BRIEF COMMUNICATIONS

Italian Randomized Trial Among Women With Hysterectomy: Tamoxifen and Hormone-Dependent Breast Cancer in High-Risk Women

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Tamoxifen improves outcome in women with breast cancer and reduces the incidence of estrogen receptor-positive (ER+) breast tumors in prevention trials. Tamoxifen use is associated with an increased risk of potentially serious adverse events, principally endometrial cancer and venous thromboembolic events and, therefore, detailed knowledge of the effects of tamoxifen is important. With more cases of breast cancer being found as the follow-up time increases, it is now possible to perform more detailed analysis of the Italian Randomized Trial of Tamoxifen. Women with hysterectomy (N = 5408) were randomly assigned to receive 20 mg tamoxifen per day (N = 2700) or placebo (N = 2708). After a median of 81.2 months of follow-up, 79 case subjects (34 in the tamoxifen arm and 45 in the placebo arm) were diagnosed with breast cancer. We were able to identify a group of women at increased risk of ER+ breast cancers (high-risk group) on the basis of baseline as well as reproductive and hormonal characteristics (height, age at menarche, parity, age at first birth, and oophorectomy). Tamoxifen administered to women in the high-risk group showed statistically significantly reduced incidence of breast cancer (tamoxifen, 3 and placebo, 15; *P* = .003), but no such effect was seen in the low-risk group (tamoxifen, 31 and placebo, 30; *P* = .89). The positive effect of tamoxifen on breast cancer among high-risk women is most marked for ER+ tumors (tamoxifen, 1 and placebo, 11; *P* = .002). Chemoprevention of breast cancer with tamoxifen appears to be effective in women at high risk of ER+ tumors but not among women at low risk, who may well be protected naturally by late age at menarche or early first pregnancy, or artificially by removal of the ovaries. Tamoxifen could be offered as a preventive agent to women identified at high-risk of breast cancer because of hormone-related risk factors. Such a strategy would greatly reduce the numbers of women who would need to take tamoxifen to obtain the same absolute reduction in breast cancer. These findings are exploratory and need to be confirmed in other randomized trials. [J Natl Cancer Inst 2002;94:160–5]

Tamoxifen has been demonstrated to be effective in prolonging disease-free survival and overall survival in women with breast cancer *(1)*. An overview of the four randomized prevention trials indicates a 38% reduction (95% confidence interval [CI] = 28% to 46%) in incidence of breast cancer (Cuzick J, Powles T, Veronesi U, Forbes J, Edwards R, Ashley S, et al.: unpublished data). The reduction was confined to estrogen receptor-positive (ER+) tumors (reduction was 48%, 95% CI = 36% to 58%) and a slight, although not statistically significant, increase of ER– tumors was noted. The risk of endometrial cancer was increased (odds ratio [OR] = 2.4, 95% CI = 1.5 to 4.0) as was the risk of venous thromboembolic events (OR = 1.9, 95% CI = 1.4 to 2.7). Overall there was no effect on non-breast-cancer mortality, and the only cause showing a mortality increase was pulmonary embolism (tamoxifen, 6 and placebo, 2). It was concluded that tamoxifen cannot yet be recommended as a preventive agent to the general population, and continued follow-up of the current trials is essential if a subgroup of high-risk, healthy women is to be identified in which the risk–benefit ratio is sufficiently positive to recommend usage. Gail et al. *(2)* have previously attempted a similar subgroup analysis on the National Surgical Adjuvant Breast and Bowel Project (NSABP) P1 dataset, clearly demonstrating that tamoxifen is most beneficial for younger women with an elevated risk of breast cancer.

The demonstration of the effectiveness of the Gail Model in predicting risk of breast cancer in the NSABP P1 trial *(3)* indicates the utility of having some means of identifying women at increased risk of breast cancer. Huang et al. *(4)* have attempted to indicate lifestyle risk factors for ER+/progesterone-positive (PR+) breast tumors, those most susceptible to prevention by tamoxifen. The strongest predictors of ER+/PR+ in postmenopausal women included age at menarche, nulliparity, age at first birth, and body mass index.

To investigate the effect of tamoxifen on breast cancer incidence and mortality, a double-blinded, placebo-controlled, randomized trial of tamoxifen was undertaken in Italy in women who did not have breast cancer. In view of the potential adverse effect on endometrial cancer, the study was restricted to women who had undergone hysterectomy. This group had an overall risk of

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See "Appendix" for a list of physicians and scientists in the Italian Tamoxifen Study Group and their affiliations.

