

# Treatment adherence: any real impact on outcome?

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# Adherence to hormonal therapy- the magnitude of the problem

Despite the proven survival benefit of adjuvant hormonal therapy, a substantial proportion of patients discontinue treatment. While endocrine therapy adherence is relatively high in adjuvant trials, adherence to adjuvant therapy in clinical practice is relatively poor and associated with increased risk of mortality.

# Adherence to hormonal therapy- the magnitude of the problem

There is heterogeneity between studies in terms of outcome measures, type of effect sizes, definitions of adherence and predictor variables..

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# Adherence to hormonal therapy- the magnitude of the problem

- Among 8,769 women who filled at least one prescription for HT, 2,761 (31%) discontinued therapy.
- Of those who continued HT, 1,684 (28%) were non-adherent.

Characteristics	All patients (8769)				Patients continued therapy (6008)			
	No. of patients discontinued (2761)	% 31.5	No. of patients continued (6008)	% 68.5	No. of patients non-adhered (1684)	% 28	No. of patients adhered (4324)	% 72
Age at diagnosis (years)								
<50	472	17.1	1000	16.6	287	17.0	713	16.5
50-64	1015	36.8	2594	43.2	691	41.0	1903	44.0
≥65	1274	46.1	2414	40.2	706	42.0	1708	39.5

# Adherence and Persistence to Adjuvant Hormonal Therapy in Early Stage Breast Cancer Patients – A Population-Based Retrospective Cohort Study in Israel

- Retrospective population based cohort of breast cancer survivors in Maccabi Health Services (MHS), Israel.
- 4178 women with early breast cancer diagnosed between 2000-2008 were followed for a median 7.8 years.
- Over 95% of patients received tamoxifen as the initial hormonal agent.
- The proportion of adherent patients (>80% of days covered) ranged from 81% to 84% during years 1-4 and decreased to less than 60% in subsequent years.
- Approximately 75% of patients were continuously adherent during five years of therapy.

## Adherence and Persistence to Adjuvant Hormonal Therapy in Early Stage Breast Cancer Patients – A Population-Based Retrospective Cohort Study in Israel

- In Israel, approximately 23% of new users of adjuvant hormonal therapy, mostly with tamoxifen, discontinue therapy early.
- **Rates of discontinuation and non-adherence were highest among young (<45 years) and underweight women.**
- A history of hypertension is associated with increased adherence and persistence.

# Adherence to adjuvant endocrine therapy

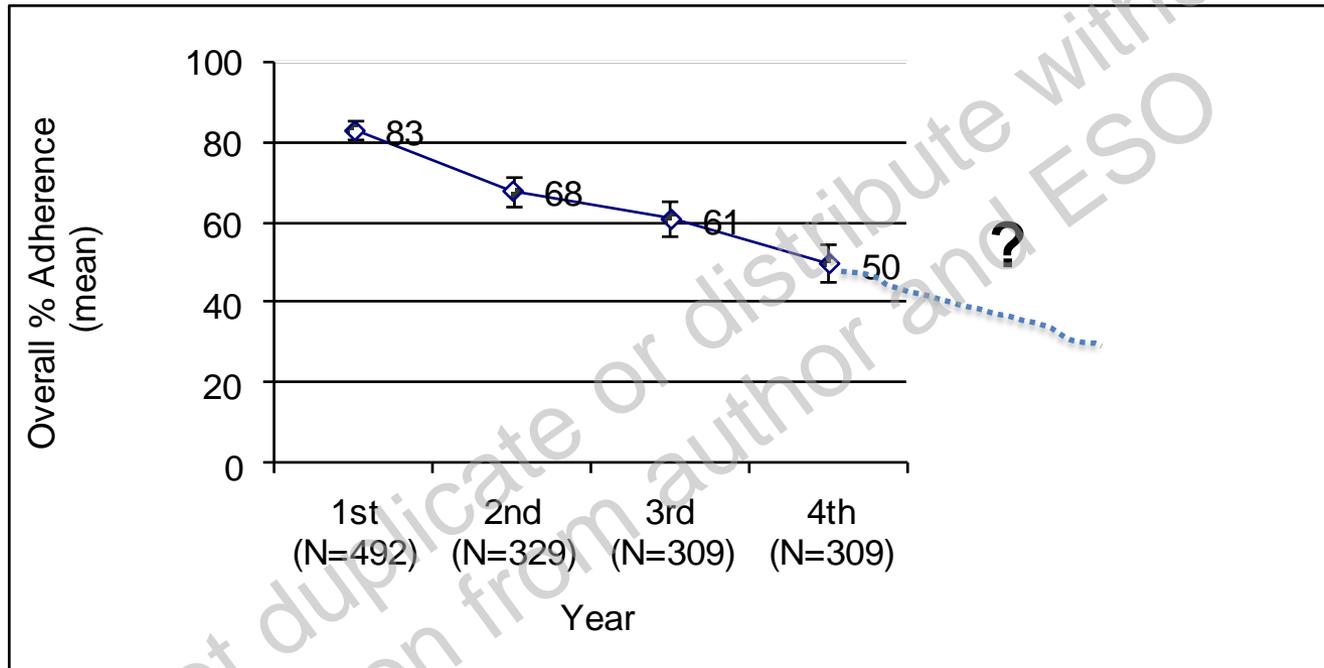
Table 1. Systematic reviews of adherence to adjuvant endocrine therapy

	Tamoxifen	Aromatase inhibitor
Adherence (range) <sup>a,b</sup>	41%–88%	52%–91%
Therapy discontinuation (range) <sup>a</sup>	15%–20% within year 1	5%–25% within 2 years
Five-year therapy discontinuation from meta-regression analysis <sup>b</sup>	47.2% (95% CI, 41.1%–53.5%)	31.0% (95% CI, 25.9 %–37.5%)

<sup>a</sup>Murphy et al. (21).

