Long-Term Results of Tamoxifen Prophylaxis for Breast Cancer—96-Month Follow-up of the Randomized IBIS-I Trial

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For the International Breast Cancer Intervention Study (IBIS) I Investigators

Background Initial results from the first International Breast Cancer Intervention Study (IBIS-I) found that tamoxifen reduced the risk of invasive estrogen receptor (ER)–positive tumors by 31% in women at increased risk for breast cancer, but most of the follow-up at this time was during the active treatment phase. We report an updated analysis of IBIS-I that focuses on the period after active treatment was completed, a time for which little evidence from other trials is available.

Methods A total of 7145 women who were aged 35–70 years and at increased risk of breast cancer were randomly assigned to receive either tamoxifen (20 mg/day) or placebo for 5 years. The primary outcome measure was the incidence of breast cancer (including ductal carcinoma in situ), but side effects were also investigated. Relative risks were computed as the ratio of incidence rates. All statistical tests were two-sided.

Results After a median follow-up of 96 months after randomization, 142 breast cancers were diagnosed in the 3579 women in the tamoxifen group and 195 in the 3575 women in the placebo group (4.97 versus 6.82 per 1000 woman-years, respectively; risk ratio [RR] = 0.73, 95% confidence interval [CI] = 0.58 to 0.91, $P = .004$). The prophylactic effect of tamoxifen was fairly constant for the entire follow-up period, and no diminution of benefit was observed for up to 10 years after randomization. However, side effects in the tamoxifen group were much lower after completion of the active treatment period than during active treatment. For example, deep-vein thrombosis and pulmonary embolism were statistically significantly higher in the tamoxifen arm than in the placebo arm during active treatment (52 versus 23 cases, RR = 2.26, 95% CI = 1.36 to 3.87) but not after tamoxifen was stopped (16 versus 14 cases, RR = 1.14, 95% CI = 0.52 to 2.53). The two arms did not differ in the risk of ER-negative invasive tumors (35 in each arm, RR = 1.00, 95% CI = 0.61 to 1.65) across the entire follow-up period, but the risk of ER-positive invasive breast cancer was 34% lower in the tamoxifen arm (87 versus 132 cases, RR = 0.66, 95% CI = 0.50 to 0.87).

Conclusions The risk-reducing effect of tamoxifen appears to persist for at least 10 years, but most side effects of tamoxifen do not continue after the 5-year treatment period.

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Tamoxifen is effective not only in treating breast cancer (1) but also in preventing this disease (2). An overview of four randomized prevention trials evaluating tamoxifen showed a 38% reduction in breast cancer incidence in women at high risk of breast cancer who took tamoxifen for 5 years (2). This overview also showed that tamoxifen prevents only estrogen receptor (ER)–positive breast cancer (which was reduced by approximately 50%) but has no beneficial effect on ER-negative cancers. Tamoxifen's role in prevention is also limited because of its side effect profile. In particular, venous thrombolic events were increased by almost twofold and endometrial cancer by almost 2.5-fold in the tamoxifen arm compared to the placebo arm in the prevention trials (2). Several authors have attempted to estimate the risk–benefit ratio of tamoxifen for prophylaxis (3–7). However, these analyses have been based mostly on cancers occurring during active treatment,

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See "Appendix" for the full list of names and affiliations of the IBIS collaborators.

See "Notes" following "References."

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and the impact in the 5 years following active treatment is important in assessing overall benefit. In the adjuvant setting, 5 years of tamoxifen treatment has been shown to have a carryover effect, leading to a reduction in recurrence in the 5 years following active treatment (1). If the same phenomenon occurs for the prevention of new cancers and if side effects do not persist, then the overall risk–benefit ratio could be substantially more favorable than has been previously estimated (3–7).

Recently, an update of findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trial after 7 years of follow-up (8) found that breast cancer rates remained low in the tamoxifen arm after active treatment ended. However, rates were also reduced in the placebo arm. Because all patients were unblinded, an unknown number of control subjects received tamoxifen or raloxifene; also the follow-up protocol was reduced, so that any long-term effect of tamoxifen is difficult to interpret (9).