See "Notes" following "References."

breast cancer slightly lower than that of the general population, because in approximately half the women (48%), the procedure had been accompanied by bilateral oophorectomy.

Between October 1992 and December 1997, a total of 5408 women were randomly assigned into the Italian Randomized Trial of Tamoxifen to receive tamoxifen or placebo. The participating women had a median follow-up of 55.3 months for evaluating the side effects of the treatment and 81.2 months for evaluating major endpoints, such as death and cancer diagnosis until February 1, 2001 (Fig. 1). A total of 79 case subjects with breast cancer have been identified. There is no statistically significant difference in breast cancer incidence between the placebo arm (n = 45) and the tamoxifen arm (n = 34) *(5)*.

Women with early age at menarche and women with late age at first birth experienced an excess of breast cancer. The risk was reduced in women who had both ovaries removed (Table 1). Height, which has been shown to be associated with an increased risk of breast cancer *(6),* is also a risk factor among the study participants. When the effect of tamoxifen on breast cancer risk was examined, it seemed to be greatest among those women at the most increased breast cancer risk because of the factors described above (Table 1). Breast cancer risk increased according to family history, but there was no effect of tamoxifen according to this variable, although the number of women who reported a family history of breast cancer was very small (Table 1).

We defined a group of women at high-risk of ER+ breast cancer using a dichotomy based on baseline characteristics. This group comprises 702 (13.0%) women taller than 160 cm (the median height of the group), with at least one functioning ovary, who had menarche at no older than age 13 and no full-term pregnancy before age 24. The remaining group of 4693 (87.0%) women was classified as the low-risk group. Information on required baseline characteristics was missing for 13 women. The risk of breast cancer in the high-risk group in this study was increased threefold over that of the low-risk group (hazard ratio [HR] = 3.32; 95% CI = 1.78 to 6.17) (Table 1).

Intervention with tamoxifen statistically significantly reduced the incidence of breast cancer in the high-risk group (P = .003) but had no effect in the low-risk group (P = .89) (Fig. 2, A). The effect of tamoxifen in the high-risk group was to reduce the risk of breast cancer by 82% (HR = 0.18, 95% CI = 0.05 to 0.62), whereas the effect in the low-risk group was an increase of 3% (HR = 1.03, 95% CI = 0.62 to 1.70) (Table 1).

After 7 years of follow-up, the fitted cumulative rate of breast cancer (using Cox proportional hazards regression) was 1.52% (95% CI = 0.97% to 2.06%) in the tamoxifen arm versus 1.47% (95% CI = 0.93% to 2.00%) in the placebo arm of the low-risk group and 0.93% (95% CI = 0.00% to 1.99%) in the tamoxifen arm versus 4.90% (95% CI = 2.32% to 7.44%) in the placebo arm of the high-risk group.

Ten of the breast cancers (six in the tamoxifen arm and four in the placebo arm) were *in situ* tumors. All were diagnosed in the low-risk group.

There was no statistically significant difference between tamoxifen and placebo arms among women who never used hormone replacement therapy (HRT) and were in the low-risk group (P = .44) (Fig. 2, B). Among women who never used HRT and were in the high-risk group, there was a statistically nonsignificant difference in favor of tamoxifen (P = .099) (Fig. 2, B). Among women who had used HRT during the trial and who were in the low-risk group, there was again a statistically nonsignificant difference in favor of tamoxifen (P = .31) (Fig. 2, B). However, among women who had used HRT and were in the high-risk group, there was a statistically significant difference in favor of tamoxifen (P = .009) (Fig. 2, B).

In the low-risk group, there was no reduction in the incidence of ER– (P = .51) or ER+ tumors (P = .87), whereas, in the high-risk group, there was a strong reduction of ER– tumors (P = .002) and a statistically nonsignificant slight reduction of ER– tumors (P = .39) (Fig. 2, C), based on a small number of events.

