Effect modifiers of low dose tamoxifen in a randomized trial in breast non-invasive disease

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Running title: Effect modifiers of low dose tamoxifen

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STATEMENT OF TRANSLATIONAL RELEVANCE

An investigator initiated phase III trial showed that low dose tamoxifen given at 5 mg/day for 3 years halved recurrence after surgery in breast non-invasive disease without increasing adverse events, thus representing a valid treatment option in women at risk for invasive breast cancer. In the current study we assessed whether benefits were greater in defined patient subgroups with a focus on menopausal status and symptoms. Our findings suggest that the efficacy of low dose tamoxifen is greater in postmenopausal women and in women with lower estradiol levels. Benefits may also be larger in women with menopausal symptoms, in never smokers and in tumors with Ki-67>10%. Our results provide further insight into low dose tamoxifen personalized treatment and open the door for an easy and safe preventive therapy in high risk individuals.
ABSTRACT

Purpose: Low-dose tamoxifen halved recurrence after surgery in a phase-III trial in breast non-invasive disease without increasing adverse events. We explored the effect of low dose tamoxifen in clinically relevant subgroups, including menopausal status, estradiol levels, smoking, body mass index and proliferation of baseline lesion.

Experimental Design: Incidence of invasive breast cancer or DCIS was the primary endpoint. Hazard ratios and interactions terms were estimated using Cox models.

Results: A favorable hazard ratio and 95% CI could be demonstrated for postmenopausal status (HR=0.30, 95% CI, 0.11, 0.82 versus HR=0.73, 95% CI, 0.30, 1.76 in premenopausal women, p-interaction=0.13), women with estradiol less than 15.8 pg/ml, presence of menopausal symptoms at baseline, and never smoking (p-interaction=0.07), although the interaction p-value was >0.05 for all characteristics. Efficacy was similar in all body mass index categories. Tumors with Ki-67 above the median level of 10% had a greater benefit (HR=0.27, 95% CI, 0.09, 0.81) than those with Ki-67 ≤10% (HR=1.58, 95% CI, 0.45, 5.60, p-interaction=0.04).

Conclusions: The efficacy of low-dose tamoxifen seems to be greater in postmenopausal women and in women with lower estradiol levels. Benefits appear to be larger also in women with menopausal symptoms, never smokers and tumors with Ki-67>10%. Our results by menopausal status provide important insight into low-dose tamoxifen personalized treatment, although caution is necessary given their exploratory nature. Observation of an improved response in tumors with Ki-67>10% is consistent but the use of the marker in this setting is investigational.

Word Count: 241 counted by Microsoft Word


Keywords: breast cancer, DCIS, tamoxifen, low dose, effect modifier epidemiology, clinical trial
INTRODUCTION

The uptake of preventive therapy in women at high risk for breast cancer is very low despite strong evidence of efficacy, primarily because of the fear of adverse events. Women at high risk include subjects with genetic and reproductive risk factors as well as women with histological diagnosis of breast intraepithelial neoplasia, which comprises atypical ductal hyperplasia (ADH), Ductal and Lobular Carcinoma in Situ (DCIS and LCIS). This group of pre-invasive disorders has the highest benefit from tamoxifen or anastrozole among high risk women, but toxicity, especially menopausal symptoms, musculoskeletal adverse events and serious adverse events such as endometrial cancer, venous thromboembolism, bone fractures and stroke have largely hampered preventive therapy uptake.

These considerations prompted us to conduct a phase-III de-escalation trial of low-dose tamoxifen, otherwise defined as “babytam”. Biomarker studies including a window of opportunity pre-surgical trial had shown that the minimal effective dose of tamoxifen was below 20 mg/day. In addition, a large observational study showed a highly significant reduction of recurrence with low dose tamoxifen in women with high risk DCIS. In the present trial, women with operated hormone sensitive or unknown breast intraepithelial neoplasia were randomized to either low dose tamoxifen, 5 mg/day or placebo for 3 years. A total of 500 women aged 75 or younger were included, and after a median follow-up of 5.1 years, low dose tamoxifen significantly decreased recurrence by 52% and contralateral breast events by 75%. Serious adverse events, including endometrial cancer and venous thromboembolic events, and patient reported outcomes were not different between arms except for a slight increase in frequency of daily hot flashes on low dose tamoxifen, consisting of less than one extra hot flash per day. Although the power of detecting rare serious adverse events was not high in our study, indirect comparison with 20 mg/day suggest that the risk of endometrial cancer and deep vein thrombosis was 2.5 lower with 5 mg/day of tamoxifen, providing a new treatment option in the management of breast intraepithelial neoplasia.
To get further insight into the efficacy of low dose tamoxifen towards a personalized preventive approach, and given the trend to a higher efficacy of full dose tamoxifen in postmenopausal women versus premenopausal women (or women aged <50 years) both in the adjuvant and preventive setting, we assessed whether its benefits were greater in patient subgroups defined by menopause related factors and biological plausibility.