The first International Breast Cancer Intervention Study (IBIS-I) is a double-blind, randomized trial of tamoxifen (20 mg/day) versus placebo for 5 years in women at increased risk of developing breast cancer (10). After a median of 49.6 months of follow-up, tamoxifen reduced the incidence of breast cancer (invasive and ductal carcinoma in situ (DCIS) combined) by 32% (69/3579 in the tamoxifen arm versus 101/3575 in the placebo arm; OR = 0.68, 95% confidence interval [CI] = 0.50 to 0.92, $P = .013$). At that time, the risk reduction did not appear to be affected by age, degree of risk, or use of hormone replacement therapy (HRT). However, the risk reduction was observed only for ER-positive breast cancer. In keeping with other trials (2), the rate of endometrial cancer was higher in the tamoxifen group than in the placebo group, although the difference was not statistically significant (11 cases versus 5 cases, respectively, $P = .20$). Also, the rate of thromboembolic events was statistically significantly higher in the tamoxifen group than in the placebo group (43 cases versus 17 cases, respectively, $P = .001$). Overall, large numbers of less serious side effects were reported in both treatment arms, but the major differences were for vasomotor and gynecologic events, which increased from 67.7% of the women in the placebo group to 81.8% in the tamoxifen group (14.1% absolute increase), and breast complaints, which were reduced from 18.9% in the placebo group to 14.7% in the tamoxifen group (4.2% absolute decrease). A statistically significant excess of deaths from all causes was observed in the tamoxifen group compared with the placebo group (25 versus 11, $P = .028$), but no specific cause appeared to be elevated. The IBIS-I trial remains blinded after the initial report, and here we report efficacy results with a median follow-up of 96 months.

CONTEXT AND CAVEATS

Prior knowledge

Tamoxifen reduces the risk of breast cancer in women at high risk of the disease during active treatment, but less is known about the period after active treatment. Tamoxifen also increases the risk of endometrial cancer, thromboembolic events, and other side effects.

Study design

Women in a randomized chemoprevention trial who had been assigned to take tamoxifen or placebo for 5 years were followed for a median of 8 years.

Contribution

Tamoxifen reduced the incidence of all breast cancers (invasive plus ductal carcinoma in situ) by 27% overall (from 6.82 to 4.97 events per 1000 woman-years), and the reduction was fairly constant over the entire follow-up period. Incidence rates of ER-positive invasive breast cancers in the tamoxifen group were 26% lower than those in the placebo group during active treatment and 44% lower during the subsequent years. Rates of deep-vein thrombosis, pulmonary embolism, and endometrial cancer were higher in the tamoxifen arm than the placebo arm during active treatment but not in the subsequent years.

Implications

The preventive effect of tamoxifen on breast cancer in high-risk women is undiminished for at least 5 years beyond active treatment but the risk of serious side effects drops, leading to an improved risk–benefit ratio.

Limitations

Information on side effects was obtained somewhat differently during active treatment and in subsequent years. Women in the trial were permitted to take hormone replacement therapy, which could have confounded the results. Even longer follow-up is needed to determine the full extent of the risk reduction associated with tamoxifen prophylaxis.

Patients and Methods

Trial Design and Follow-up

From April 1992 through March 2001, 7154 women aged 35–70 years were entered into the trial and randomly assigned in a double-blind manner to receive tamoxifen (20 mg/day) or placebo for 5 years (10). To be eligible, women had to have risk factors for breast cancer indicating at least a twofold relative risk if they were 45–70 years of age, a fourfold relative risk if they were 40–44 years of age, or a 10-fold relative risk if they were 35–39 years of age and to have none of the exclusion factors given below.

Specifically, women were eligible from age 45 years if they had 1) a mother or sister diagnosed with breast cancer before the age of 50 years, 2) two first- or second-degree relatives with breast cancer at any age, or 3) a first-degree relative with breast cancer at any age, and either were nulliparous or had a previous hyperplastic benign lesion. Women were eligible from the age of 40 years if they had 1) atypical ductal or lobular hyperplasia, 2) a first-degree relative with bilateral breast cancer at any age, or 3) two first- or second-degree relatives with breast cancer, one of whom was diagnosed before age 50 years. Women were eligible from the age of 35 years if they had either 1) lobular carcinoma in situ or 2) two first-degree relatives with breast cancer, both diagnosed before the age of 50 years. Lastly, any women with an estimated 10-year risk of 5% or more, based on a complex model (11), were also eligible as risk equivalent after approval by the study chairman (J. Cuzick).

