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ORIGINAL ARTICLE

Characteristics of adverse events of endocrine therapies among older patients with breast cancer

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Abstract

Purpose To clarify the profile of adverse events from endocrine therapies in older patients.

Methods We surveyed 15 subjective symptoms including hot flashes, sweating, knuckle stiffness, knee/shoulder joint pain, limb numbness, lethargy, forgetfulness, depressive state, irritated state, genital bleeding, leukorrhea increase, vaginal dryness, bone fracture, and weight gain by a questionnaire among 2044 patients over 55 years old (total number of answered sheets, 8875) and compared the results according to age (56–69 years old vs. ≥ 70 years old) and type of therapy (aromatase inhibitors (AIs) vs. selective estrogen receptor modulators (SERMs)). Among patients 56–69 years old, 6093 and 314 responses were from patients treated with AIs (1477 patients) and SERMs (123 patients), respectively, and 2292 and 176 responses were from those ≥ 70 years old treated with AIs (581 patients) and SERMs (51 patients), respectively.

Results In patients ≥ 70 years old, sweating, knuckle stiffness, knee/shoulder joint pain, limb numbness, and lethargy were significantly more frequent/severe with AIs than with SERMs. In those aged 56–69, knuckle stiffness and vaginal dryness were significantly more frequent with AIs than with SERMs, but the opposite occurred for hot flashes, leukorrhea increase, genital bleeding, and weight gain.

Conclusions Among patients ≥ 70 years old, many symptoms were significantly more frequent/severe with AIs than with SERMs, compared with those aged 56–69, which suggests a difference in the profile of adverse events according to the type of endocrine therapy and the patient's age. It is important to consider the benefits and risks of each treatment to optimize endocrine therapy for older patients.

Keywords Aromatase inhibitor · Endocrine therapy · Older · Tamoxifen · Questionnaire · Postmenopausal

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Introduction

Most breast cancers proliferate in response to estrogens. In postmenopausal women, estrogens from the ovaries decreased and production of estrogens from peripherally localized aromatase is important [1]. Selective estrogen receptor modulators (SERMs), such as tamoxifen, were the standard endocrine therapy for estrogen-responsive tumors until aromatase inhibitors (AIs) replaced SERMs to treat postmenopausal patients. The therapeutic advantage (recurrence reduction) of AIs to SERMs was demonstrated by several randomized trials and meta-analyses, and the use of AIs is standard for postmenopausal breast cancer patients [2]. Estrogens are physiologically important hormones not only in female reproductive organs, such as the breasts or uterus, but also in various organs irrespective of menopausal status or sex [3–7]. Menopausal disorders are caused by a rapid decrease in ovarian estrogens.

Long-term estrogen deficiency is an etiological factor for osteoporosis [5], and dysfunctions in estrogen-related systems are associated with various geriatric diseases such as Alzheimer's disease or cancers [3, 4, 7, 8]. Most adverse events of breast cancer endocrine therapies are caused by estrogen-deficient conditions, but differences occur according to the type of endocrine therapy. For example, the main considerations for AIs include bone health, joint pain, or musculoskeletal symptoms, and the major risks for SERMs are associated with a partial ER-agonistic effect, which causes some disorders promoted by estrogens (e.g., endometrial cancer or thrombosis) [9–16].

The number of older breast cancer patients is rapidly increasing in developed countries, which reflects an aging society. In older patients where systemic and metabolic functions have decreased, adverse events from endocrine therapies may be more serious than breast cancer survival. Older patients are usually excluded from most clinical trial studies (or only healthy older patients are included) [17], and the benefits and risks of endocrine therapies for this group are largely unknown [18–20]. Despite the lack of precise clinical data, this group has been treated with AIs unless they have problems that may become more serious with AI administration (e.g., low bone mineral density as a risk factor for bone fracture). Recently, de-escalation of endocrine therapy has been discussed, and tamoxifen monotherapy has regained attention for low-risk postmenopausal patients [21], but the benefits of de-escalation have not been analyzed. Here, we focused on the profile of adverse events from endocrine therapies in older patients. We surveyed 15 subjective symptoms by a questionnaire among patients over 55 years old (y/o) at the time the questionnaire was administered and compared the results according to age (56–69 y/o or ≥ 70 y/o) and type of therapy used (SERMs or AIs).