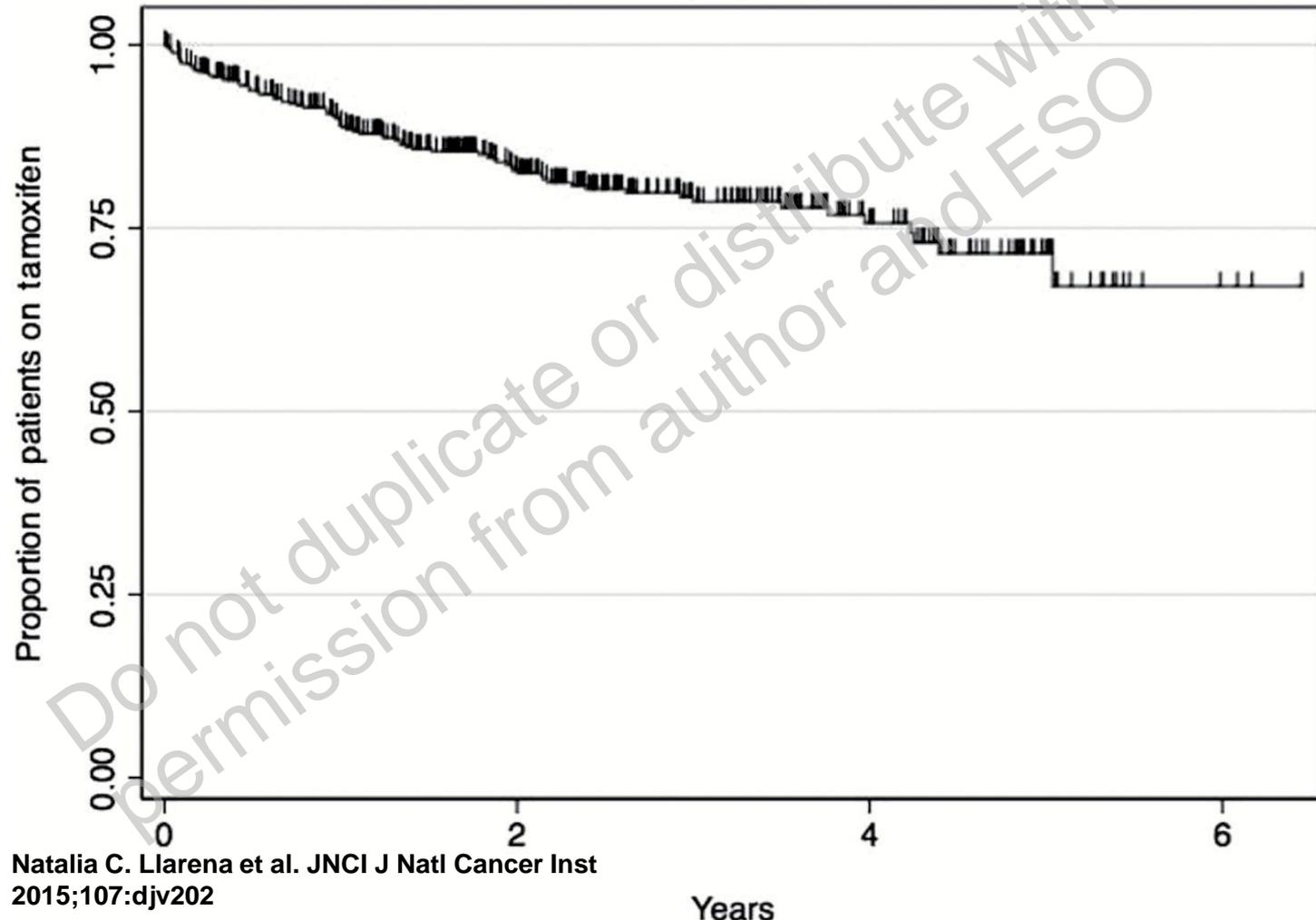
<sup>b</sup>Huiart et al. (22).

# Adherence to Adjuvant Hormonal Therapy Wanes Over Time



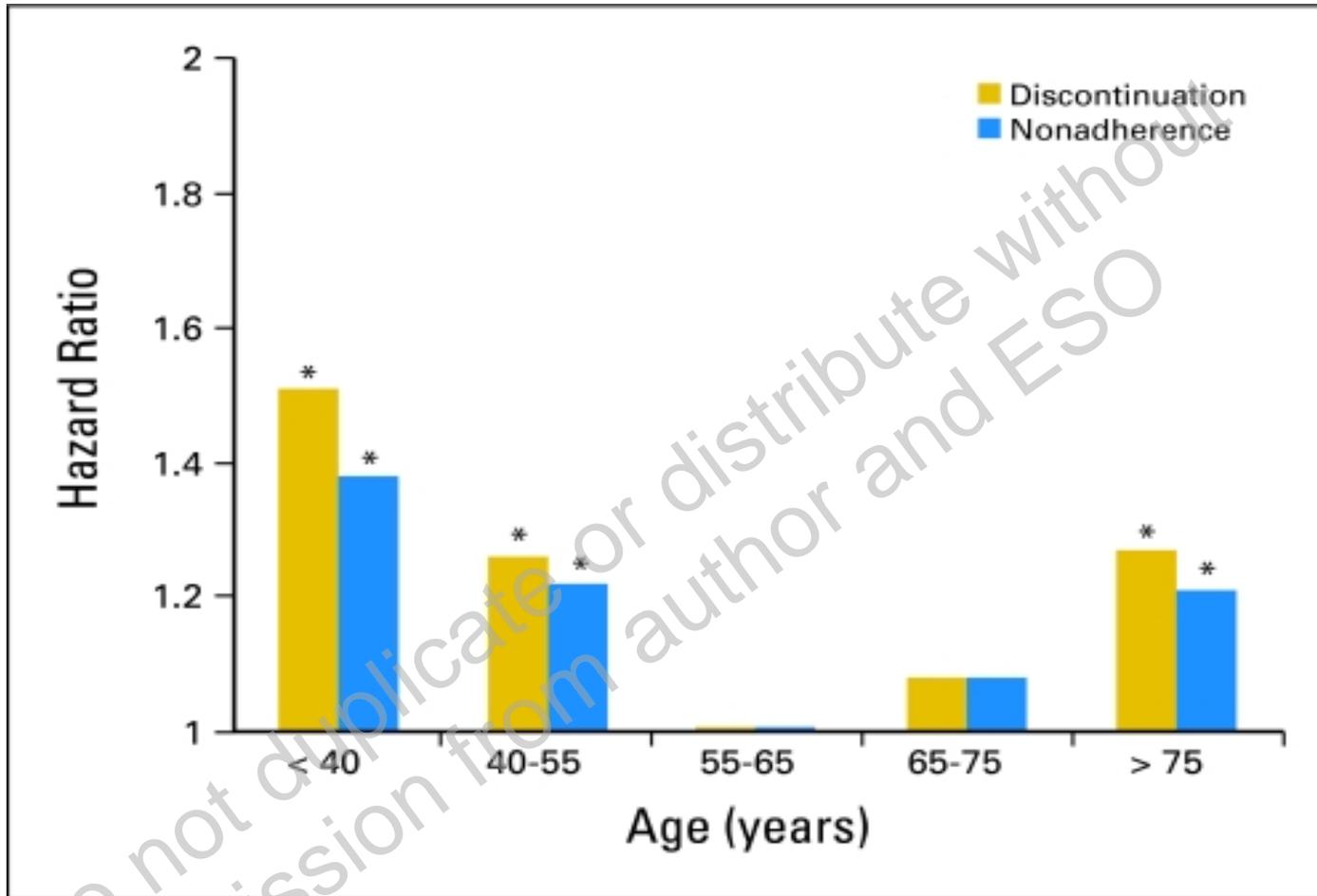
**Average Adherence in New Jersey Medicare/Medicaid  
Population in Years 1-4 of Tamoxifen**