Women were excluded from participation in the study if they had any previous invasive cancer (excluding nonmelanoma skin cancer), had a previous deep-vein thrombosis or pulmonary embolism, were current users of anticoagulants, or wished to become pregnant. The trial was conducted under the auspices of

the U.K. Coordinating Committee for Cancer Research (now part of the National Cancer Research Network) and was approved by the local ethics committees for each participating center. After initial discussion with an IBIS-I doctor and a reflection period of at least 24 hours, written informed consent was obtained from all participants. The Data Monitoring Committee reviewed the initial results of the NSABP P1 (12) study in 1998 and IBIS-I study in 2002 (10) and at both times recommended that the IBIS-I trial continued in a blinded fashion. In each case, women were informed of these results and reconsented to continue their participation. The trial is registered with controlled-trials.com as ISRCTN91879928.

Use of HRT was permitted during the trial for menopausal symptoms, but the protocol stipulated that women should be restricted to the lowest level necessary for symptom control. Women were defined as postmenopausal if they had experienced 12 consecutive months of amenorrhea or had had an oophorectomy. Women were also categorized as postmenopausal if they were aged 50 years or older and had had a hysterectomy, either alone or in combination with an oophorectomy. The remaining women were defined as premenopausal.

During the 5 years of active treatment, women were followed up every 6 months by a clinic visit or phone call. Compliance was measured by pill counts at each 6-month follow-up visit. All women have now completed their 5 years of active treatment and are being followed by an annual mailed questionnaire for women in the United Kingdom (60% of women) and Europe (3%) or annual clinic visit for women in Australia and New Zealand (37%). For most women diagnosed with breast cancer, the cancer was detected at the same hospital through which they participated in the IBIS-I study. In addition, in the United Kingdom, the central IBIS office is notified on a quarterly basis of all cancers and deaths in trial participants using data obtained from the mandatory U.K. national registration system. Consequently, we believe that the detection rates are high and unbiased with regard to treatment arm. Both investigators and patients remain blinded to treatment allocation. Treatment allocation has been disclosed (i.e., the code broken) for 777 (10.9%) women who did not develop breast cancer. Of these, the codes for 493 (63.4%) women were broken after they completed the 5 years of active treatment. In many cases, the code was broken by prearrangement with the local clinician to provide unblinding at year 6.

In the United Kingdom and Europe, side effects were assessed differently during the active treatment phase and subsequent follow-up so that the results in these two periods are not directly comparable. In Australia and New Zealand, the same procedures were used for the entire follow-up period. During both follow-up periods, a checklist of predefined side effects was used and a free-text field was available for recording unexpected events. The predefined illness categories were myocardial infarction, other cardiovascular events, thromboembolic diseases, gynecologic problems, visual disturbances, fractures, osteoporosis, and any non–breast cancer. In addition, the following side effects were predefined: nausea, vomiting, hot flushes, headaches, vaginal discharge, vaginal dryness, and vaginal bleeding. Each was recorded as mild, moderate, or severe. During the treatment phase, these questions were asked directly, and a detailed checklist was provided. In the follow-up phase, a less detailed list was used, and it was sent directly to the participants and returned by postal mail. For postal replies, any of the recorded illness listed above were confirmed from medical records. All patients received follow-up questionnaires regardless of whether or not they were unblinded. Approximately, 85% of all women returned at least one questionnaire. Most patients still remain blinded, and therefore a valid assessment of differences between treatment groups can be made within each period.