Patients and methods

A questionnaire survey was administered to patients who had surgery for breast cancer and were being treated with adjuvant endocrine therapies at an outpatient clinic in the Cancer Institute Hospital from 2008 to 2013. Patients were surveyed during routine clinical practice when the patients visited the hospital for periodic postoperative screening, which were scheduled about every 6 months. Most patients answered the questionnaire when required (mostly every 6 months), because it was part of the routine clinical practice. The contents of the questionnaire are shown in Fig. 1. A total of 16,119 responses were obtained from 3808 women aged 24–96, and 8875 from 2044 patients over 55 y/o at the time the questionnaire was administered. Among patients 56–69 y/o, 6093 and 314 responses were from patients treated with AIs (1477 patients) and SERMs (123 patients), respectively, and 2292 and 176 responses were from those ≥ 70 y/o treated with AIs (581 patients) and SERMs (51 patients), respectively.

In the questionnaire, the presence/degree of 15 symptoms were assessed including two autonomic symptoms (hot flashes and sweating), three musculoskeletal symptoms (knuckle stiffness, knee/shoulder joint pain, and limb numbness), two systemic symptoms (easy fatigability and lethargy), three neuropsychiatric symptoms (forgetfulness, depressive state, and irritated state), three genital symptoms (genital bleeding, leukorrhea increase, and vaginal dryness), bone fracture, and weight gain. Subjective symptoms, such as hot flashes, sweating, knuckle stiffness, knee/shoulder joint pain, limb numbness, easy fatigability, lethargy, forgetfulness, depressive state, irritated state, and vaginal dryness, were divided into four levels: absence, mild, moderate, or severe. The presence of genital bleeding, leukorrhea increase, or bone fracture was noted. Weight gain was divided into four levels: absence, gain < 5 kg, 5–10 kg, and > 10 kg.

Statistical analyses were performed by chi-square test using JMP12.0.1 (SAS Institute, Cary, NC) to compare the results between SERMs and AIs or between 56–69 y/o and ≥ 70 y/o. $P < 0.05$ was considered significant, and the Bonferroni adjustment was added appropriately ($P < 0.05/15 = 0.0033$).

Results

The presence/degree of each symptom is summarized in Table 1 and Fig. 2. The presence/degree of hot flashes among those ≥ 70 y/o did not differ between SERMs and AIs, but hot flashes were experienced with SERMs more frequently/severely than with AIs among patients aged 56–69 ($P < 0.0001$). Comparing symptoms with each endocrine therapy according to age, hot flashes were lower in ≥ 70 y/o than in 56–69 y/o regardless of the type of endocrine therapy ($P < 0.0001$). Sweating was more frequent/severe in patients treated with AIs than with SERMs among those ≥ 70 y/o ($P = 0.0011$), but the opposite occurred for those 56–69 y/o ($P = 0.0142$). Sweating was also lower in ≥ 70 y/o than in 56–69 y/o regardless of the type of endocrine therapy ($P < 0.0001$).

Knuckle stiffness was more frequent/severe in patients treated with AIs than with SERMs irrespective of age ($P < 0.0001$). Knuckle stiffness was lower in ≥ 70 y/o than in 56–69 y/o with both therapies ($P < 0.0001$ for AIs and $P = 0.0029$ for SERMs). Knee/shoulder joint pain was also more frequent/severe with AIs than with SERMs regardless of age ($P = 0.0229$ for 56–69 y/o and $P = 0.0013$ for ≥ 70 y/o), but the frequency/severity of the symptom was not significantly different between the two age groups regardless of therapy. Limb numbness was more frequent/severe in patients treated with AIs than with SERMs among patients ≥ 70 y/o ($P = 0.0010$), but no difference was observed among those aged 56–69. For each therapy, this

Fig. 1 A blank interview sheet including the contents of the questionnaire (translated into English)

To patients being treated with endocrine therapy

In order to appropriately deal with the adverse events of endocrine therapy, please answer the following questions. In each question, please select one which is most suitable for your condition since your last visit.

Name:
ID:
Age:
Date:

Drug name: ☐Norvadex ☐Fareston ☐Arimidex ☐Femara ☐Aromasin

	Absent	Mild, suffering less	Moderate, not restricting daily life	Severe, restricting daily life
Have hot flashes	□	□	□	□
Sweat a lot	□	□	□	□
Have knuckle stiffness or pain	□	□	□	□
Have knee/shoulder joint pain	□	□	□	□
Have limb numbness	□	□	□	□
Get fatigued easily	□	□	□	□
Are lethargic	□	□	□	□
Forget easily	□	□	□	□
Are depressed	□	□	□	□
Are irritated easily	□	□	□	□
Have vaginal dryness	□	□	□	□
Have genital bleeding	No	Yes		
Have increased leukorrhea	No	Yes		
Recent bone fracture	No	Yes		
Weight gain	Absent or decrease	<5 kg	5-10 kg	>10 kg

symptom was lower among ≥ 70 y/o than 56–69 y/o ($P = 0.0285$ for AIs and $P = 0.0048$ for SERMs).