# Proportion of patients continuing tamoxifen by year among premenopausal patients younger than age 45



Natalia C. Llarena et al. JNCI J Natl Cancer Inst  
2015;107:djv202

# Age as a predictor



Patient age as a predictor of discontinuation and nonadherence to endocrine therapy among 8,769 women diagnosed with stage I-III hormone receptor–positive breast cancer who initiated adjuvant hormonal therapy at Kaiser Permanente of Northern California (KPNC), 1996 to 2006. (\*)  $P < .05$ .

predictors of nonadherence and  
nonpersistence

**WHY DO THEY STOP TREATMENT?**

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# Barriers and facilitators of adjuvant hormone therapy adherence and persistence in women with breast cancer: a systematic review

Studies published in English measuring associations between adherence or persistence and any predictor variables were included

Sixty-one eligible articles were identified. Most studies focused on clinical and demographic factors with inconsistent results .

Patient Preference and Adherence, Moon Z, Feb 2017.

# Summary of results

- The percentage of women categorized as adherent ranged from 47% to 97% (mean =74%, SD =13%) and fell from an average of 79% in the first year of treatment to 56% in the fourth or fifth year. – depends on the methodology used!
- Discontinuation ranged from 9% to 63% (mean =30%, SD =12%). Discontinuation rose from an average of 21% in the first year to 48% in the fifth year.

# Clinical factors

- The majority of clinical factors showed no consistent associations with adherence or showed mixed results
- Regarding overall side effects, two studies showed a negative relationship with adherence and three studies found no significant effects
- Hot flushes/vasomotor symptoms, incontinence, gastrointestinal symptoms and sex-related symptoms were not associated with adherence, whereas weight concerns were associated with decreased odds of adherence.
- Cognitive, gynecological, musculoskeletal and sleep/fatigue-related symptoms were associated with lower odds of adherence in some studies, but the effects

# Clinical factors

Persistence:

Five studies found that experiencing any/severe side effects was associated with decreased odds of persistence, but three studies found no significant effects.

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**Table 5** Relationship between side effects and HT adherence/persistence

Variable	Number of studies showing positive/negative effect	
	Adherence	Persistence
Any side effects	2× negative <sup>27*,29</sup> 3× no effects	3× negative <sup>35*,46*,47</sup> 2× no effects
Severe side effects	0	2× negative <sup>25,48</sup> 1× no effects
Overall hormone/ menopause related	0	1× positive <sup>51*</sup> 2× negative <sup>10,50</sup>
Hot flushes/vasomotor symptoms/sweating	5× no effects	1× positive <sup>48</sup> 1× negative <sup>49</sup> 1× no effects
Overall sleep/fatigue related	2× no effects	2× no effects
Gynecological symptoms	1× positive <sup>42*</sup> 2× negative <sup>40*,41*</sup> 3× no effects	1× positive <sup>51*</sup> 2× no effects
Sex-related symptoms	4× no effects	2× no effects
Joint aches and pains/ osteoporosis	2× negative <sup>40*,41*</sup> 2× no effects	2× no effects
Weight concerns	2× negative <sup>40*,41</sup> 1× no effects	1× no effects
Incontinence/bladder control	3× no effects	1× no effects
Hair thinning/loss	0	1× positive <sup>51*</sup>
Headaches	0	1× negative <sup>51*</sup>
Loss of appetite	0	1× negative <sup>51*</sup>
Gastrointestinal symptoms	2× no effects	0
Cognitive symptoms	2× negative <sup>40*,41*</sup> 1× no effects	0

**Notes:** Individual symptoms that were only tested in one study and were not significant are not listed (shortness of breath, eyesight changes, breast sensitivity,