Statistical Methods

Randomization was performed by telephone or fax at the IBIS center in London for the U.K. and European centers and at the IBIS center in Sydney, Australia, for the centers in Australia and New Zealand. The primary endpoint was breast cancer incidence (including DCIS). Cause-specific mortality and side effects were secondary endpoints. Analyses were by intention-to-treat. Incidence rates for breast cancer and major side effects were calculated by dividing the number of observed events by the number of woman-years of follow-up for each group and/or period. Follow-up accrued until the development of breast cancer, death, or the cutoff date for this analysis (April 1, 2006). Relative risks were computed as the ratios of incidence rates. Confidence intervals and *P* values are based on exact distributions, assuming that the events followed independent Poisson distributions in the two groups. Interactions between treatment and subgroups were based on likelihood ratio tests for an added interaction term. Minor side effects that could occur repeatedly (see Table 7) were compared using binomial statistics as simple ratios of proportions of patients ever reporting the side effect in the specific period. All *P* values are two-sided, and confidence intervals are at the 95% level. No adjustments were made for covariates. All calculations were performed using STATA software, version 8.2 (StataCorp, College Station, TX).

Results

Baseline Characteristics and Follow-up

As in the first report of the IBIS-I trial (10), a total of 7154 women were included in this analysis, 3575 in the placebo group and 3579 in the tamoxifen group. Of the 7154 women, 4410 (62%) had two or more first- or second-degree relatives with breast cancer and 3433 (48%) had a mother or a sister who developed breast cancer before age 50 years. A total of 6939 (97%) of the women reported some family history of breast cancer, and 572 (8%) had a benign lesion associated with an increased risk of developing breast cancer. The mean age at study entry was 50.7 years, and 3913 (54.7%) women were between the ages of 45 and 54 years. In addition, 3857 (53.8%) women were postmenopausal at study entry and 3999 (55.9%) had a body mass index of more than 25 kg/m^2. In total, 2876 (40.2%) women used HRT at some point during the trial. More detailed information on baseline characteristics by trial arm is shown in Table 1.

The cutoff date of follow-up for this analysis was April 1, 2006. Median follow-up was 95.6 months, and a total of 57 128 woman-years of follow-up (28 573 in the placebo group and 28 555 in the tamoxifen group) have been accrued. Of these, 35 704 woman-years (17 846 in the tamoxifen group and 17 858 in the placebo

Table 1. Baseline characteristics and use of hormone replacement therapy (HRT) according to treatment arm*

Characteristics	Placebo (N = 3575)	Tamoxifen (N = 3579)
Demography		
Mean (SD) age, y	50.8 (6.7)	50.7 (7.0)
Postmenopausal†	1922 (53.7)	1935 (54.1)
HRT use, No. (%)		
During trial	1414 (39.6)	1462 (40.8)
Before trial only	380 (10.6)	399 (11.1)
Never	1761 (49.3)	1715 (47.9)
Anthropometry		
Mean (SD) height, cm	162.9 (6.4)	162.8 (6.6)
Mean (SD) weight, kg	71.4 (14.0)	71.7 (14.5)
Mean (SD) BMI, kg/m^2	26.9 (5.1)	27.0 (5.3)
Hysterectomy, No. (%)		
All	1283 (35.9)	1232 (34.4)
With both ovaries retained	737 (20.6)	711 (19.9)
One ovary removed	207 (5.8)	229 (6.4)
Both ovaries removed	327 (9.2)	281 (7.9)

* SD = standard deviation; BMI = body mass index.

† Women were defined as postmenopausal if they had 12 consecutive months of amenorrhea or had had an oophorectomy. See "Patients and Methods" for details.

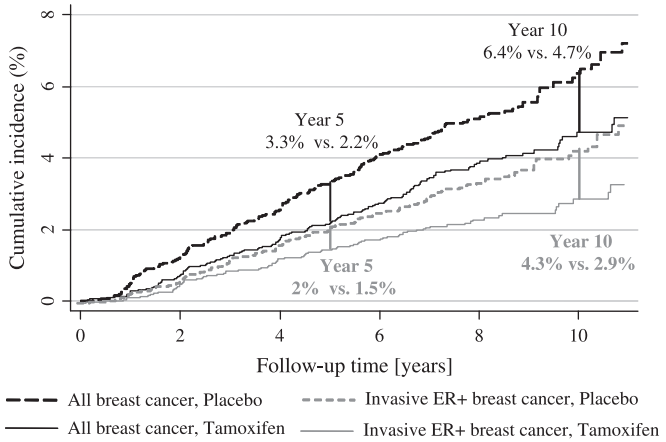


Fig. 1. Cumulative incidence rates for all breast cancers and invasive estrogen receptor (ER)–positive breast cancers according to treatment arm.