Easy fatigability was more frequent/severe in patients treated with AIs than with SERMs among patients ≥ 70 y/o ($P < 0.0001$). However, among those aged 56–69, the symptom was as frequent as that among patients ≥ 70 y/o treated with AIs, irrespective of the kind of endocrine therapy. Easy fatigability with SERMs was lower among ≥ 70 y/o than 56–69 y/o ($P = 0.0007$), but this was not the case with AIs. Lethargy was more frequent/severe in patients treated with AIs than with SERMs among patients ≥ 70 y/o ($P = 0.0004$), but the opposite occurred among those aged 56–69 ($P = 0.0446$). Lethargy with SERMs was lower among ≥ 70 y/o than 56–69 y/o ($P < 0.0001$), but this was not the case with AIs.

Table 1 Presence/degree of 15 subjective symptoms according to patient age or type of endocrine therapy

Symptoms	Degree	Age						*P* value	
		56–69 y/o			≥ 70 y/o			56–69 y/o vs. ≥ 70 y/o	
		Type of endocrine therapy			Type of endocrine therapy			Type of endocrine therapy	
		AIs (%)	SERMs (%)	*P* value	AIs (%)	SERMs (%)	*P* value	AIs	SERMs
Hot flashes	Absent	4399 (72.4)	187 (59.9)	< 0.0001**, favors AIs	1901 (83.3)	149 (85.6)	0.5848	< 0.0001**, less in ≥ 70 y/o	< 0.0001**, less in ≥ 70 y/o
	Mild	959 (15.8)	61 (19.6)		227 (10.0)	16 (9.2)			
	Moderate	702 (11.6)	64 (20.5)		148 (6.5)	8 (4.6)			
	Severe	18 (0.3)	0 (0.0)		5 (0.2)	1 (0.6)			
Sweating	Absent	3830 (63.1)	174 (55.8)	0.0142*, favors AIs	1596 (70.1)	146 (83.9)	0.0011**, favors SERMs	< 0.0001**, less in ≥ 70 y/o	< 0.0001**, less in ≥ 70 y/o
	Mild	1211 (20.0)	66 (21.6)		361 (15.9)	18 (10.3)			
	Moderate	989 (16.3)	71 (22.8)		302 (13.3)	10 (5.8)			
	Severe	36 (0.6)	1 (0.3)		19 (0.8)	0 (0.0)			
Knuckle stiffness	Absent	2841 (46.8)	197 (63.1)	< 0.0001**, favors SERMs	1310 (57.4)	138 (78.4)	< 0.0001**, favors SERMs	< 0.0001**, less in ≥ 70 y/o	0.0029**, less in ≥ 70 y/o
	Mild	1413 (23.3)	58 (18.6)		442 (19.4)	24 (13.6)			
	Moderate	1707 (28.1)	55 (17.6)		494 (21.6)	14 (8.0)			
	Severe	115 (1.9)	2 (0.6)		38 (1.7)	0 (0.0)			
Knee/shoulder pain	Absent	3347 (55.2)	193 (61.9)	0.0229*, favors SERMs	1285 (56.3)	123 (69.9)	0.0013**, favors SERMs	0.3707	0.2193
	Mild	1193 (19.7)	64 (20.5)		410 (18.0)	29 (16.5)			
	Moderate	1371 (22.6)	48 (15.4)		529 (23.2)	23 (13.1)			
	Severe	154 (2.5)	7 (2.2)		59 (2.6)	1 (0.0)			
Limb numbness	Absent	3764 (62.0)	201 (64.6)	0.6608	1484 (65.2)	141 (80.1)	0.0010**, favors SERMs	0.0285*, less in ≥ 70 y/o	0.0048*, less in ≥ 70 y/o
	Mild	1133 (18.7)	58 (18.7)		410 (18.0)	19 (10.8)			
	Moderate	1080 (17.8)	49 (15.8)		358 (15.7)	15 (8.5)			
	Severe	91 (1.5)	3 (1.0)		25 (1.1)	1 (0.6)			
Easy fatigability	Absent	3760 (61.8)	194 (61.8)	0.4166	1388 (60.6)	139 (79.0)	< 0.0001**, favors SERMs	0.1421	0.0007**, less in ≥ 70 y/o
	Mild	1419 (23.3)	68 (21.7)		516 (22.5)	26 (14.8)			
	Moderate	845 (13.9)	51 (16.2)		361 (15.8)	11 (6.3)			
	Severe	58 (1.0)	1 (0.3)		26 (1.1)	0 (0.0)			
Lethargy	Absent	4291 (70.5)	209 (66.8)	0.0446*, favors AIs	1556 (68.2)	143 (82.2)	0.0004**, favors SERMs	0.1370	< 0.0001**, less in ≥ 70 y/o
	Mild	1192 (19.6)	62 (19.8)		487 (21.4)	27 (15.5)			
	Moderate	562 (9.2)	42 (13.4)		218 (9.6)	3 (1.7)			
	Severe	38 (0.6)	0 (0.0)		20 (0.9)	1 (0.6)			
Forgetfulness	Absent	3643 (60.1)	171 (54.8)	0.0895	1315 (57.7)	122 (69.3)	0.0183*, favors SERMs	0.0004**, more in ≥ 70 y/o	0.0048*, less in ≥ 70 y/o
	Mild	1648 (27.2)	94 (30.1)		595 (26.1)	32 (18.2)			
	Moderate	732 (12.1)	47 (15.1)		355 (15.6)	22 (12.5)			
	Severe	39 (0.6)	0 (0.0)		16 (0.7)	0 (0.0)			