# Targeted Adverse Events Reported during Follow-up, According to Treatment Assignment.

**Table 2. Targeted Adverse Events Reported during Follow-up, According to Treatment Assignment.\***

Adverse Event	Exemestane plus Ovarian Suppression (N=2318)				Tamoxifen plus Ovarian Suppression (N=2325)			
	Any Event		Grade 3 or 4 Event		Any Event		Grade 3 or 4 Event	
	no. of patients with event	% (95% CI)	no. of patients with event	% (95% CI)	no. of patients with event	% (95% CI)	no. of patients with event	% (95% CI)
Allergic reaction or hypersensitivity	115	5.0 (4.1–5.9)	11	0.5 (0.2–0.8)	107	4.6 (3.8–5.5)	9	0.4 (0.2–0.7)
Injection-site reaction	168	7.2 (6.2–8.4)	1	<0.1 (0.0–0.2)	187	8.0 (7.0–9.2)	1	<0.1 (0.0–0.2)
Hot flushes	2125	91.7 (90.5–92.8)	232	10.0 (8.8–11.3)	2169	93.3 (92.2–94.3)	279	12.0 (10.7–13.4)
Depression	1165	50.3 (48.2–52.3)	87	3.8 (3.0–4.6)	1164	50.1 (48.0–52.1)	102	4.4 (3.6–5.3)
Sweating	1264	54.5 (52.5–56.6)	—	—	1371	59.0 (56.9–61.0)	—	—
Insomnia	1348	58.2 (56.1–60.2)	89	3.8 (3.1–4.7)	1361	58.5 (56.5–60.5)	100	4.3 (3.5–5.2)
Fatigue	1420	61.3 (59.2–63.2)	73	3.1 (2.5–3.9)	1463	62.9 (60.9–64.9)	67	2.9 (2.2–3.6)
Hypertension	527	22.7 (21.0–24.5)	151	6.5 (5.5–7.6)	509	21.9 (20.2–23.6)	169	7.3 (6.2–8.4)
Cardiac ischemia or infarction	16	0.7 (0.4–1.1)	7	0.3 (0.1–0.6)	7	0.3 (0.1–0.6)	3	0.1 (0.0–0.4)
Thrombosis or embolism	24	1.0 (0.7–1.5)	19	0.8 (0.5–1.3)	50	2.2 (1.6–2.8)	45	1.9 (1.4–2.6)
Nausea	721	31.1 (29.2–33.0)	17	0.7 (0.4–1.2)	671	28.9 (27.0–30.7)	13	0.6 (0.3–1.0)
Musculoskeletal symptoms	2057	88.7 (87.4–90.0)	254	11.0 (9.7–12.3)	1766	76.0 (74.2–77.7)	122	5.2 (4.4–6.2)
Osteoporosis	894	38.6 (36.6–40.6)	10	0.4 (0.2–0.8)	586	25.2 (23.5–27.0)	6	0.3 (0.1–0.6)
Fractures	158	6.8 (5.8–7.9)	29	1.3 (0.8–1.8)	120	5.2 (4.3–6.1)	18	0.8 (0.5–1.2)
Vaginal dryness	1214	52.4 (50.3–54.4)	—	—	1101	47.4 (45.3–49.4)	—	—
Decreased libido	1042	45.0 (42.9–47.0)	—	—	950	40.9 (38.9–42.9)	—	—
Dyspareunia	707	30.5 (28.6–32.4)	53	2.3 (1.7–3.0)	601	25.8 (24.1–27.7)	32	1.4 (0.9–1.9)
Urinary incontinence	304	13.1 (11.8–14.6)	6	0.3 (0.1–0.6)	414	17.8 (16.3–19.4)	7	0.3 (0.1–0.6)
CNS cerebrovascular ischemia	5	0.2 (0.1–0.5)	4	0.2 (0.0–0.4)	11	0.5 (0.2–0.8)	8	0.3 (0.1–0.7)
CNS hemorrhage	15	0.6 (0.4–1.1)	1	<0.1 (0.0–0.2)	21	0.9 (0.6–1.4)	2	0.1 (0.0–0.3)
Glucose intolerance†	54	2.3 (1.8–3.0)	11	0.5 (0.2–0.8)	54	2.3 (1.7–3.0)	15	0.6 (0.4–1.1)
Hyperglycemia†	61	2.6 (2.0–3.4)	13	0.6 (0.3–1.0)	80	3.4 (2.7–4.3)	15	0.6 (0.4–1.1)
Any targeted adverse event	2279	98.3 (97.7–98.8)	710	30.6 (28.8–32.6)	2285	98.3 (97.7–98.8)	683	29.4 (27.5–31.3)

\* The information here includes data from the 4643 patients in the safety population who received a protocol-assigned treatment. Targeted adverse events and other adverse events of grade 3 or higher were categorized according to the *Common Terminology Criteria for Adverse Events*, version 3.0.<sup>11</sup> Dashes indicate that grade 3 or 4 was not a possible grading for that adverse event. No patient had a targeted adverse event of grade 5. CNS denotes central nervous system.

† Glucose intolerance (diabetes) and hyperglycemia were added as targeted adverse events in 2011 and therefore may be underreported.

# Health care factors

Adherence:

Consultations with an oncologist or mastologist increased odds of adherence in two studies compared to women without these consultations. Experiencing more hospitalizations was associated with lower odds of adherence Higher monthly prescription costs were associated with decreased odds of adherence in four studies, but two studies found no significant effects.

# Health care factors

Persistence:

Five studies showed that odds of persistence **increased by 21%–66% if treatment was received by an oncologist or a gynecologist as opposed to a general practitioner**

while two studies found no significant effect. Five studies found that being prescribed more medications per month was associated with increased odds of persistence; however, an additional study showed the opposite effect and three studies found no significant effects. Three studies found that women who were hospitalized more were less likely to persist with treatment, but one study found no significant effects.

**Women who used complementary or alternative therapies had lower odds of persistence.**

# Demographic factors- age

## Adherence:

- Nine studies showed **lower odds of adherence for women under the age of 40/50 years**, one study found the opposite, and three studies showed no significant effects.
- Six studies found that older women (.65/75 years) were less likely to be adherent. However, two studies found the opposite effect and six studies found no effects.

# Demographic factors-age

Persistence:

There was a trend suggesting that younger (45/50 years) women had lower odds of persistence, but this was not always supported. Nine studies showed that older women were less likely to persist with treatment

# Psychosocial factors

Optimism showed a positive effect on persistence, and **expressing a future desire for fertility had a negative effect on persistence.**

There was some evidence suggesting that medication beliefs were related to adherence. Three studies showed that “necessity beliefs”, defined as judgments of personal need for the treatment, were significantly related to increased adherence. The adherence estimator measures relationship quality, value of doctor’s opinion, frequency of physician communication, and self-efficacy in patient–physician communication were positively associated with adherence.