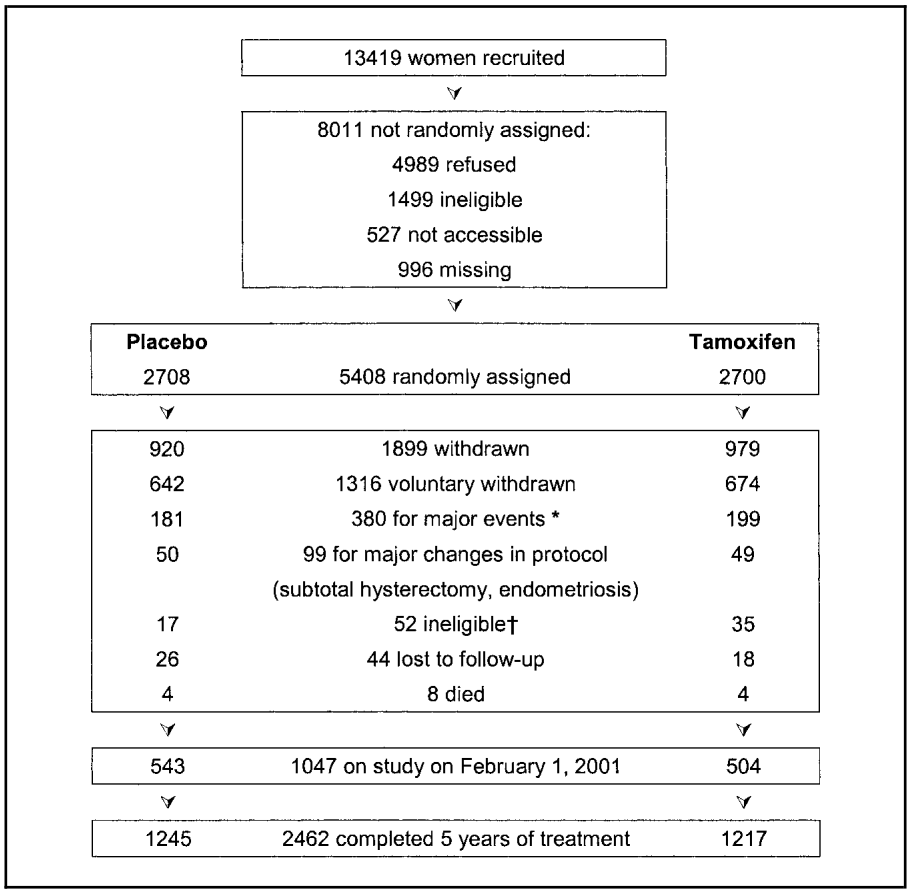

Fig. 1. Italian Tamoxifen Intervention Trial profile study design, February 1, 2001. *, Major events include cardiovascular disease, venous thromboembolic event, tumor, liver disease, allergic reaction, and occular, gastrointestinal, and hematologic conditions. †, Ineligible because women had either partial hysterectomy or a past medical condition listed as an exclusion criteria.

Table 1. Risk factors for breast cancer and effect of tamoxifen on reduction of breast cancer among exposed and unexposed women expressed as hazard ratios (HRs) with 95% confidence intervals (CIs)

Characteristics*	No. of breast cancer subjects		Breast cancer risk† HR (95% CI)	Effect of tamoxifen on breast cancer risk‡ HR (95% CI)
	Placebo arm (N = 2708)	Tamoxifen arm (N = 2700)		
All subjects (N = 5408)	45	34		0.75 (0.48 to 1.18)
Age, y				
⩽49 (n = 2073)	14	12	1.00	0.75 (0.34 to 1.63)
50–54 (n = 1649)	15	12	1.29 (0.62 to 2.67)	0.86 (0.40 to 1.88)
55–59 (n = 1063)	9	7	1.09 (0.47 to 2.53)	0.92 (0.34 to 2.50)
⩾60 (n = 623)	7	3	1.65 (0.66 to 4.08)	0.18 (0.03 to 1.05)
Previous biopsy for benign breast disease				
No (n = 4578)	36	25	1.00	0.69 (0.42 to 1.16)
Yes (n = 805)	9	9	1.46 (0.70 to 3.03)	1.04 (0.39 to 2.83)
Blood relatives with breast cancer				
0 (n = 4275)	33	24	1.00	0.73 (0.43 to 1.24)
1 (n = 931)	10	10	1.37 (0.68 to 2.79)	0.94 (0.38 to 2.32)
⩾2 (n = 202)	2	0	1.74 (0.42 to 7.26)	N/A
Use of HRT				
Never (n = 3809)	28	28	1.00	0.99 (0.59 to 1.69)
At baseline only (n = 238)	1	1	0.64 (0.09 to 4.71)	0.62 (0.04 to 10.7)
During intervention (n = 595)	5	2	1.14 (0.44 to 2.96)	0.46 (0.09 to 2.38)
Always (n = 751)	11	3	2.07 (1.02 to 4.19)	0.38 (0.10 to 1.44)
Height, cm				
<160 (n = 2230)	11	10	1.00	1.00 (0.42 to 2.37)
160–164 (n = 1734)	17	14	2.06 (0.96 to 4.39)	0.77 (0.38 to 1.59)
⩾165 (n = 1428)	17	10	2.53 (1.18 to 5.40)	0.53 (0.23 to 1.24)
Ovary function				
Preserved (n = 2533)	27	18	1.00	0.63 (0.35 to 1.16)
Lost (n = 2620)	18	13	0.63 (0.35 to 1.15)	0.76 (0.37 to 1.58)
Unknown (n = 242)	0	3	N/A	N/A
Age at menarche, y				
⩽13 (n = 3924)	38	21	1.00	0.59 (0.35 to 1.01)
⩾14 (n = 1471)	7	13	0.48 (0.22 to 1.09)	1.62 (0.64 to 4.11)
Age at first birth, y				
⩽20 (n = 753)	2	3	1.00	2.84 (0.28 to 29.1)
21–23 (n = 1323)	9	7	2.19 (0.47 to 10.2)	0.84 (0.31 to 2.29)
⩾24 (n = 2697)	27	16	3.27 (0.78 to 13.8)	0.58 (0.31 to 1.08)
Nulliparous (n = 622)	7	8	3.51 (0.73 to 17.0)	1.66 (0.54 to 5.15)
Overall risk§				
Low-risk (n = 4693)	30	31	1.00	1.03 (0.62 to 1.70)
High-risk (n = 702)	15	3	3.32 (1.78 to 6.17)	0.18 (0.05 to 0.62)