Table 1 (continued)

Symptoms	Degree	Age						*P* value	
		56–69 y/o			≥ 70 y/o			56–69 y/o vs. ≥ 70 y/o	
		Type of endocrine therapy			Type of endocrine therapy			Type of endocrine therapy	
		AIs (%)	SERMs (%)	*P* value	AIs (%)	SERMs (%)	*P* value	AIs	SERMs
Depressive state	Absent	4804 (79.0)	233 (74.7)	0.0993	1827 (80.0)	156 (88.6)	0.0356*, favors SERMs	0.1763	0.0010**, less in ≥ 70 y/o
	Mild	867 (14.3)	59 (18.9)		316 (13.8)	16 (9.1)			
	Moderate	389 (6.4)	20 (6.4)		126 (5.5)	4 (2.3)			
	Severe	22 (0.4)	0 (0.0)		14 (0.6)	0 (0.0)			
Irritated state	Absent	4783 (78.9)	247 (78.9)	0.1323	1885 (82.8)	157 (90.2)	0.0392*, favors SERMs	0.0003**, less in ≥ 70 y/o	0.0036*, less in ≥ 70 y/o
	Mild	922 (15.2)	56 (17.9)		287 (12.6)	15 (8.6)			
	Moderate	336 (5.5)	10 (3.2)		93 (4.1)	1 (0.6)			
	Severe	23 (0.4)	0 (0.0)		12 (0.5)	1 (0.6)			
Leukorrhea increase	Absent	5819 (96.6)	252 (84.6)	< 0.0001**, favors AIs	2215 (98.1)	142 (86.1)	< 0.0001**, favors AIs	0.0002**, less in ≥ 70 y/o	0.6649
	Present	206 (3.4)	46 (15.4)		43 (1.9)	23 (13.9)			
Vaginal dryness	Absent	5021 (82.8)	277 (90.5)	0.0023**, favors SERMs	2122 (93.5)	164 (98.2)	0.0990	< 0.0001**, less in ≥ 70 y/o	0.0057*, less in ≥ 70 y/o
	Mild	698 (11.5)	24 (7.8)		111 (4.9)	3 (1.8)			
	Moderate	329 (5.4)	5 (1.6)		34 (1.5)	0 (0.0)			
	Severe	19 (0.3)	0 (0.0)		3 (0.1)	0 (0.0)			
Genital bleeding	Absent	6025 (99.2)	298 (97.1)	0.0002**, favors AIs	2258 (99.7)	165 (98.8)	0.0680	0.0095*, less in ≥ 70 y/o	0.2310
	Present	51 (0.8)	9 (2.9)		7 (0.3)	2 (1.2)			
Bone fracture	Absent	5908 (97.7)	303 (97.7)	0.9924	2185 (96.3)	165 (94.3)	0.1939	0.0002**, more in ≥ 70 y/o	0.0469*, more in ≥ 70 y/o
	Present	137 (2.3)	7 (2.3)		85 (3.7)	10 (5.7)			
Weight gain	Absent	4281 (70.5)	188 (60.0)	< 0.0001**, favors AIs	1841 (80.6)	141 (80.1)	0.3279	< 0.0001**, less in ≥ 70 y/o	< 0.0001**, less in ≥ 70 y/o
	< 5 kg	1516 (25.0)	95 (30.4)		388 (17.0)	31 (17.6)			
	5–10 kg	262 (4.3)	30 (9.6)		54 (2.4)	3 (1.7)			
	> 10 kg	12 (0.2)	0 (0.0)		2 (0.1)	1 (0.6)			