# Psychosocial factors

Persistence:

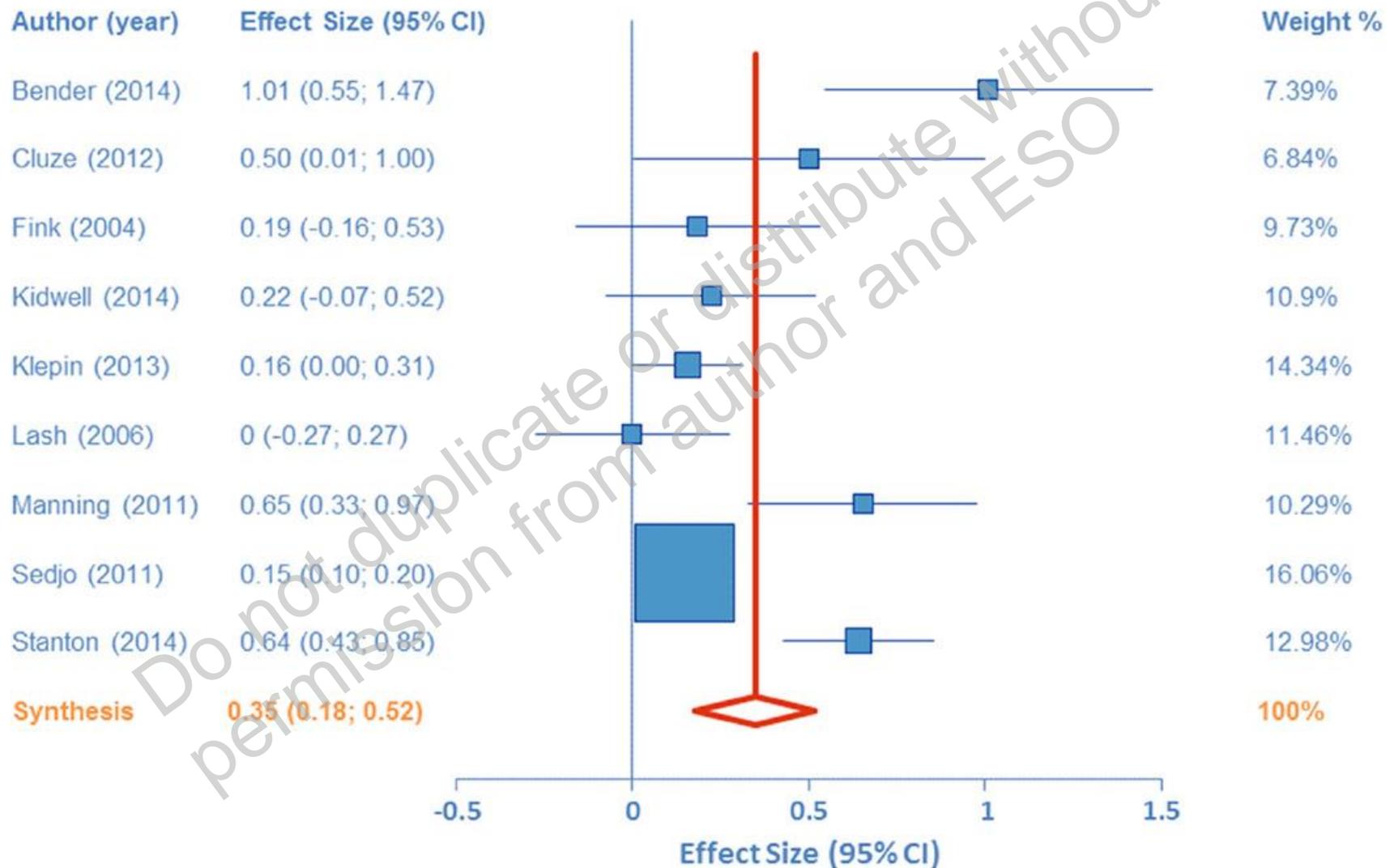
believing that the benefits of the treatment do not outweigh the harms, was associated with three times lower odds of persistence within the first 2 years of therapy.

Positive and negative emotions regarding HT were associated with increased/decreased odds of adherence.<sup>35</sup>

# Psychosocial factors

- Results for patient–physician relationship were mixed .
- being able to ask questions and understanding information, self-efficacy in patient–physician interaction, and receiving the right amount of support were significantly related to increased persistence.