*Information is missing for a few women; therefore, the total subjects in some strata do not add up to the number assigned to both arms; HRT = hormone replacement therapy; N/A = not applicable.

†Hazard ratios and 95% confidence intervals are adjusted for age and treatment.

‡Hazard ratios and 95% confidence intervals are adjusted for age.

§The high-risk group includes women taller than 160 cm, with at least one functioning ovary, who had menarche at no older than age 13 and no full-term pregnancy before age 24; the low-risk group includes the remaining women.

It is important to emphasize several points when considering the findings from this subgroup analysis *(7,8)*. More work should be done on predicting women at increased risk of ER+ breast cancer. The dichotomy used in this analysis was not used as a stratification factor at the time of randomization to receive a given treatment, and it is vital to confirm these findings in the other randomized trials. If these findings are replicated in other studies, it may then prove possible to improve the utility of this dichotomy in the specific setting of identifying women who may be likely to have the greatest benefit from tamoxifen for breast cancer prevention. Family history alone is associated with ER–/PR– breast cancers *(4)*, and it is possible that a re-analysis of the NSABP P1 restricted to women with a high-risk of ER+/PR+ breast cancer might show a larger protective effect for women in this group.

In conclusion, tamoxifen's effect appears to be restricted to women who are predicted to be at high risk of the hormone-dependent form of breast cancer. This is a potentially important finding, which requires confirmation from other trials before the clinical and public health implications are clear. If our findings are true, then the same reduction in the absolute numbers of breast cancers could be obtained by restricting treatment to the group of women at higher risk (which, in this study, was about one eighth of the total cohort). From a public health perspective, this strategy would greatly improve the cost-effectiveness of the intervention and would greatly reduce the overall side effects in a population by avoiding treatment-related symptoms in the majority of women therein.

APPENDIX

The Italian Tamoxifen Study Group includes the following physicians and scientists who contributed to this trial (all organizations are in Italy unless otherwise noted): A. Ferrari, Ambulatorio Raphael, Calcinato; E. Chiesa, P. Gallotti, Associazione Life per la prevenzione e la cura dei Tumori, Vigevano; S. Bruno, M. Podda, G. Pardi, Azienda