METHODS

Subject and treatment

The study characteristics (EudraCT Number: 2007-007740-10; ClinicalTrials.gov Identifier: NCT01357772) and main clinical findings of the trial have recently been reported. The trial was approved in Italy by the Italian Medicines Agency (AIFA) and by the Ethical Committees for the Coordinating Center (E.O. Ospedali Galliera Ethical Committee) and the Participating Sites. The study was conducted in accordance with the Declaration of Helsinki and guidelines on Good Clinical Practice (ICH E6). All patients were informed of the objectives of the study and were invited to voluntarily participate. Patients who agreed to participate provided written consent before any study-specific procedure that could be withdrawn at any time without consequences for further treatment. Patients received a copy of their rights. The participant flow diagram is illustrated in the supplementary figure 1 (S1). Briefly, women aged 75 or younger with ECOG performance status ≤1 and excised hormone sensitive (estrogen or progesterone receptor ≥1%) or unknown breast intraepithelial neoplasia, including ADH (20%), DCIS (70%) and LCIS (10%), were randomized to either low dose tamoxifen, 5 mg/day or placebo for 3 years. Only women with high-grade or comedo/necrosis DCIS received 50 Gy adjuvant radiotherapy. Women received physical examination every 6 months and had an annual mammography and transvaginal ultrasounds for 3 years of treatment and 2 years of follow-up. Main exclusion criteria were: any prior invasive cancer, any tamoxifen contraindications, mental disorders, pregnancy, grade 2 or higher biochemical alterations, prior use of antiestrogens, current use of selective serotonin reuptake inhibitors. All breast events occurring during the trial were centrally adjudicated by a clinical committee.
Treatment compliance was assessed by pill count. Adherence was defined at each study visit as the use of at least 85% of assigned pills of the 6 month study period. The primary endpoint was the incidence of invasive breast cancer or DCIS. Toxicity was assessed by the NCI-CTCAE version 3. Since menopausal symptoms are a major cause of treatment drop-out in tamoxifen trials\textsuperscript{16,17}, patient-reported menopausal symptoms at baseline were recorded by the Breast Cancer Prevention Trial Symptom Scale\textsuperscript{18}, which calculates scores on each 5 point Likert scale by averaging a number of items during the last 4 weeks before each semiannual visit, including vasomotor symptoms, bladder incontinence, sexual and vaginal problems, musculoskeletal pain/arthralgia, cognitive problems (forgetfulness, difficulty concentrating and easily distracted) and weight gain. Menopause was defined as amenorrhea for at least 3 months and serum FSH above 45 mIU/mL and serum estradiol levels below 10 pg/mL. Six women originally classified as premenopausal women according to the interval from last menses were reclassified as postmenopausal according to hormone levels. Ki-67 labeling index (LI) was not mandatory in the protocol and was assessed in a subgroup of intraepithelial disorders at the entering institutions on a clinical basis and not performed centrally by IHC according to international recommendations and validation studies\textsuperscript{19,20} using the Mib-1 monoclonal antibody (Dako).

**Laboratory methods**

The analyzes were performed in batches at a single laboratory at the European Institute of Oncology. We adopted an ultrasensitive RIA method (DSL4800, Immunotech, Prague, Czech Republic) for the measurement of estradiol levels in postmenopausal women. The sensitivity of the assay is 2.2 pg/mL. The interassay coefficient of variation of our in-housed pooled serum sample (mean: 63.8 pg/mL; standard deviation 7.2; 60 replicates) was 11.3%. For the determination of estradiol levels in premenopausal women we adopted a CMIA technology designed for the ARCHITECT automated instrument (Abbott Diagnostics, Milan, Italy). The lower limit of detectability of the assay is <10 pg/mL. The interassay coefficient of variation of our in-housed pooled serum sample (mean: 75.1 pg/mL; standard deviation 4.6; 10 replicates) was 6.1%. Blood
collection according to the day since last menses in premenopausal was the following: days 1-7, n=33, days 8-14, n=27, days 15-21, n=28, days 22-28, n=20, days 29+, n=41.