# Depression as a predictor of adherence



# Adherence to Tamoxifen and incidence of depression

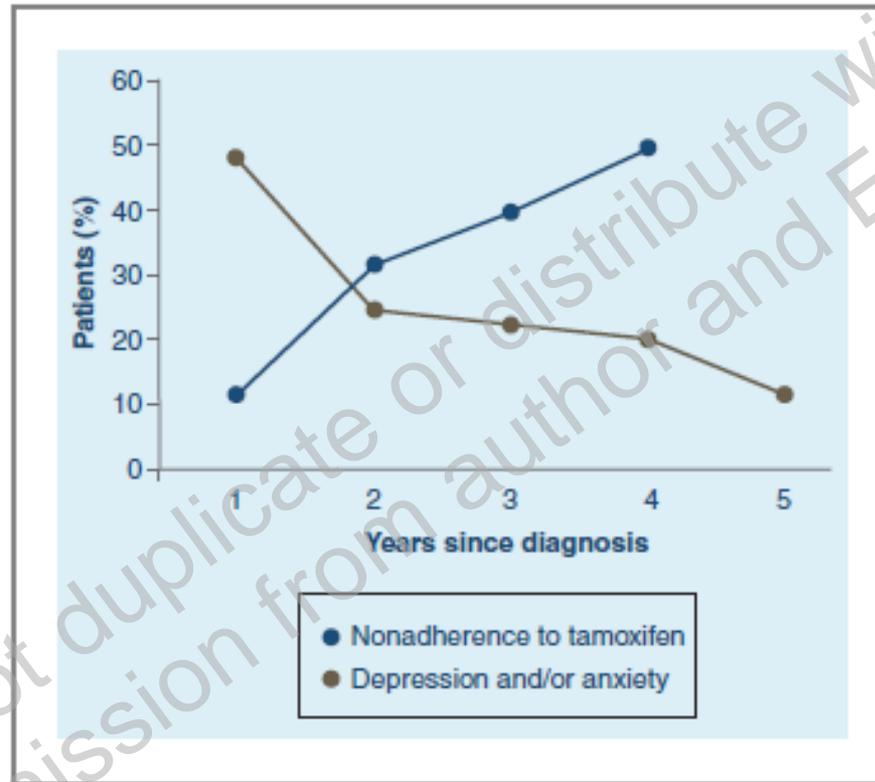


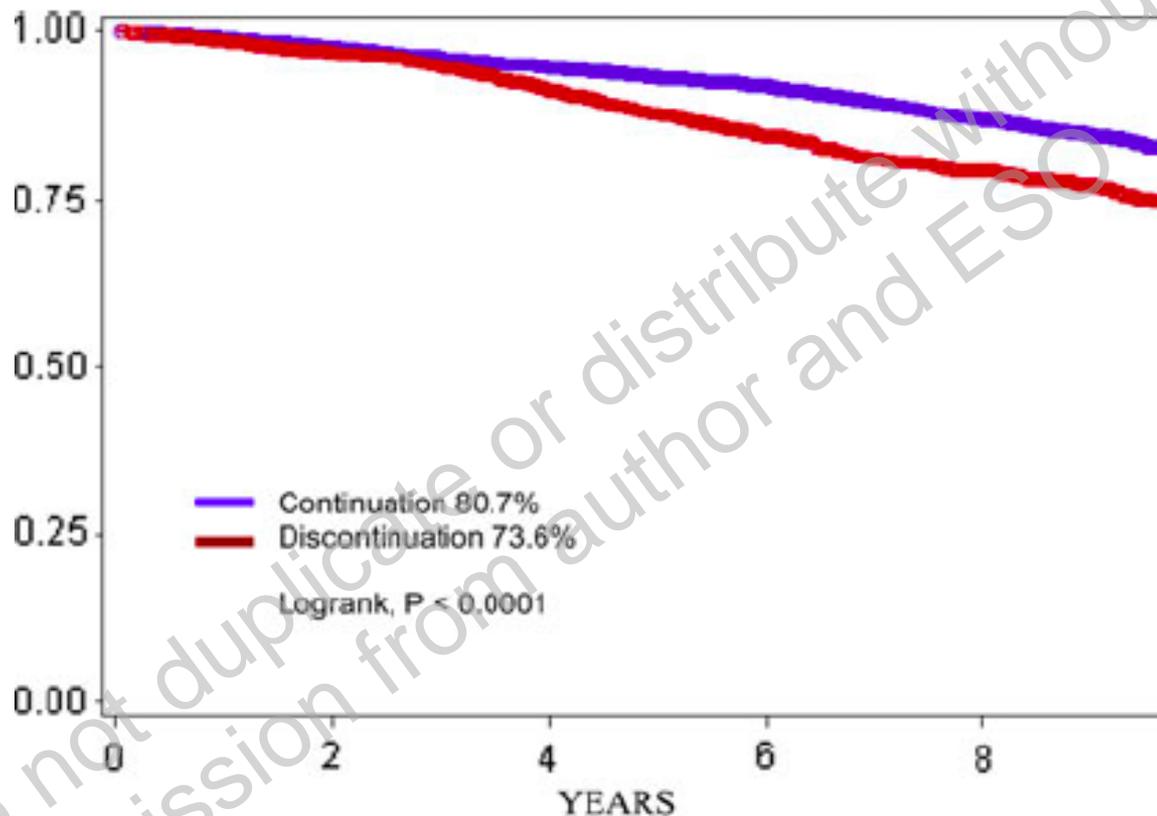
Figure 1. Nonadherence rates for adjuvant tamoxifen therapy in clinical practice and incidence of depression and/or anxiety in breast cancer patients with early stage disease.

# Adherence and outcome

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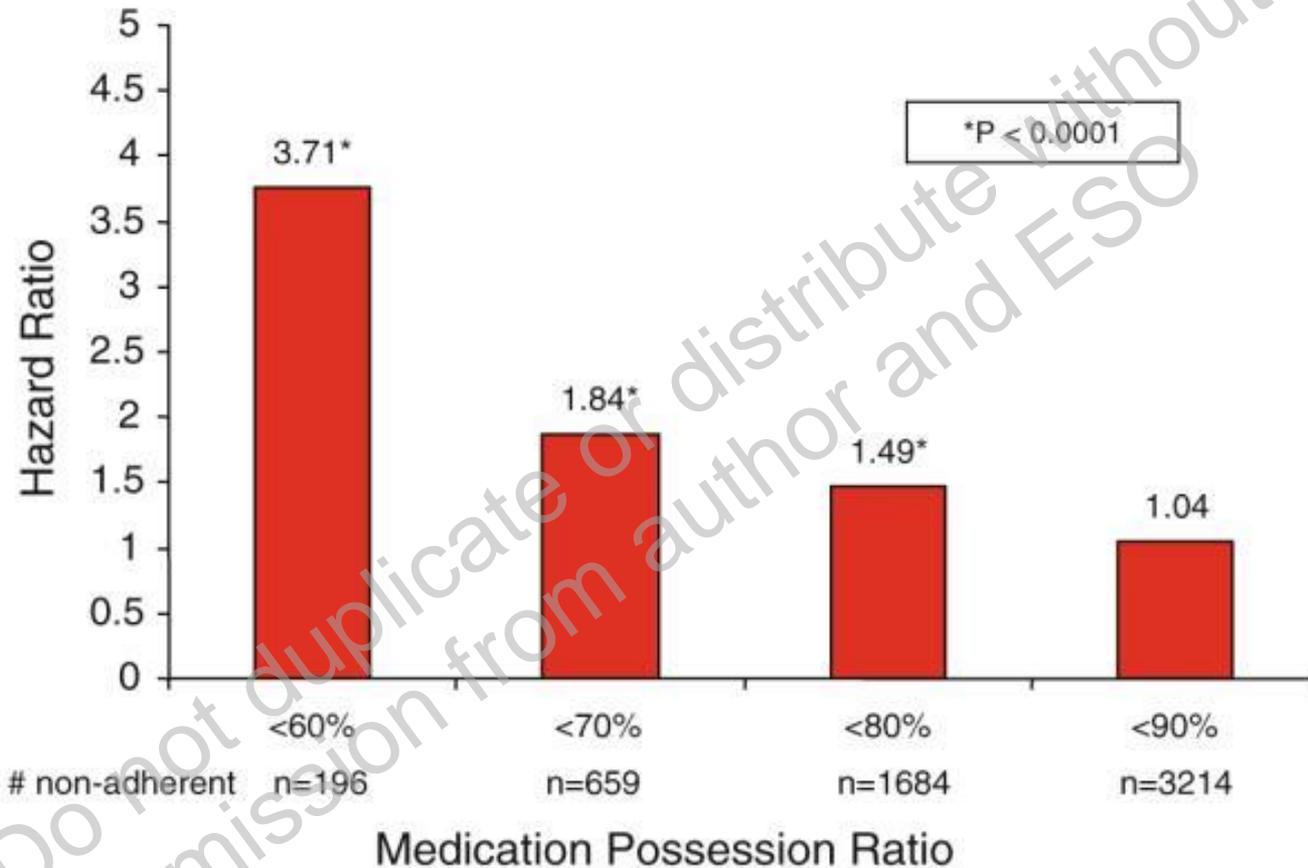
# Adherence Matters!