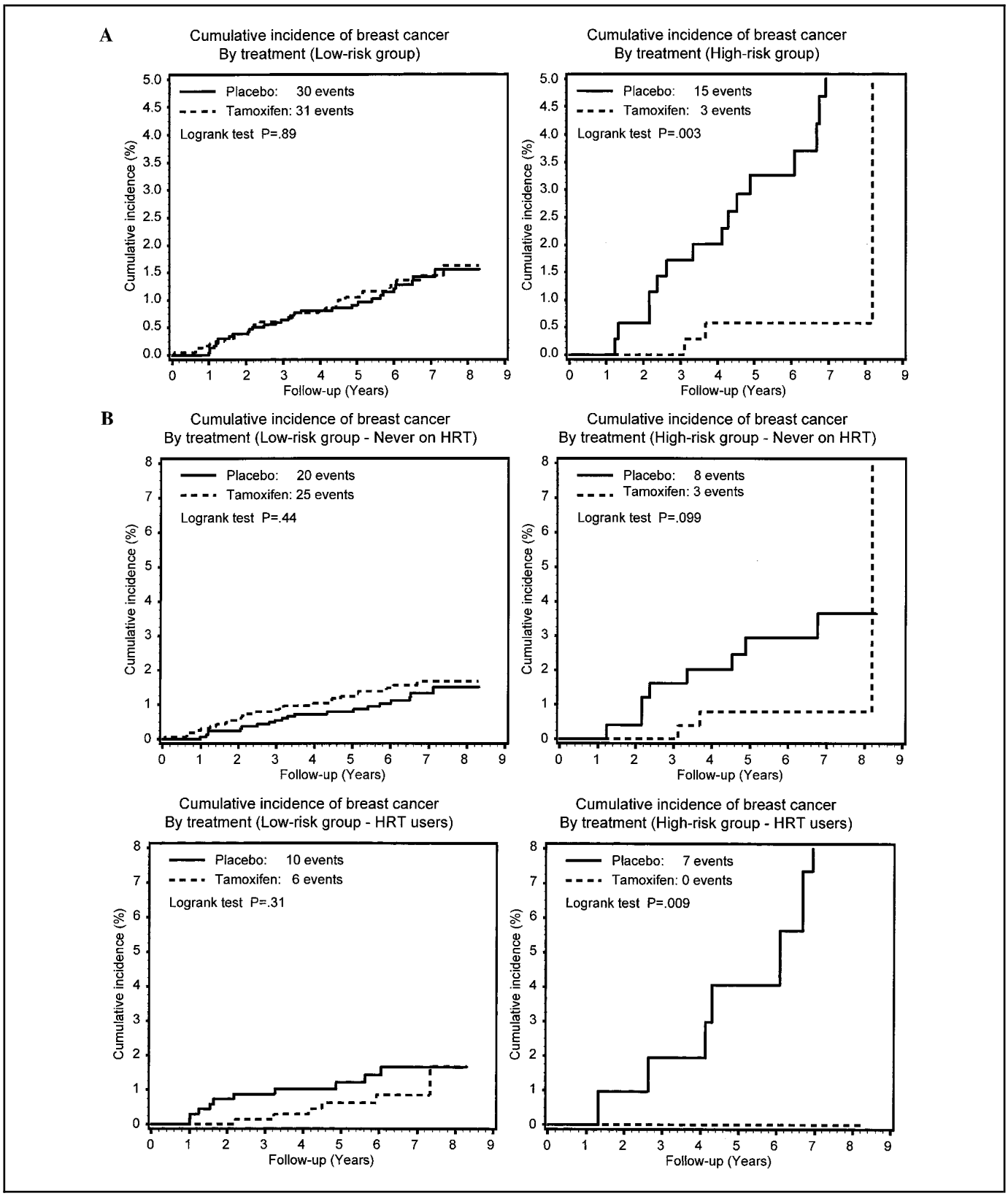

Fig. 2. Legend and Fig. 2C on next page.

