

Supplementary material

Side effects of low dose tamoxifen: Results from a six-armed randomized controlled trial in healthy women

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Supplementary Methods. KARISMA 48-item symptom questionnaire including origin of questions.

Question: Please mark your response for each question as it applies to the past 30 days.

	Source ^a	Not at all	A little bit	Some-what	Quite a bit	Very much	Don't know/ refuse
I have hot flashes	FACT ES	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have cold sweats	FACT ES	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have night sweats	FACT ES	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have vaginal discharge	FACT ES	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have vaginal itching/irritation	FACT ES	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have vaginal bleeding or spotting	FACT ES	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have vaginal dryness	FACT ES	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have pain or discomfort with intercourse	FACT ES	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have lost interest in sex	FACT ES	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have gained weight	FACT ES	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I feel dizzy	FACT ES	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have been vomiting	FACT ES	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have diarrhea	FACT ES	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have headache	FACT ES	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I feel bloated	FACT ES	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have sensitive/tender breasts	FACT ES	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have mood swings	FACT ES	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I feel irritable	FACT ES	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have pain in my joints	FACT ES	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have muscle cramps	SMPC	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have skin rashes	SMPC	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have fragile mucous membranes	SMPC	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have sight/ eye changes	SMPC	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have abdominal obesity	KARISMA	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have heart palpitations	KARISMA	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

I have dry eyes	KARISMA	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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Question: Here is a list of symptoms. How much did the symptom bother or distress you during the past 30 days.

		Not at all	A little bit	Some-what	Quite a bit	Very much	Don't know/ refuse
Difficulty concentrating	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pain	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lack of energy	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cough	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feeling nervous	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dry mouth	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nausea	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feeling drowsy	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Numbness/tingling in hands/feet	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Difficulty sleeping	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Problems with urination	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Shortness of breath	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feeling sad	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Worrying	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Itching	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lack of appetite	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Difficulty swallowing	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Change in the way food tastes	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hair loss	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Constipation	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Swelling of arms/legs	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
"I don't look like myself"	MSAS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

^a Sources of origin:

- FACT ES= Functional Assessment of Cancer Therapy - Endocrine Symptoms, version 4, Additional concerns [24]
- MSAS= Memorial Symptom Assessment Scale [28]
- SMPC= Summary of Product Characteristics (Mylan 20 mg) [8]
- KARISMA= Identified through literature or anecdotally

Supplementary Table 1. Mean Likert-score at baseline in the five symptoms significantly related to tamoxifen exposure regardless of menopausal status, by dose and menopausal status.

<i>Characteristic</i>	Tamoxifen dose in mg						
	All	0	1	2.5	5	10	20
Number of women included	1175	202	193	194	188	199	199
<i>Baseline symptom score</i>	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
<i>Hot flashes</i>							
All (n:1167)	0.51 (0.46, 0.56)	0.46 (0.35, 0.56)	0.51 (0.51, 0.39)	0.42 (0.31, 0.53)	0.55 (0.42, 0.67)	0.44 (0.33, 0.56)	0.68 (0.55, 0.81)
Premenop. (n: 451)	0.27 (0.22, 0.33)	0.21 (0.08, 0.35)	0.31 (0.16, 0.46)	0.20 (0.05, 0.35)	0.19 (0.07, 0.32)	0.24 (0.12, 0.36)	0.47 (0.29, 0.65)
Postmenop. (n: 716)	0.66 (0.59, 0.72)	0.59 (0.44, 0.73)	0.65 (0.48, 0.81)	0.56 (0.40, 0.71)	0.77 (0.59, 0.94)	0.57 (0.41, 0.73)	0.82 (0.64, 1.00)
<i>Cold sweats</i>							
All (n:1170)	0.16 (0.14, 0.19)	0.16 (0.09, 0.22)	0.17 (0.10, 0.23)	0.13 (0.07, 0.18)	0.21 (0.13, 0.29)	0.16 (0.09, 0.23)	0.17 (0.10, 0.24)
Premenop. (n: 449)	0.12 (0.09, 0.16)	0.13 (0.03, 0.23)	0.13 (0.04, 0.21)	0.13 (0.05, 0.22)	0.13 (0.03, 0.22)	0.08 (0.02, 0.14)	0.14 (0.04, 0.25)
Postmenop. (n: 716)	0.19 (0.15, 0.23)	0.17 (0.08, 0.26)	0.20 (0.11, 0.29)	0.12 (0.04, 0.20)	0.27 (0.15, 0.38)	0.20 (0.10, 0.31)	0.18 (0.08, 0.29)
<i>Night sweats</i>							
All (n:1170)	0.65 (0.60, 0.70)	0.67 (0.55, 0.80)	0.63 (0.50, 0.75)	0.59 (0.47, 0.70)	0.60 (0.48, 0.72)	0.64 (0.52, 0.76)	0.78 (0.65, 0.91)
Premenop. (n: 452)	0.54 (0.47, 0.62)	0.52 (0.33, 0.72)	0.51 (0.35, 0.67)	0.43 (0.28, 0.57)	0.46 (0.26, 0.66)	0.54 (0.36, 0.72)	0.80 (0.58, 1.01)
Postmenop. (n: 718)	0.72 (0.65, 0.79)	0.75 (0.59, 0.91)	0.71 (0.53, 0.88)	0.69 (0.53, 0.86)	0.69 (0.53, 0.85)	0.70 (0.54, 0.86)	0.78 (0.61, 0.94)
<i>Vaginal discharge</i>							