AIs aromatase inhibitors, *SERMs* selective estrogen receptor modulators

*$P < 0.05$, **$P < 0.05/15 = 0.0033$

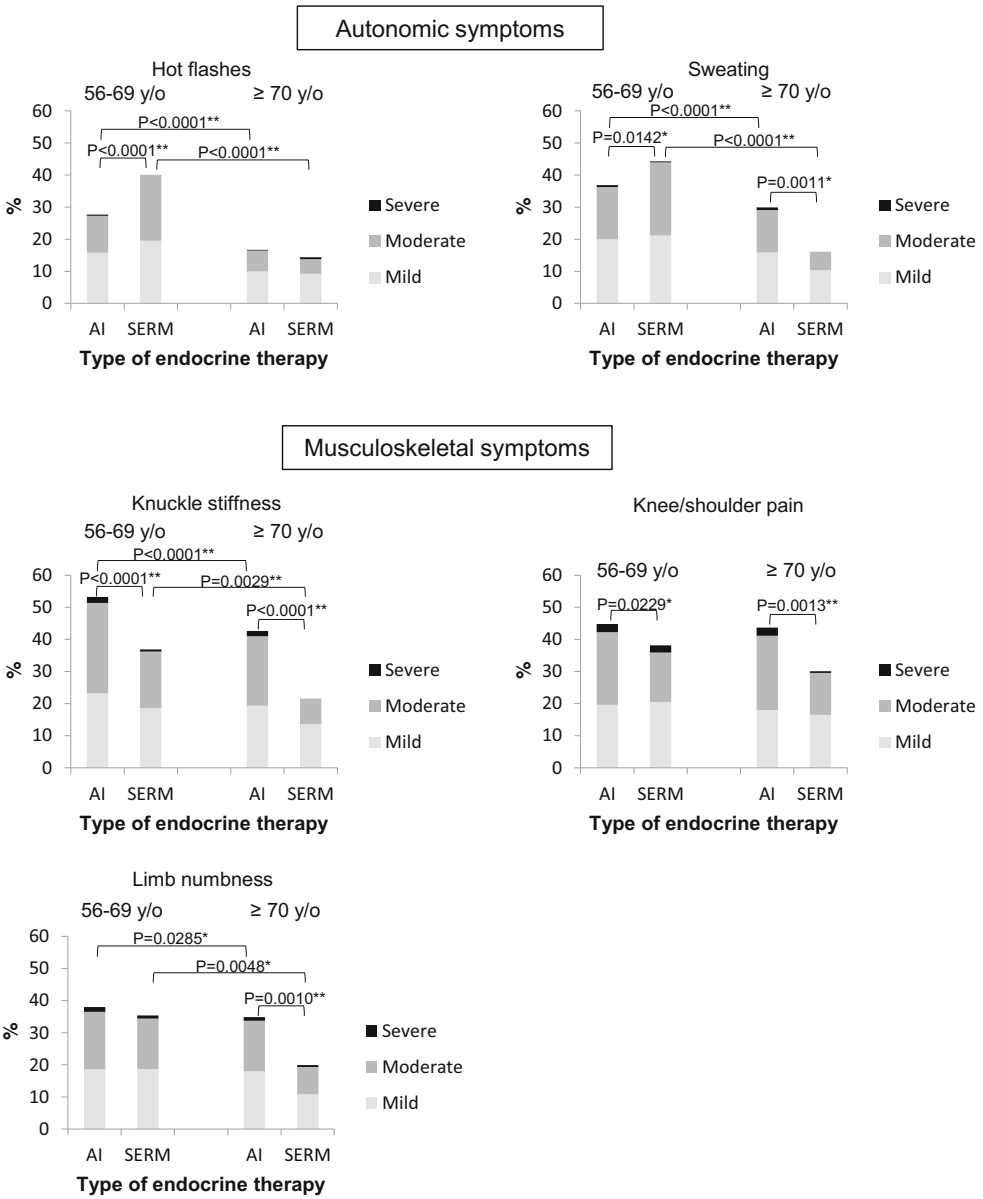

Fig. 2 Graphs showing the presence/degree of 15 subjective symptoms according to patient age or type of endocrine therapy. AI aromatase inhibitors, SERM selective estrogen receptor modulators

Forgetfulness was more frequent/severe in patients treated with AIs than with SERMs among those ≥ 70 y/o ($P = 0.0183$). However, among those aged 56–69, forgetfulness was more frequent/severe with SERMs than with AIs ($P = 0.0895$). This symptom was more frequent in those aged ≥ 70 than those aged 56–69 among patients treated with AIs ($P = 0.0004$), but the opposite occurred for those treated with SERMs ($P = 0.0048$). For a depressive state, the frequency/severity was higher with AIs than with SERMs among patients ≥ 70 y/o ($P = 0.0356$), but the opposite occurred among those aged 56–69 ($P = 0.0993$). This symptom with SERMs was lower among ≥ 70 y/o than 56–69 y/o ($P = 0.0010$), but this was not the case with AIs. For an irritated state, the frequency/severity was higher with AIs than with SERMs among patients ≥ 70 y/o ($P = 0.0392$), but this was not the case among those aged 56–69. This symptom with both therapies was lower among ≥ 70 y/o than 56–69 y/o ($P = 0.0003$ for AIs and $P = 0.0036$ for SERMs).