**Statistical analysis**

The cumulative incidences of invasive breast cancer and DCIS (primary endpoint) was estimated with the Kaplan-Meier method, which was also adopted to estimate treatment adherence by pill count at different follow-up times. All analyses included all randomized patients, according to the intention-to-treat principle. Censoring to last available follow-up visit was applied in the absence of a clinical event. Cox proportional-hazards modeling was performed in order to calculate hazard ratios in subgroups. Per protocol pre-specified subgroup analyses were interval from diagnosis to study entry (≤12 versus 13-60 months), ADH+DCIS vs. LCIS and ER-positive vs. unknown disease. The results of these subgroup analyses were reported previously. Additional unplanned subgroup analyses were based on menopause related factors and biological plausibility consistent with the known effects of tamoxifen and included the following covariates: menopausal status, menopause related symptoms according to Stanton et al, baseline estradiol levels, BMI, smoking status which is known to decrease tamoxifen adherence and efficacy in prevention trials, Ki-67 labeling index of the primary intraepithelial neoplasm.

Further subgroup analyses according to ipsilateral or contralateral recurrence were not considered appropriate given the very low number of events in each strata. We performed and showed tests for interaction for all potential effect modifiers adding the specific interaction term within the Cox models. Since the study was not designed primarily to evaluate the effect of the interaction, we decided to increase the type I error rate (i.e. the likelihood that the study will find an interaction when, in fact, there is no such interaction in the population), which has the effect of reducing the type II error rate and thus increasing the power (1 minus the type II error rate) of the interaction test. Consequently, to identify potential effect modifiers of clinical interest, we adopted a cut-off p-value for the interaction test equal to 0.20 (i.e., a <20% probability that there is no such interaction in the population). Also, we did not apply any adjustment for multiplicity due to the exploratory nature of
the subgroups analyses. Results are shown with 95% confidence intervals and two-sided P-values.

We performed all analyses using STATA, version 14.2 (STATA, College Station, TX, USA).

RESULTS

The influence of menopause and menopause related covariates on low dose tamoxifen efficacy are depicted in figure 1. Menopausal status exhibited a borderline significant effect modification of low dose tamoxifen after adjustment for age, BMI, hot flashes and smoking status at baseline (p-interaction=0.13). Similarly, after adjustment for age, menopausal status, BMI and smoking status, the effect of low dose tamoxifen was more pronounced in women with lower levels of estradiol at baseline as well as women with baseline menopausal symptoms, including hot flashes, bladder incontinence, vaginal problems, musculoskeletal pain, cognitive problems and particularly in women who reported cognitive problems and weight gain (low p-values for interaction).

Kaplan Meier curves according to menopausal status are shown in figure 2. The unadjusted HR for low dose tamoxifen on the primary endpoint were 0.73 (95% CI, 0.30, 1.76) in premenopausal women (n=209) and 0.30, 95% CI, 0.11, 0.82 in postmenopausal (n=291).

In a subgroup of women (n=406) we measured estradiol levels at baseline. In figure 3, Kaplan Meier curves of time to recurrence by median estradiol level (15.8 pg/mL) and treatment arm are shown. The unadjusted HRs for low dose tamoxifen on the primary endpoint were 0.60 (95% CI, 0.23, 1.55) in women with estradiol above the median (n=202, mainly premenopausal women) and 0.23 (0.07, 0.81) in women below the median level, mainly postmenopausal women (n=204). Among postmenopausal women only, the effect of low dose tamoxifen was equal (HR=0.25) in women with median values below or above the median value of 11.7 pg/mL (not shown). The effect of low dose tamoxifen on time to recurrence was similar according to BMI category (Figure 4).