All (n:1170)	0.49 (0.45, 0.53)	0.40 (0.30, 0.49)	0.51 (0.40, 0.61)	0.51 (0.40, 0.61)	0.51 (0.40, 0.61)	0.45 (0.35, 0.56)	0.57 (0.46, 0.67)
Premenop. (n: 451)	0.90 (0.82, 0.98)	0.76 (0.56, 0.96)	0.89 (0.69, 1.08)	1.03 (0.83, 1.22)	0.96 (0.76, 1.16)	0.85 (0.65, 1.05)	0.94 (0.74, 1.13)
Postmenop. (n: 719)	0.23 (0.19, 0.26)	0.21 (0.12, 0.29)	0.23 (0.15, 0.32)	0.17 (0.09, 0.25)	0.22 (0.13, 0.32)	0.21 (0.12, 0.30)	0.33 (0.23, 0.42)

Muscle cramps

All (n:1173)	0.45 (0.41, 0.50)	0.49 (0.38, 0.59)	0.48 (0.37, 0.60)	0.44 (0.32, 0.55)	0.42 (0.31, 0.53)	0.40 (0.30, 0.51)	0.48 (0.36, 0.59)
Premenop. (n: 453)	0.26 (0.20, 0.30)	0.20 (0.10, 0.30)	0.24 (0.11, 0.36)	0.26 (0.13, 0.39)	0.21 (0.06, 0.36)	0.17 (0.08, 0.26)	0.44 (0.25, 0.64)
Postmenop. (n: 720)	0.57 (0.51, 0.64)	0.64 (0.50, 0.78)	0.66 (0.49, 0.83)	0.55 (0.38, 0.72)	0.55 (0.39, 0.71)	0.54 (0.39, 0.70)	0.50 (0.35, 0.65)

Abbreviations: CI= Confidence interval

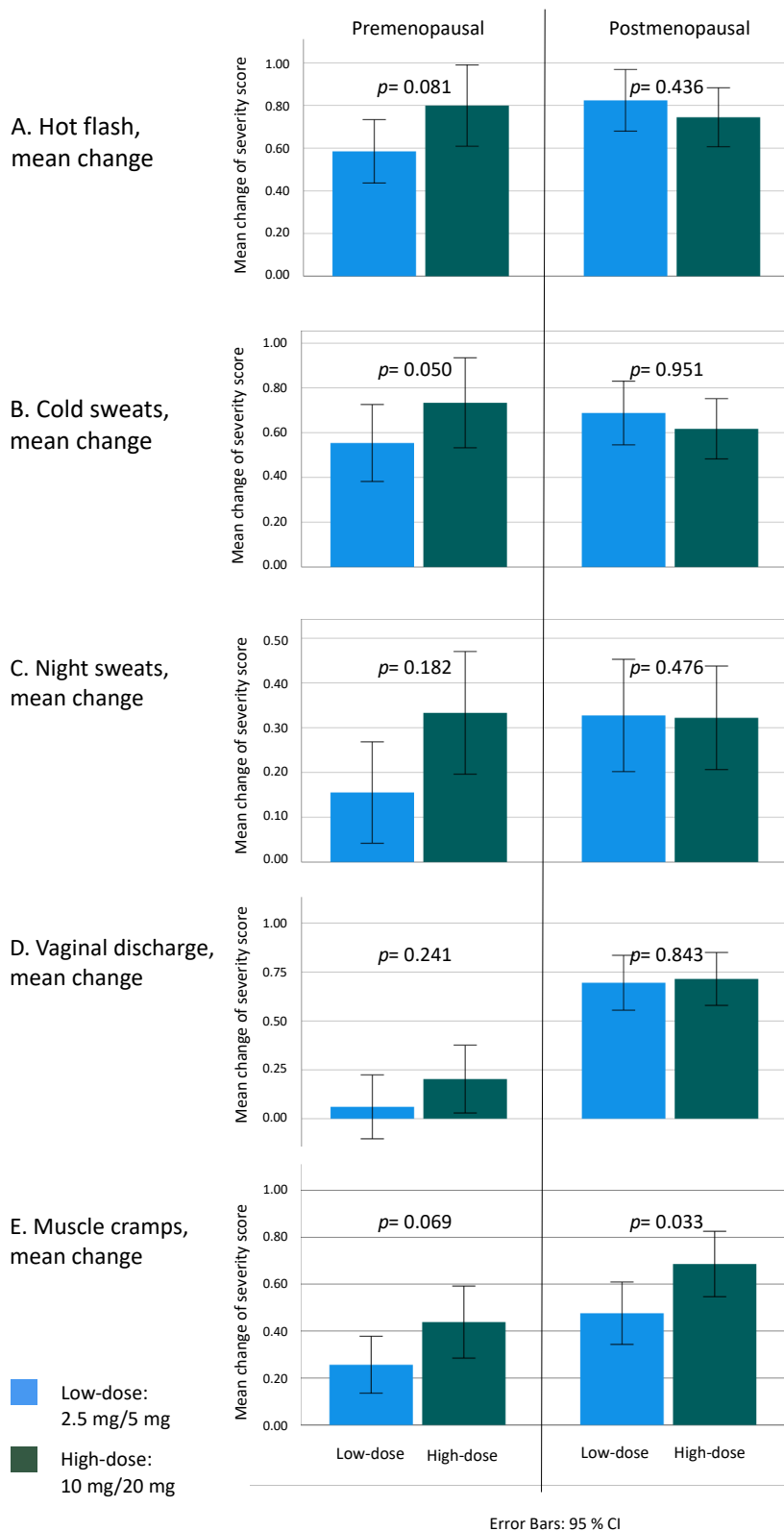
Supplementary Table 2. Mean individual change of three anthropometric measures, from start to end of treatment, comparing all doses including placebo to the 20 mg tamoxifen arm, for all women combined and stratified by menopausal status.