Discontinuation is Associated with Decreased Overall Survival



**Survival Distribution in 8769 Women with Stage 1-3 Breast Cancer in Kaiser Permanente Northern California**

# Adherence and outcome



Association between degree of adherence and all-cause mortality among 5,979 patients who continued adjuvant hormonal treatment, KPNC. 1996–2007. Results based on individual multivariate analysis compared to the rest of the cohort, controlling for clinical and socio-demographic variables

# Triple negative – guidelines adherence

Schwentner *et al.* *BMC Cancer* 2013, **13**:487  
<http://www.biomedcentral.com/1471-2407/13/487>



**RESEARCH ARTICLE**

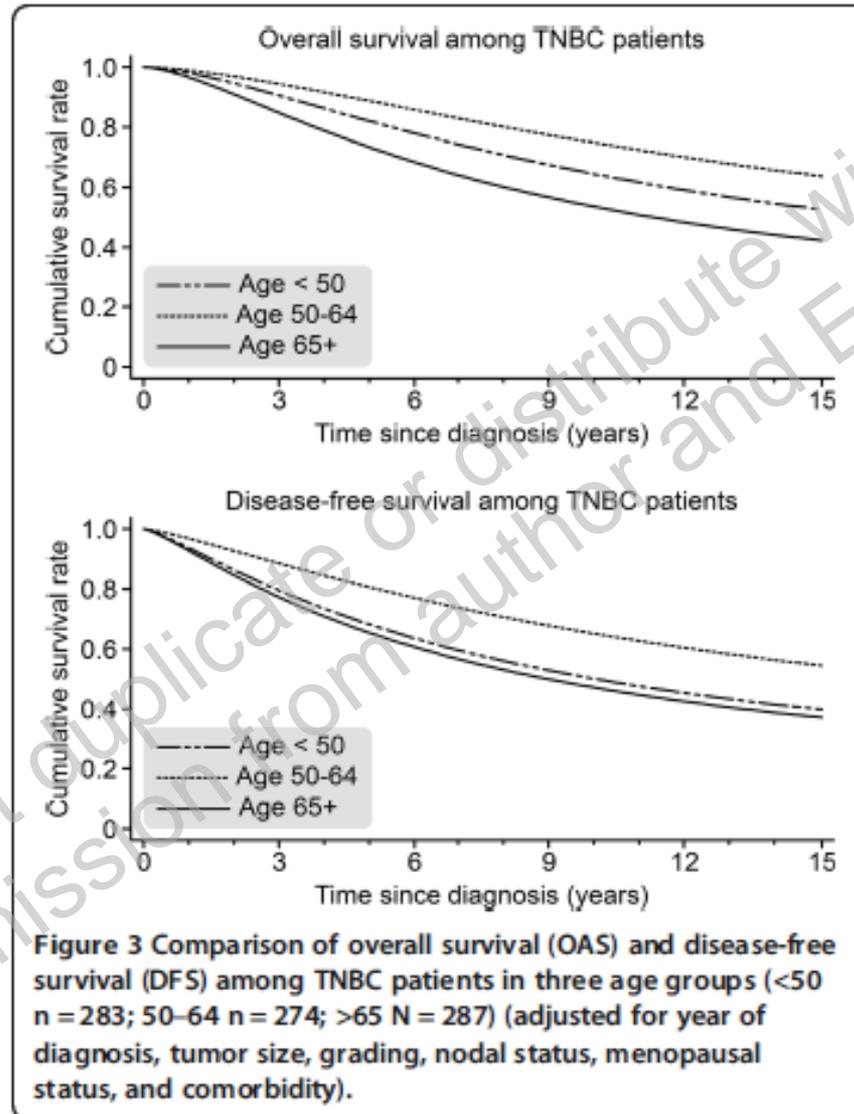
**Open Access**

## Adherence to treatment guidelines and survival in triple-negative breast cancer: a retrospective multi-center cohort study with 9156 patients