Leukorrhea increase was significantly more frequent with SERMs than with AIs irrespective of age ($P < 0.0001$). This symptom was lower among patients ≥ 70 y/o than 56–69 y/o in those treated with AIs ($P = 0.0002$), but this was not the case for those treated with SERMs. However, vaginal dryness was significantly more frequent/severe with AIs than with SERMs among patients aged 56–69 ($P = 0.0023$), and the frequency/severity was lower among patients ≥ 70 y/o than those aged 56–69 irrespective of the type of endocrine therapy ($P < 0.0001$ for AIs and $P = 0.0057$ for SERMs). Genital

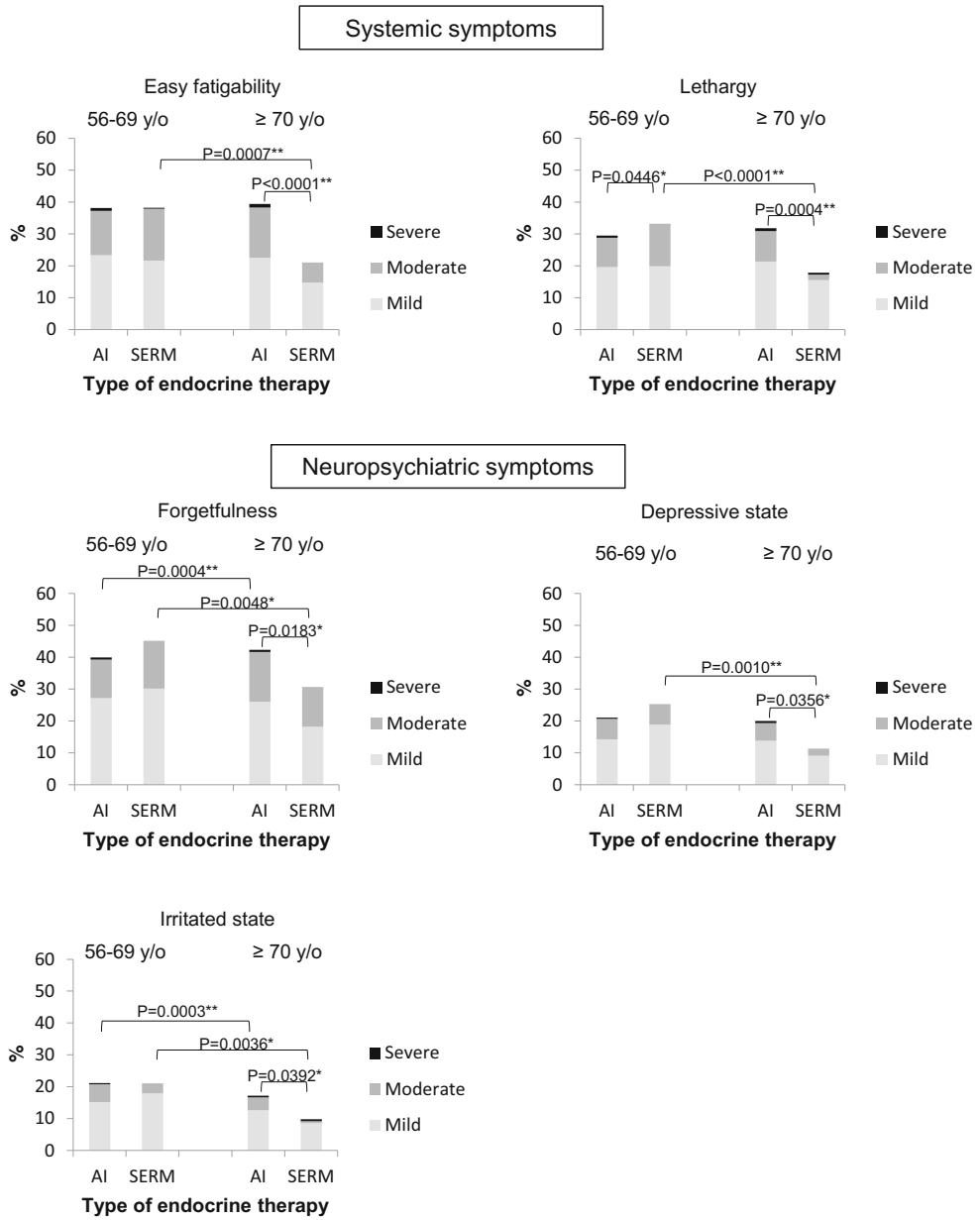

Fig. 2 (continued)

bleeding was a rare symptom irrespective of the age or type of therapy, but the frequency was higher with SERMs than with AIs among patients aged 56–69 y/o ($P = 0.0002$), which was similar to those ≥ 70 y/o ($P = 0.0680$). Among patients treated with AIs, this symptom was less frequent in patients ≥ 70 y/o than those aged 56–69 ($P = 0.0095$), but this was not the case for those treated with SERMs.