Treatment efficacy according to smoking status is illustrated in figure 5. Never smokers (n=323) had a tendency to a greater benefit from low dose tamoxifen (HR=0.31, 0.13-0.73) than former smokers (n=73, HR=0.62, 0.10-3.71) and current smokers (n=98, HR=1.44, 95% CI, 0.39-5.38, p-interaction=0.07, adjusted for adherence=0.11). Smokers were half premenopausal (49%) and half
postmenopausal (51%), so there is no confounding effect of menopausal status to explain the trend to a lower tamoxifen efficacy in smokers. Smoking habit also modified treatment adherence. Adjusting for age, BMI and menopausal status at baseline, the risk of non-adherence was higher in current smokers compared to former/never smokers in the low dose tamoxifen arm (HR=0.53, 0.32-0.88), but not in the placebo arm (HR=0.92, 0.55-1.54) (p-interaction=0.13, Supplementary Figure 2).

Measurement of the proliferation index Ki-67 in the primary lesions was available in a subgroup of 262 cases, 66% in DCIS, 36% in ADH and 27% in LCIS. The effect of low dose tamoxifen on the primary endpoint was significantly modified by Ki-67 (p-interaction=0.04, figure 6). Tumors with Ki-67 above the median level of 10% (n=133) had a greater benefit from low dose tamoxifen (HR=0.27, 0.09-0.81) than those with Ki-67 ≤10% (n=145, HR=1.58, 0.45-5.60).

**DISCUSSION**

Our exploratory study suggests that the efficacy of low dose tamoxifen on the primary endpoint (invasive breast cancer or DCIS) is greater in postmenopausal women as well as in women with lower estradiol levels at baseline, in women with menopausal symptoms, in never smokers and in tumors with Ki-67 above 10%.

In the worldwide overview of adjuvant trials\(^{15}\), there was a significant trend to a greater efficacy of tamoxifen on recurrence in women aged 55 or older compared to younger women. Likewise, in the NSABP-P1 prevention trial there was a trend to a greater risk reduction in women aged ≥60 years compared with women aged 50-59 years and women aged <49 years\(^{1,23}\). Conversely, in the IBIS-I trial the efficacy of full dose tamoxifen was not greater in women aged >50 years\(^{24}\). Importantly, toxicity was much greater in postmenopausal women in the NSABP-P1 trial\(^{1,23}\), where tamoxifen pharmacodynamics tends to switch towards agonistic effects at target organs under low estrogen levels\(^{25-27}\). In our trial, there was no association between menopausal status or age and low dose tamoxifen on adverse events\(^{12}\).
In our trial, the numerically and borderline statistically significant higher efficacy of low dose tamoxifen in postmenopausal women and in women with menopausal symptoms may be explained by the different levels of circulating estrogens. All menopausal symptoms analyzed in the Stanton et al questionnaire\textsuperscript{18} can indeed be elucidated by the estrogen drop at menopause\textsuperscript{28}. Conversely, several reports have shown the levels of estradiol in premenopausal women on 20 mg of tamoxifen to be increased by 200-300\%\textsuperscript{29-31}, which might attenuate its antitumor effect by overcoming the levels of active metabolites endoxifen and 4OH-tamoxifen\textsuperscript{32}. In our trial, the levels of estradiol in premenopausal women increased by only 30\% at 1 year and returned to baseline after 3 years\textsuperscript{33}, in line with prior studies of 5 mg/day, where the increase of circulating estradiol in premenopausal women was much lower than with the full dose\textsuperscript{34}. Our hypothesis is that low levels of active tamoxifen metabolites are still sufficient to inhibit low circulating estradiol levels in postmenopausal women or women with menopausal/hypoestrogenic symptoms, whereas in premenopausal women low dose tamoxifen might be less effective because of the moderate increase in estrogen levels. Measurements of tamoxifen and metabolites and CYP2D6 genotype are currently underway in our trial to shed lights into this important issue. Interestingly, a dose reduction of tamoxifen from 20 mg to 10 mg daily resulted in halving of endoxifen levels and a significant subjective improvement of hot flashes during treatment\textsuperscript{35}, in line with our findings of only a mild increase in hot flashes frequency with low dose tamoxifen versus placebo\textsuperscript{12}. Given the excellent efficacy and toxicity profile of low dose tamoxifen in postmenopausal women, a primary prevention trial versus an aromatase inhibitor to define the most acceptable agent in terms of efficacy and safety/tolerability is warranted. Aromatase inhibitors may well be more effective than tamoxifen\textsuperscript{36} but their tolerability and long term compliance remains an important issue both in treatment and prevention setting\textsuperscript{37}. Importantly, body mass index did not influence low dose tamoxifen efficacy, consistent with prior studies at 20 mg/day and in contrast with aromatase inhibitors\textsuperscript{38,39}. This is reassuring as one might
theoretically expect a lower efficacy of a low dose in overweight/obese women who represent a large fraction of the population with breast neoplasms in western countries.