group) were accrued during the active treatment phase (years 0–4) and 21 424 woman-years (10 709 in the tamoxifen group and 10 715 in the placebo group) during the follow-up period (from year 5 onward). This additional follow-up represents a median addition of more than 46 months and an almost doubling of woman-years at risk since the first report. The cumulative numbers of woman-years of randomized treatment were 14 009 (placebo) and 12 772 (tamoxifen). In total, 4861 (67.9%) women completed the full 5 years of treatment (2574 [72%] of those in the placebo group versus 2287 [63.9%] of those in the tamoxifen group).

Breast Cancer

A total of 337 breast cancers (invasive and DCIS combined) were reported before the cutoff date. The incidence rate in the tamoxifen group was 27% lower than in the placebo group (142 versus 195 cases; risk ratio [RR] = 0.73, 95% CI = 0.58 to 0.91, P = .004). The annual incidence rate was 6.82 per 1000 woman-years in the placebo group and 4.97 per 1000 woman-years in the tamoxifen group. The estimated absolute reduction in cumulative incidence after 10 years of follow-up was 1.7% (i.e., from 6.4% in the placebo group to 4.7% in the tamoxifen group), which represents a 1.5-fold greater reduction than the 1.1% estimated absolute reduction after 5 years (i.e., from 3.3% in the placebo group to 2.2% in the tamoxifen group) (Fig. 1).

The reduction in incidence for all breast cancers in the tamoxifen arm was 32% in years 0–4 (i.e., the period of active treatment) and 18% in subsequent years (beginning at year 5) (Table 2). Incidence rates of ER-positive invasive breast cancers in the tamoxifen group were 26% lower than those in the placebo group during years 0–4 (54 versus 73 cases, respectively) and 44% lower during years 5 and beyond (33 versus 59 cases, respectively). Thus, the 1.4% reduction in absolute risk of ER-positive invasive breast cancer after 10 years of follow-up—i.e., from 4.3% in the placebo group to 2.9% in the tamoxifen group (Fig. 1)—was almost three times as large as the 0.5% reduction (from 2% to 1.5%) seen at year 5. The benefit of tamoxifen was fairly constant over time and extended for at least 10 years, especially for ER-positive cancers, where the relative effect size became somewhat larger at longer follow-up times (Fig. 2). This continuing and undiminished benefit suggests that there may be a substantial benefit associated with 5 years of tamoxifen use that accrues after treatment has been completed.

A number of subgroups were examined to determine whether the tamoxifen benefit was affected by patient's characteristics or by the type of tumor that was prevented. The results are shown in Table 2 and Fig. 3. No clear evidence for subgroup-specific differences in the treatment effect was found, as evidenced by a statistically significant result from a test for heterogeneity. The invasive status, lymph node status, size, and grade of breast tumors were similar between the two treatment arms. However, in keeping with previous results (2), the incidence of ER-negative invasive breast cancers was not reduced in the tamoxifen arm compared with the placebo arm, whereas the incidence of ER-positive invasive breast cancers was 34% lower in the tamoxifen arm than in the placebo arm (87 versus 132; RR = 0.66, 95% CI = 0.50 to 0.87). ER-negative tumors were relatively more common in the tamoxifen arm than in the placebo arm after active treatment (and less common during treatment), but this was not statistically significant (P = .13).

Of potential interest was a non–statistically significant interaction (P = .11) between HRT use and treatment (Table 3). Among women who never used HRT or who used it only before the trial, there was a statistically significant reduction in ER-positive breast cancers in the tamoxifen arm compared with the placebo arm (for all breast cancers, 76 versus 126 cases, RR = 0.62, 95% CI = 0.46 to 0.83; for ER-positive cancers, 37 versus 77 cases, RR = 0.49, 95% CI = 0.32 to 0.74). However, for women who used HRT at some stage during the trial, no clear effect of tamoxifen was seen, either overall (66 versus 69 cases, RR = 0.92, 95 % CI = 0.65 to 1.31) or for ER-positive tumors (40 versus 43 cases, RR = 0.89, 95% CI = 0.57 to 1.41). Results were similar regardless of the HRT preparations used, i.e., estrogen only or combined estrogen and progestin (data not shown). HRT use was not associated with