There was no significant difference in the frequency of bone fracture according to the type of endocrine therapy irrespective of age, but the frequency was higher in ≥ 70 y/o than in 56–69 y/o irrespective of therapy ($P = 0.0002$ for AIs and $P = 0.0469$ for SERMs). Weight gain was more frequent/severe in patients treated with SERMs than with AIs among those aged 56–69 ($P < 0.0001$). Among patients ≥ 70 y/o, the frequency/severity in weight gain was not different according to the type of endocrine therapy and was much lower than in those aged 56–69 irrespective of endocrine therapy ($P < 0.0001$).

Discussion

We found that many symptoms were different in frequency/degree according to the type of endocrine therapy or the patient's age. Among patients ≥ 70 y/o, 9 of 15 symptoms were more frequent/severe with AIs than with SERMs. However, among patients aged 56–69, only 3 of 15 symptoms were more frequent/severe with AIs than with SERMs, and 6 of

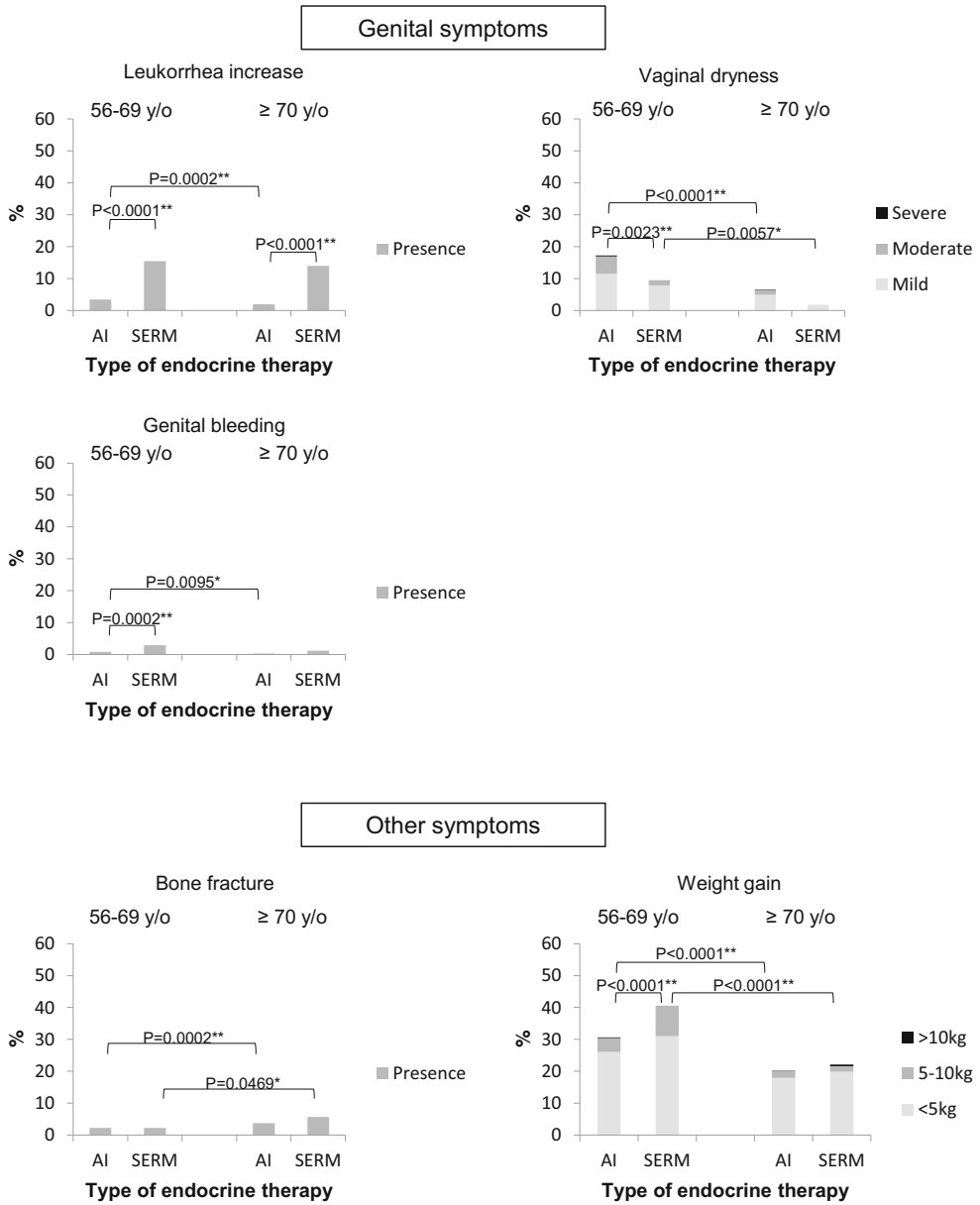

Fig. 2 (continued)

15 symptoms were less frequent with AIs than with SERMs. In addition, 7 of 15 symptoms were lower in those ≥ 70 y/o than 56–69 y/o irrespective of the type of endocrine therapy.