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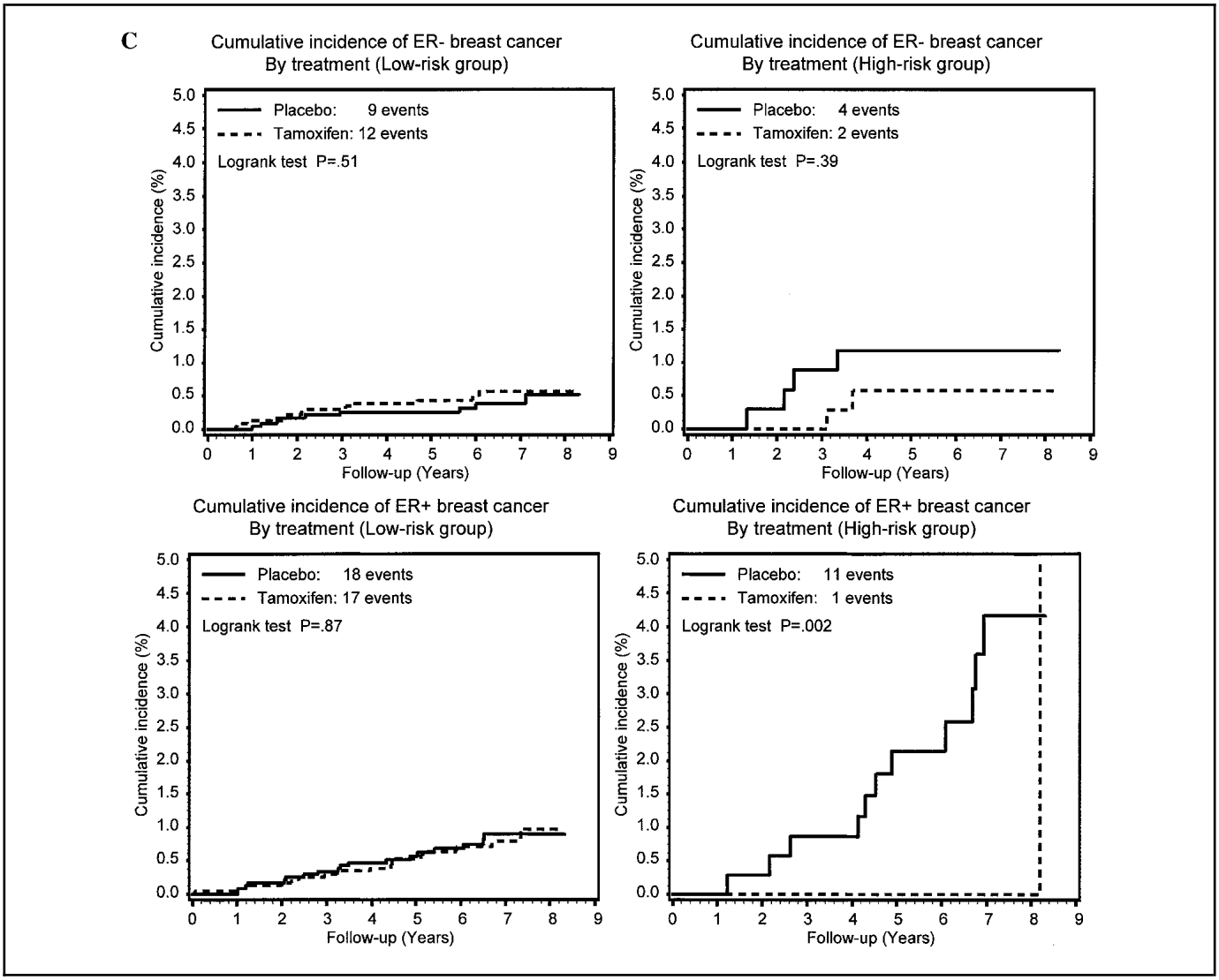

(Continued from previous page). Fig. 2. A) Cumulative incidence (%) of breast cancer among women randomly assigned to receive tamoxifen or placebo in the Italian Tamoxifen Intervention Trial according to hormone-related risk factors. The numbers of women at risk at years 2, 5, and 8 are 2336, 1864, and 70, respectively, in the tamoxifen arm and 2349, 1861, and 80, respectively, in the placebo arm of the low-risk group and 352, 292, and 31, respectively, in the tamoxifen arm and 348, 281, and 21, respectively, in the placebo arm of the high-risk group. **B**) Cumulative incidence (%) of breast cancer according to hormone-related risk profile and use of hormone replacement therapy (HRT). Among those who never used HRT, the numbers of women at risk at years 2, 5, and 8 are 1640, 1340, and 54, respectively, in the tamoxifen arm and 1666, 1350, and 63, respectively, in the placebo arm of the low-risk group and 255, 212, and 22, respectively, in the tamoxifen arm and 246, 202, and 20, respectively, in the placebo arm of the high-risk group. Among HRT users, the number of women at risk at years 2, 5, and 8 are 696, 524, and 16, respectively, in the tamoxifen arm and 683, 511, and 17, respectively, in the placebo arm of the low-risk group and 97, 80, and 9, respectively, in the tamoxifen arm and 102, 79, and 1, respectively, in the placebo arm of the high-risk group. **C**) Cumulative incidence (%) of estrogen receptor-negative (ER–) and estrogen receptor-positive (ER+) breast cancer according to hormone-related risk profile. The number of women at risk at years 2, 5, and 8 are 2336, 1864, and 70, respectively, in the tamoxifen arm and 2349, 1861, and 80, respectively, in the placebo arm of the low-risk group, and 352, 292, and 31, respectively, in the tamoxifen arm and 348, 281, and 21, respectively, in the placebo arm of the high-risk group.

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NOTES

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