Table 2. Event rates and risk of breast cancer by treatment arm according to selected patient and cancer characteristics*

Characteristic	No. of events		Rate per 1000 woman-years		
	Placebo (N = 3575)	Tamoxifen (N = 3579)	Placebo	Tamoxifen	RR† (95% CI)
Total	195	142	6.82	4.97	0.73 (0.58 to 0.91)
Invasiveness					
Invasive	168	124	5.88	4.34	0.74 (0.58 to 0.94)
DCIS	27	17	0.94	0.60	0.63 (0.32 to 1.20)
Unknown	0	1	–	–	–
Age, y					
≤50	87	56	5.63	3.64	0.65 (0.45 to 0.91)
>50	108	86	8.24	6.54	0.79 (0.59 to 1.06)
Menopausal status‡					
Premenopausal	88	58	6.25	4.20	0.67 (0.47 to 0.95)
Postmenopausal	107	84	7.58	5.86	0.77 (0.57 to 1.04)
HRT use					
During the trial	69	66	6.00	5.52	0.92 (0.65 to 1.31)
Before the trial only	30	17	11.11	5.77	0.52 (0.27 to 0.97)
Never	96	59	6.68	4.33	0.64 (0.46 to 0.90)
Follow-up time					
During treatment	116	78	6.50	4.37	0.67 (0.50 to 0.90)
ER-positive§	73	54	4.09	3.03	0.74 (0.51 to 1.07)
ER-negative§	26	19	1.46	1.06	0.73 (0.38 to 1.37)
After treatment	79	64	7.37	5.98	0.81 (0.57 to 1.14)
ER-positive§	59	33	5.51	3.08	0.56 (0.35 to 0.87)
ER-negative§	9	16	0.84	1.49	1.78 (0.74 to 4.57)
ER status§					
Positive	132	87	4.62	3.05	0.66 (0.50 to 0.87)
Negative	35	35	1.23	1.23	1.00 (0.61 to 1.65)
Unknown/not done	1	2	–	–	–
ER/PgR status§					
ER+/PgR+	90	59	3.15	2.07	0.66 (0.46 to 0.92)
ER+/PgR−	21	17	0.74	0.60	0.81 (0.40 to 1.61)
ER+/PgR unknown	21	11	0.74	0.39	0.52 (0.23 to 1.14)
ER−/PgR−	30	27	1.05	0.95	0.90 (0.52 to 1.57)
ER−/PgR+	2	4	–	–	–
ER−/PgR unknown	3	4	–	–	–
Grade§					
Low	28	27	0.98	0.95	0.96 (0.55 to 1.70)
Intermediate	84	53	2.94	1.86	0.63 (0.44 to 0.90)
High	50	41	1.75	1.44	0.82 (0.53 to 1.27)
Unknown	6	3	–	–	–
Nodal status§					
Positive	49	37	1.71	1.30	0.76 (0.48 to 1.18)
Negative	114	83	3.99	2.91	0.73 (0.54 to 0.98)
Unknown/not done	5	4	–	–	–
Size, cm§					
≤1	51	39	1.78	1.37	0.77 (0.49 to 1.18)
>1–2	78	44	2.73	1.54	0.56 (0.38 to 0.83)
>2	38	39	1.33	1.37	1.03 (0.64 to 1.65)
Unknown	1	2	–	–	–

* RR = risk ratio; CI = confidence interval; DCIS = ductal carcinoma in situ; HRT = hormone replacement therapy; ER = estrogen receptor; PgR = progesterone receptor.

† RR for women in the tamoxifen group relative to women in the placebo group.