Interestingly, in our study low dose tamoxifen efficacy was influenced by smoking status at two levels, adherence and smoking. Firstly, current smoking decreased adherence in women taking tamoxifen but not in women taking placebo. While the influence of smoking in decreasing compliance has previously been described in the NSABP-P1 trial, the selective effect on adherence just in the active arm of our double blind placebo controlled trial is novel and not easy to explain. Smoking may induce a “chemical rash” in the participants taking low dose tamoxifen which leads to a selective tamoxifen withdrawal compared to smokers taking placebo. A second level of effect modification induced by smoking habit was the ~70% reduction of recurrence noted in never smokers which was blunted in current smokers. This finding is in line with the results of the NSABP-P1 trial, where smoking was both a risk factor for breast cancer and an inhibitory factor of tamoxifen efficacy compared with former or never smokers. In their analysis, Land et al attributed this decreased efficacy mainly to the loss of adherence. Our results indicate that the trend to a lower efficacy of low dose tamoxifen in current smokers is at least partially independent of treatment adherence and suggest an additional hypothesis, i.e., smoking attenuates low dose tamoxifen efficacy due to direct and indirect mechanisms on the estrogen receptor pathway, which is activated by tobacco smoking condensate through different metal estrogens. While further confirmatory studies are necessary, our findings strengthen the importance of counseling women receiving tamoxifen to quit smoking in order to avoid loss of efficacy.

Our results suggest that tumors with higher proliferation and recurrence rate tend to respond well to low dose tamoxifen, with over 70% risk reduction. It is possible that the tumor requires a minimum threshold of proliferation to be sensitive to the drug, or that a short period of observation is not sufficient to demonstrate a difference in events in women with low Ki-67 levels. Caution is necessary in interpreting our results given the lower number of observations and the investigational...
nature of this biomarker in the setting of non-invasive breast cancer which is not a standard practice and has not been validated by international guidelines.

Conclusions

In conclusion, low dose tamoxifen given for 3 years is effective in women with pre-invasive disease and provides a valid and potentially safer alternative to full dose tamoxifen, as indicated by the new ASCO guidelines for breast cancer risk reduction. There was a tendency to a large benefit in postmenopausal women and in women with menopausal symptoms which might be explained by the presence of low circulating estrogens being effectively counteracted by low drug levels. Body mass index did not influence low dose tamoxifen effect. Current smoking may decrease both adherence and efficacy to low dose tamoxifen, possibly because of an activation of the ER pathway by tobacco smoking condensate. Subjects with higher tumor proliferation had a significant benefit to low dose tamoxifen. Although biologically plausible our subgroup analyses were unplanned and based on small numbers, so findings should be taken with caution. Given the excellent efficacy and toxicity profile, however, a prevention trial in postmenopausal women comparing low dose tamoxifen to an aromatase inhibitor is warranted.
ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interest.

DATA AVAILABILITY STATEMENT

Andrea DeCensi and Matteo Puntoni had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data may be shared upon request for collaborative studies.
REFERENCES


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APPENDIX

Abbreviations

ADH: Atypical Ductal Hyperplasia; ASCO: American Society of Clinical Oncology; BMI: Body Mass Index; CI: Confidence Interval; CMIA: Chemiluminescent Microparticle Immuno Assay; CYP2D6: Cytochrome P450 2D6; DCIS: Ductal Carcinoma in Situ; ECOG: Eastern Cooperative Oncology Group; ER: estrogen-receptor; FSH: follicle-stimulating hormone; HR: Hazard Ratio; IBIS I: International Breast Cancer Intervention Study I; IHC: Immunohistochemistry; LCIS: Lobular Carcinoma in Situ; LI: Labeling Index; NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Events; NSABP-P1: National Surgical Adjuvant Breast and Bowel Project; RIA: Radioimmunoassay; 4OH-Tamoxifen: 4-Hydroxy-Tamoxifen.

