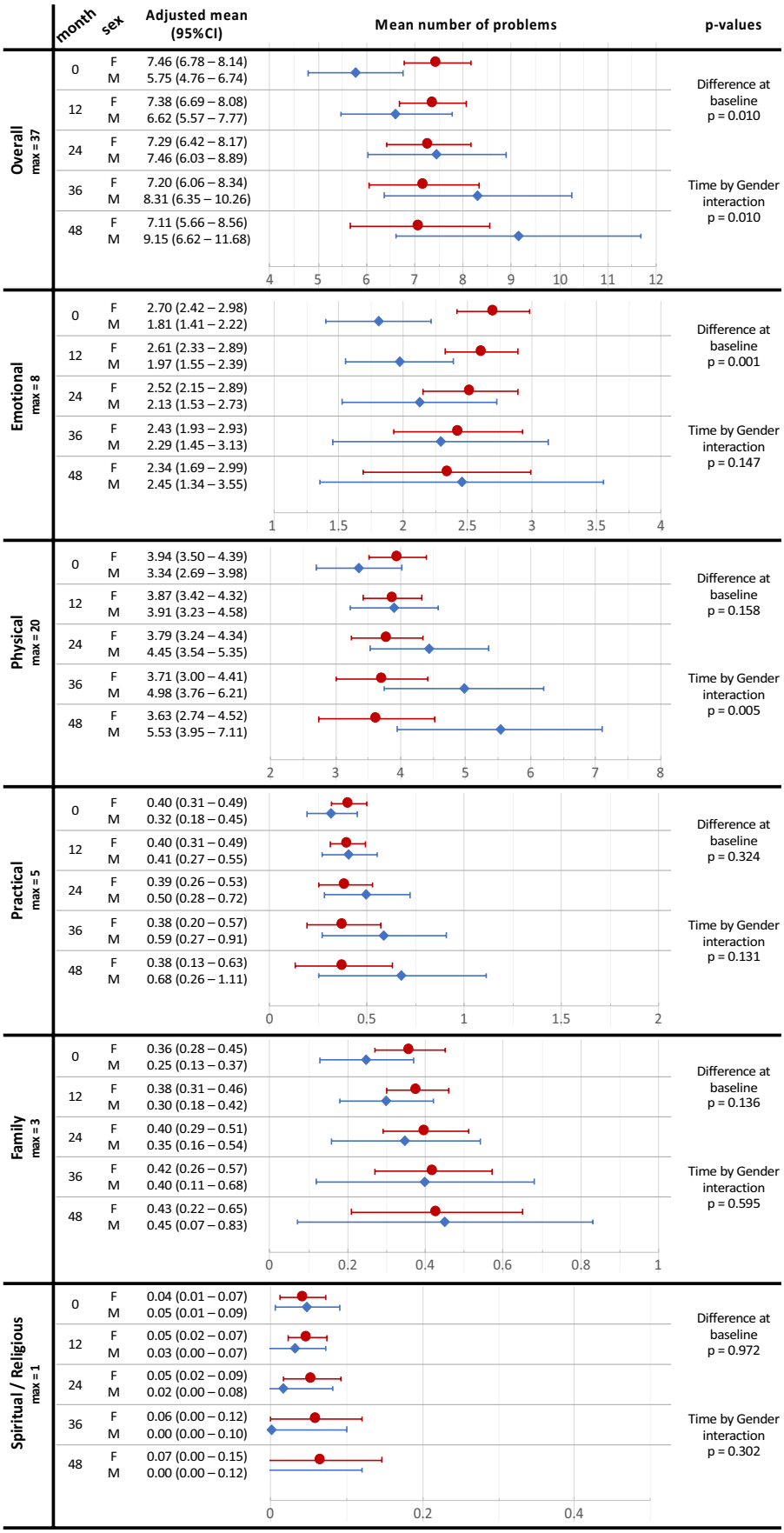

Fig. 2 Estimated mean number of distress problems overall and by area according to gender at different time points. The number of problems was adjusted for age, level of education, marital status, main diagnosis, stage, line of therapy, and use of chemotherapy at baseline. The number of subjects at each time point was as follows: baseline, $n = 164$ (108 females and 56 males); 12 months, $n = 92$ (63 females and 29 males); and 24 months, $n = 38$ (29 females and 9 males). The 95% CI and p value derived from the mixed models take into account the variability due to a lower number of subjects during follow-up. Therefore, even if this loss of observations may affect the accuracy of the point estimate (beta), the trend observed in the mixed models is still accurate

of gender-related differences in coping strategies. Although our study did not specifically address the role of hormonal components, these factors are known to impact the health of patients with cancer [39, 40]. A hormonal component is important given the known ability of estrogens to adapt to distress based on their neurotrophic and neuroprotective actions. Estrogens, via their signaling mechanisms and interactions with multiple neurotransmitter systems in our brain, have heavy involvement in cognition and mood [41]. Moreover, the modulatory roles of estrogen receptors and estrogen signaling on brain function have been highlighted, with studies reporting their neuroprotective effects on the brain by promoting neurotrophin synthesis and protecting the brain from inflammation and stress [42].

The ability to adapt depends upon the coping strategies. While women tend to rely upon psychological support based on emotional aspects, men are more focused on strategies of problem solving. The consequence is that women benefit more from help care strategies that are typically offered, including psychological support and psychotherapy. In contrast, men's difficulties coping with the disease over time illustrate the necessity to act preventively to favor recognition of these difficulties. Therefore, men manifest lower distress at their initial visit, possibly because of mechanisms of negation and defense generally associated with a low level of emotional distress.

Our study has some limitations, including the small group of investigators, which was composed of two health professionals, which may limit the generalizability of our findings. Second, we did not assess the efficacy of the psychological session in terms of distress reduction after the session, so our hypothesis of a beneficial effect remains to be proven.

Our findings of an increase in distress over time in men strongly suggest that men should be helped to get in touch with their emotions and needs since the beginning of their disease trajectory. Our scheme of a double visit in immediate sequence is oriented precisely to achieve this goal. The psychological session with the psycho-oncologist is a space, even a mental one, for focusing on the emotions related to the patient's experience of illness at that moment and helps both the patient and the doctor not to neglect these emotional aspects. The highest distress in male cancer survivors over time is also related to the increase in physical symptoms, and while it is true that symptoms can be the cause of an increased distress, it is also true that a higher distress determines a lower tolerance to physical symptoms that are lived with greater intensity and amplified. For example, symptoms such as pain, nausea, and insomnia have an emotional component that is important to consider for better care [43].

In conclusion, our findings indicate that women with cancer tend to have stable distress during follow-up, whereas men tend to worsen it, especially because of physical and emotional problems, suggesting different coping capabilities. Our data suggest that men have greater difficulty than women in recognizing their vulnerability and in processing emotions, which determines a difficulty in adapting and a progressive increase in distress during the course of the disease. Our results suggest the importance of promoting emotional expression in male cancer survivors and focusing on their needs during the screening for distress. Screening can be very useful because it helps patients talk about their diagnosis and treatment. It provides a vocabulary for thoughts, feelings, and concerns that the patients and healthcare providers can use to communicate as they discuss the treatment protocol and what to expect in terms of quality of life.

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Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by all authors. The first draft of the manuscript was written by Gabriella Rondanina and Andrea De Censi, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests The authors declare no competing interests.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Regione Liguria (028/2019).

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare no competing interests.

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