Anthropometrics		Tamoxifen dose in mg						Association with dose p-value ^b
		0	1	2.5	5	10	20	
N		Mean change (95% CI) ^a	Mean change (95% CI) ^a	Mean change (95% CI) ^a	Mean change (95% CI) ^a	Mean change (95% CI) ^a	Mean change	
BMI (kg/m ²)								
All	1135	0.22 (0.00, 0.44)	0.15 (-0.08, 0.37)	0.41 (0.18, 0.63)	0.19 (-0.04, 0.42)	0.05 (-0.17, 0.27)	Ref.	0.004
Premenop.	436	0.28 (0.01, 0.55)	0.26 (0, 0.53)	0.42 (0.16, 0.69)	0.35 (0.08, 0.62)	0.33 (0.06, 0.59)	Ref.	0.010
Postmenop.	699	0.17 (-0.15, 0.48)	0.08 (-0.25, 0.40)	0.40 (0.08, 0.72)	0.09 (-0.23, 0.42)	-0.12 (-0.44, 0.20)	Ref.	0.062
Weight (kg)								
All	1135	0.59 (-0.02, 1.19)	0.38 (-0.22, 0.99)	1.06 (0.46, 1.67)	0.51 (-0.10, 1.13)	0.12 (-0.48, 0.72)	Ref.	0.005
Premenop.	436	0.80 (0.04, 1.56)	0.73 (-0.01, 1.47)	1.15 (0.4, 1.89)	0.96 (0.21, 1.72)	0.87 (0.12, 1.61)	Ref.	0.009
Postmenop.	699	0.43 (-0.42, 1.27)	0.18 (-0.70, 1.05)	1.02 (0.15, 1.88)	0.24 (-0.64, 1.12)	-0.34 (-1.20, 0.51)	Ref.	0.077
Waist circumference (cm)								
All	1130	0.74 (-0.81, 2.29)	-0.28 (-1.85, 1.29)	0.35 (-1.21, 1.91)	-0.61 (-2.19, 0.98)	-0.91 (-2.46, 0.63)	Ref.	0.454
Premenop.	433	3.53 (0.88, 6.17)	0.19 (-2.40, 2.78)	2.63 (0.03, 5.24)	0.73 (-1.90, 3.36)	1.80 (-0.78, 4.38)	Ref.	0.083
Postmenop.	697	-0.94 (-2.84, 0.96)	-0.50 (-2.45, 1.45)	-1.08 (-3.00, 0.85)	-1.42 (-3.38, 0.55)	-2.61 (-4.52, -0.69)	Ref.	0.623