Ethics approval and consent to participate

The trial was approved in Italy by the Italian Medicines Agency (AIFA) and by the local Ethical Committee for all enrolling sites. This study complies with the Declaration of Helsinki and guidelines on Good Clinical Practice (ICH E6). All patients are informed of the objectives of the study and are invited to voluntarily participate. Patients who agree to participate provide written consent before any study-specific procedure that can be withdrawn at any time without consequences for further treatment. Patients will receive a copy of their rights.
FIGURE TITLE AND LEGENDS

Figure 1: Forest plot of the putative effect modifiers of low dose tamoxifen with interaction terms.

Menopausal status was adjusted for age, BMI, hot flashes and smoking status at baseline ($P$-interaction=0.10). Estradiol and menopausal symptoms were adjusted for age, menopausal status, BMI and smoking status.

HRs in subgroups are adjusted for age, BMI, menopausal and smoking status at baseline.

Missing or unknown data: 33 (6.6%) for hot flashes; 34 (6.8%) for bladder control, musculoskeletal pain and cognitive/weight problems; 35 (7%) for vaginal problems; 6 (1.2%) for smoking status; 23 (4.6%) for BMI.

Figure 2: Cumulative incidence of breast cancer by allocated arm and menopausal status.

Pre-menopausal women are shown in panel A and post-menopausal women are shown in panel B. Numbers in parentheses represent the number of events (invasive breast cancer and DCIS) that occurred within each time interval by treatment arm.

Figure 3. Cumulative incidence of breast cancer by allocated arm and baseline estradiol level.

Women with baseline estradiol levels below (panel A) and above (panel B) the median (18.5 pg/mL) are shown. Numbers in parentheses represent the number of events (invasive breast cancer and DCIS) that occurred within each time interval by treatment arm.
Figure 4. **Cumulative incidence of breast cancer by allocated arm and baseline body mass index.**

Baseline normal weight (panel A), overweight (panel B) and obese women (panel C) are shown. Numbers in parentheses represent the number of events (invasive breast cancer and DCIS) that occurred within each time interval by treatment arm.

Figure 5. **Cumulative incidence of breast cancer by allocated arm and smoking status.**

Current smokers (panel A), former smokers (panel B) and never smokers (panel C) are shown. \( P \)-interaction = 0.07. Numbers in parentheses represent the number of events (invasive breast cancer and DCIS) that occurred within each time interval by treatment arm.

Figure 6. **Cumulative incidence of breast cancer by allocated arm and baseline Ki-67.**

Ki-67 \( \leq 10\% \) (median value, panel A) and Ki-67 >10\% (panel B) are shown \( P \)-interaction = 0.04. Numbers in parentheses represent the number of events (invasive breast cancer and DCIS) that occurred within each time interval by treatment arm.
**Figure 1**

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*Menopausal status subgroups HRs and p for interaction are also adjusted for hot flashes at baseline (yes/no)
Premenopausal women (n = 209):
HR, 0.73; 95% CI, 0.30 - 1.76

Postmenopausal women (n = 291):
HR, 0.30; 95% CI, 0.11 - 0.82
Figure 3

A

Estradiol ≤ 15.8 pg/mL (median) (n=204):
HR, 0.23; 95% CI, 0.07 - 0.81

Estradiol > 15.8 pg/mL (median) (n=202):
HR, 0.60; 95% CI, 0.23 – 1.55
Figure 4

A  
BMI <25 kg/m² (n = 249):  
HR, 0.51; 95% CI, 0.19 - 1.36

B  
BMI 25-29.9 kg/m² (n = 145):  
HR, 0.44; 95% CI, 0.14 - 1.40

C  
BMI 30+ kg/m² (n = 83):  
HR, 0.42; 95% CI, 0.10 - 1.77
Figure 5

A  
**Current smokers (n = 98):**
HR, 1.44; 95% CI, 0.39 - 5.38

B  
**Former smokers (n = 73):**
HR, 0.62; 95% CI, 0.10 - 3.71

C  
**Never smokers (n = 323):**
HR, 0.31; 95% CI, 0.13 - 0.73
Figure 6

**A**

Ki67 ≤ 10% (median) (n=145):
HR, 1.58; 95% CI, 0.45 - 5.60

**B**

Ki67 > 10% (median) (n=133):
HR, 0.27; 95% CI, 0.09 - 0.81
Effect modifiers of low dose tamoxifen in a randomized trial in breast non-invasive disease

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