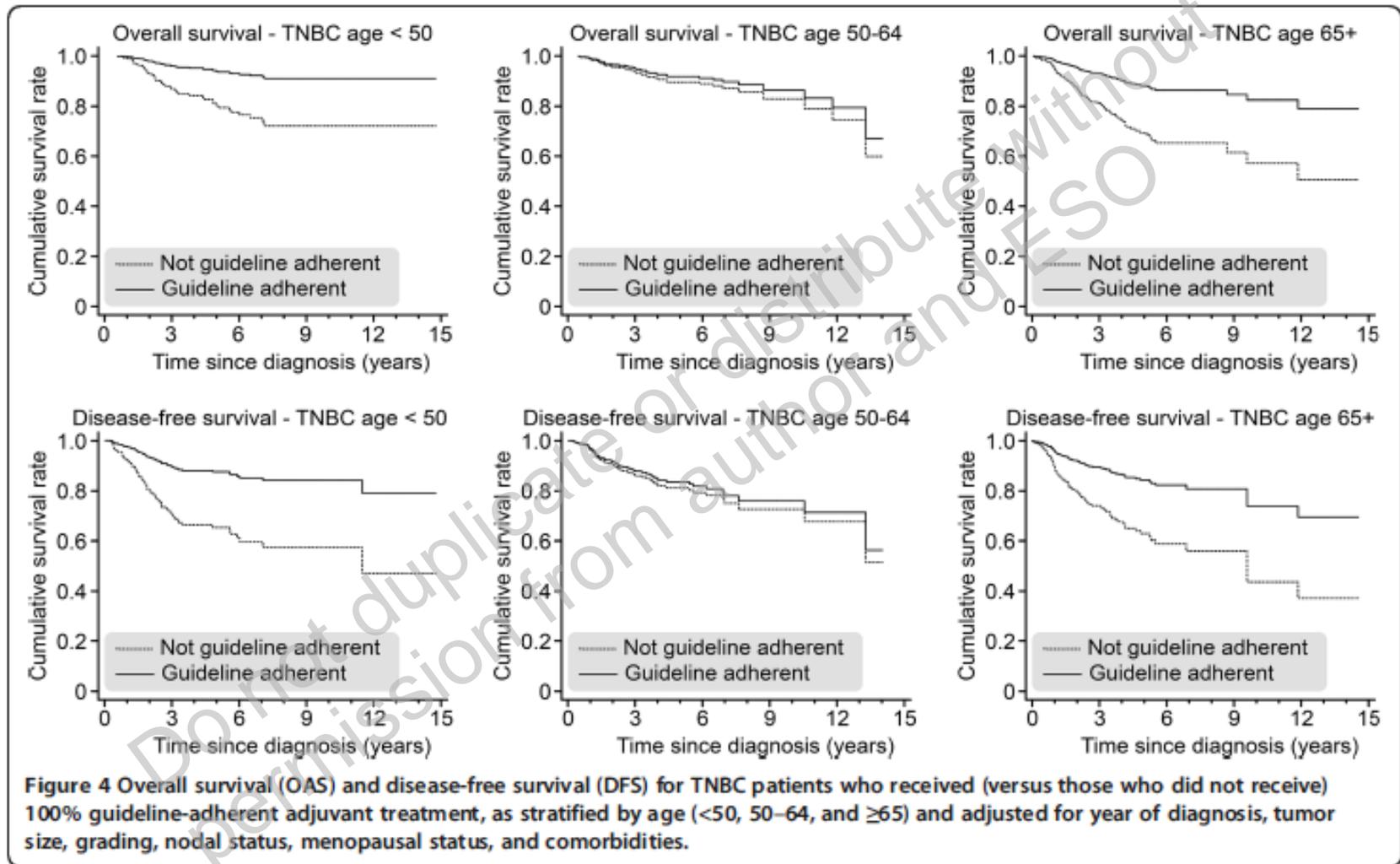
Lukas Schwentner<sup>1\*</sup>, Achim Wöckel<sup>1</sup>, Jochem König<sup>2</sup>, Wolfgang Janni<sup>1</sup>, Florian Ebner<sup>1</sup>, Maria Blettner<sup>2</sup>, Rolf Kreienberg<sup>1</sup>, Reyn Van Ewijk<sup>1</sup> for the Brenda study group

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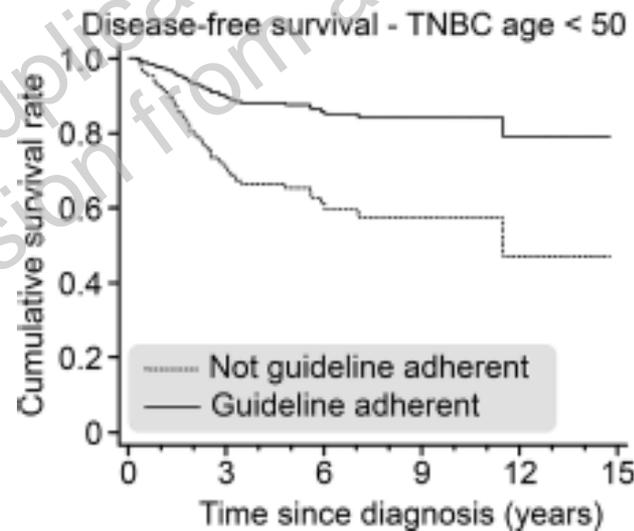
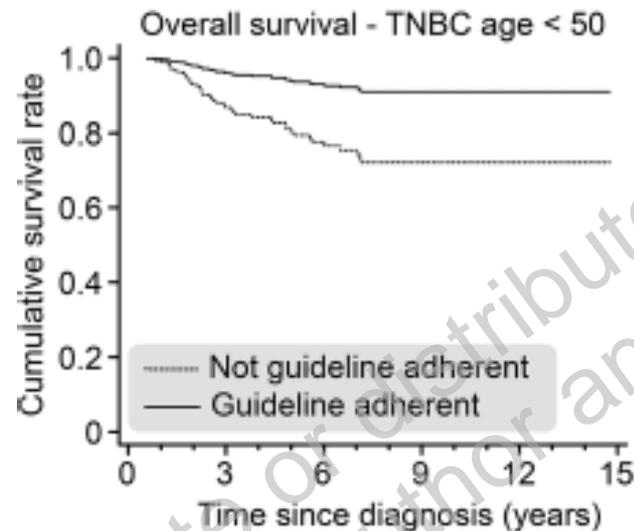
# Triple negative – age and outcome



# Triple negative – guidelines adherence



# Triple negative, young age, adherence and outcome



# What's next??

We have a problem!

Understand the determinants of nonadherence in your patients-ask your patient!

Survivorship follow-up clinics

Education

Social support

Management of side effects

Treatment by oncologist

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Thank you

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