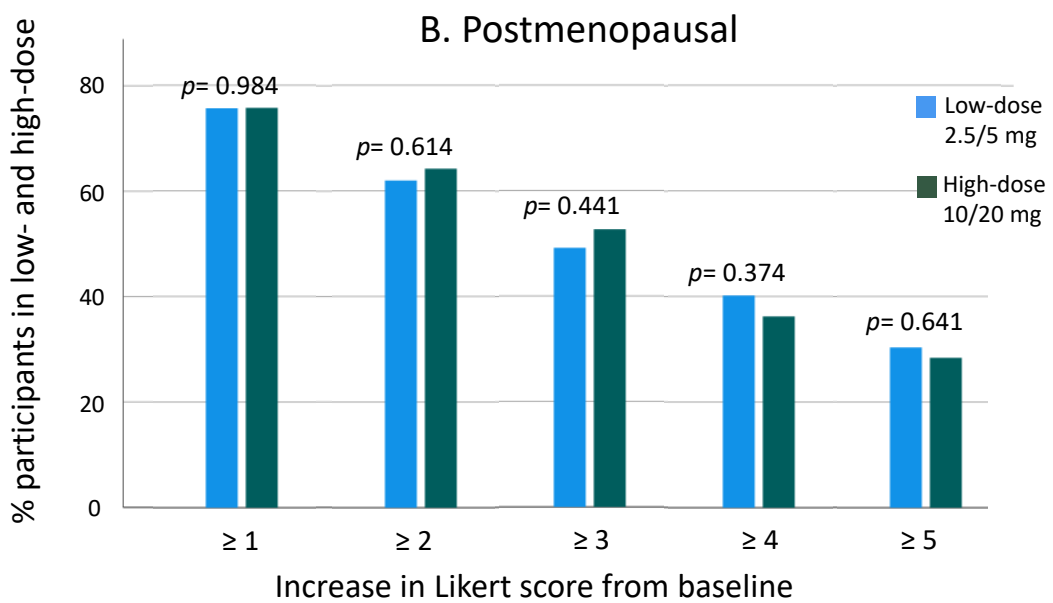
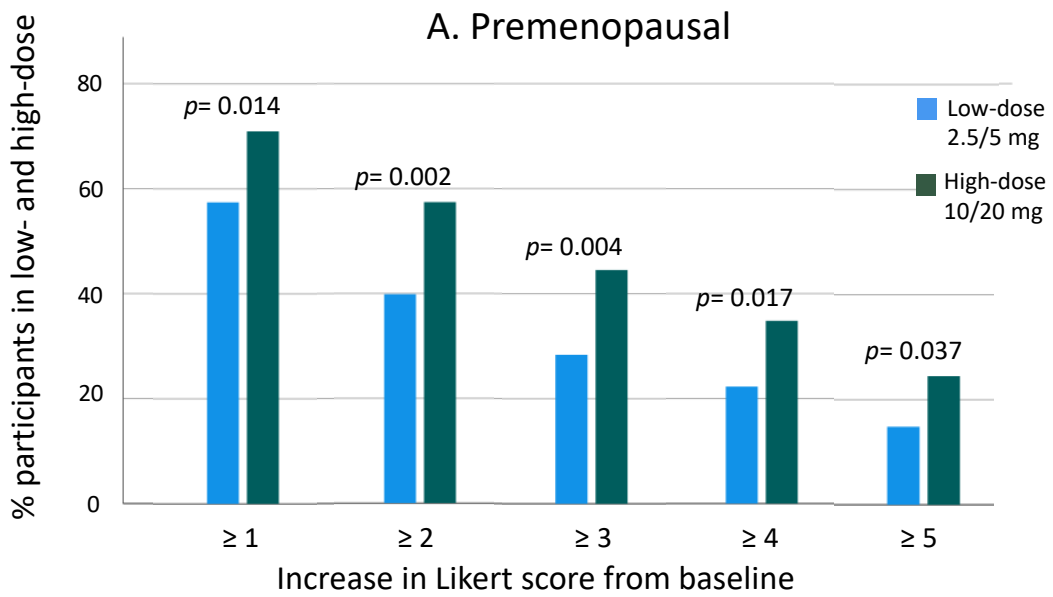
^a = Difference in mean change comparing 0 to 20 mg (ref.) tamoxifen at end of treatment (at six months or date of discontinuation)

^b = P-values for linear association between dose and symptom severity change

Significant values in bold (p < 0.05)



Supplementary Figure 1. Symptom severity change by low (2.5 mg, 5 mg) and high (10 mg, 20 mg) dose tamoxifen and stratified by menopausal status. Mean change of severity score is calculated from start to end of treatment. P-value for difference between low and high dose within each menopausal group.



Supplementary Figure 2. Proportion of women increasing by ≥ 1 , 2, 3, 4 and 5 in Likert score, comparing baseline to end of treatment in the five symptoms significantly related to tamoxifen exposure (hot flashes, cold sweats, night sweats, vaginal discharge, and muscle cramps) and stratifying by menopausal status and dose. P-value for test of difference between low and high dose.