This is the first study to compare the adverse events of SERMs and AIs that focuses on the age of patients with breast cancer. The most impressive results were that adverse events were less frequent/severe in patients ≥ 70 y/o treated with SERMs than in those treated with AIs. In contrast, among those aged 56–69, several symptoms were less frequent/severe with AIs than with SERMs. Previously, we found that AIs reduce peripheral estrogen concentrations and suggested that AIs may be unfavorable to maintain homeostasis mediated by estrogens in systemic organs [22, 23]. In contrast, SERMs have partial agonistic effects on ERs. However, the action of SERMs is complex because the dominant type of expressed ER (ER-α or ER-β) and DNA response element (e.g., ERE, AP-1) is different according to the organ or tissue, which determines whether SERMs inhibit or promote ER-mediated transcription [24–28]. There is a beneficial role for SERMs in maintaining physiological function in the central and peripheral nervous system [29–31]. In addition, SERMs reportedly have less severity in terms of musculoskeletal symptoms than AIs and improve osteoarthritis caused by AIs [14, 32]. Even after a rapid decrease in menopause, serum estrogens continue to slowly decrease with age, which is associated with a decrease in serum dehydroepiandrosterone (-sulfate) caused by an age-dependent decrease in adrenal function (adrenopause) [33]. In older women where estrogens have

decreased markedly, the agonistic effect of SERMs on ER may overwhelm the antagonistic effect in some organs. At the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2017, the panel was almost unanimous in that some postmenopausal patients can be treated with tamoxifen alone and acknowledged the importance of patient preference and tolerability [21]. Older age and comorbidity reportedly increase the risk of death from causes other than breast cancer [16, 34], and in our preliminary study for breast cancer patients ≥ 75 y/o, only 9 of 221 patients were free from comorbidity (unpublished data). Considering the benefit and risk balance of endocrine therapy, older patients with breast cancer at low recurrent risk may be one of the most suitable populations for treatment with SERMs alone.

There were several limitations in the present study. We aggregated data from an interview sheet (Fig. 1), which was answered during postoperative follow-up. Therefore, we did not have baseline clinicopathological data and geriatric baseline characteristics. Because population characteristics can strongly influence the incidence of adverse events, the present results should be considered with caution. Although AIs are standard in postmenopausal patients, they may be administered more frequently to breast cancer patients of a later stage with previous chemotherapy than SERMs. These biases in the type of endocrine therapy may affect adverse events. Furthermore, patients answered the questionnaire more than once, but it was impossible to examine changes in symptoms over time in each patient. Differentiating between adverse events from endocrine therapy and a functional decrease from aging was difficult. We also recognize that some side effects are difficult to capture in the present study setting (e.g., increased thrombosis risk on SERMs). Despite these limitations, the importance of patient-reported outcomes has recently been recognized [9, 35, 36]. Using a questionnaire on adverse events, a larger, constructed, and systematic study with baseline data will improve endocrine therapy for older patients with breast cancer.

In conclusion, among patients ≥ 70 y/o, many symptoms were significantly more frequent/severe with AIs than with SERMs compared with those aged 56–69, which suggests a different profile of adverse events according to the type of endocrine therapy and patient's age. The benefits and risks of SERMs and AIs should be further examined in older patients to optimize endocrine therapy for them.

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Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

Conflict of interest The authors have nothing to declare regarding this work. Dr. Saji reports grants and personal fees from Eisai, grants and personal fees from Chugai, grants and personal fees from AstraZeneca, grants and personal fees from Takeda, grants and personal fees from Novartis, grants and personal fees from Taiho, grants and personal fees from Nihon Kayaku, grants from Ono, personal fees from KyowaHakko-Kirin, personal fees from Pfizer, and personal fees from Daiichi Sankyo, outside the submitted work. Dr. Ohno reports grants and personal fees from Chugai, grants and personal fees from Taiho, grants and personal fees from Eisai, grants from Daiichi Sankyo, personal fees from AstraZeneca, personal fees from KyowaHakko-kirin, personal fees from Pfizer, and personal fees from Novartis, outside the submitted work.

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