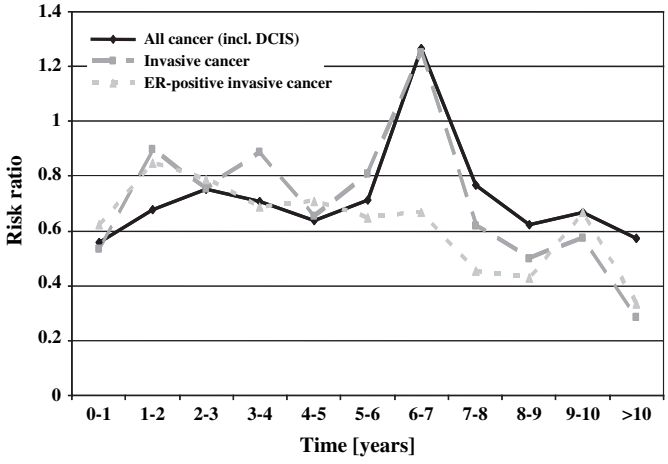
‡ Women were defined as postmenopausal if they had 12 consecutive months of amenorrhea or had had an oophorectomy. See "Patients and Methods" for details.

§ For invasive cancer only.

the development of ER-negative breast cancers, either during the active treatment period or the subsequent period.

Deaths

Specific causes of death are given in Table 4. In total, 24 deaths from breast cancer were recorded (11 in the tamoxifen group versus 13 in the placebo group, RR = 0.85, 95% CI = 0.34 to 2.05). The number of deaths from any cause was non–statistically significantly higher in the tamoxifen group than in the placebo group (65 versus 55 deaths, RR = 1.18, 95% CI = 0.81 to 1.73). The difference between the two groups in deaths from any cause is now smaller than it was in the original report (10) of the IBIS-I trial, when there



All cancer	(18, 10)	(25, 17)	(24, 18)	(24, 17)	(25, 16)	(28, 20)	(14, 19)	(13, 10)	(8, 5)	(9, 6)	(7, 4)
All invasive	(15, 8)	(19, 17)	(24, 18)	(19, 16)	(23, 15)	(21, 17)	(12, 15)	(13, 8)	(8, 4)	(7, 4)	(7, 2)
ER+ invasive	(8, 5)	(13, 11)	(19, 15)	(16, 11)	(17, 12)	(17, 11)	(12, 8)	(11, 5)	(7, 3)	(6, 4)	(6, 2)

Fig. 2. Risk ratios for all breast cancers (including ductal carcinoma in situ [DCIS]), all invasive cancers, and ER-positive invasive cancers by year of follow-up. Numbers of events in each group (placebo, tamoxifen) are shown below the graph.

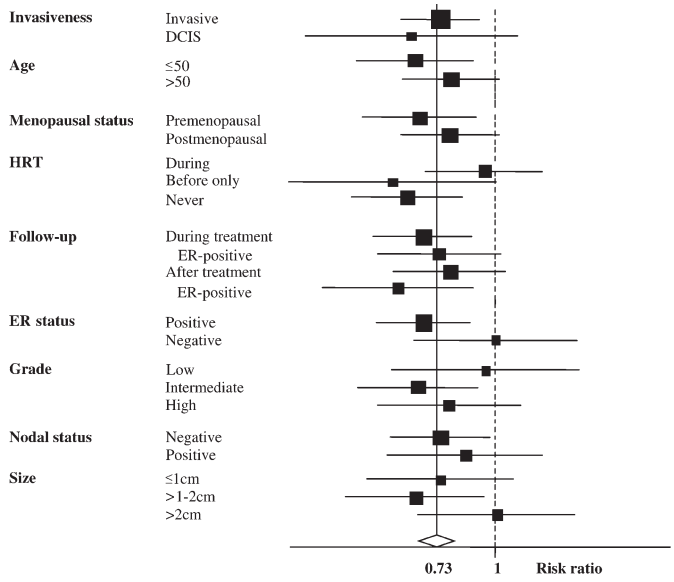


Fig. 3. Risk ratios for breast cancer according to different subgroups of tumors and women. **Solid vertical line** shows overall effect, and **diamond** shows overall 95% confidence interval. **Horizontal lines** show 95% confidence interval for the specific group. The areas of the boxes are inversely proportional to variance of estimate.

were 25 deaths in the tamoxifen arm and 11 in the placebo arm. No particular cause of death was clearly higher in the tamoxifen arm than in the placebo arm.

Endometrial Cancer

A total of 28 endometrial cancers were reported, 17 in the tamoxifen group and 11 in the placebo group (RR = 1.55, 95% CI = 0.68 to 3.65) (Table 5). The incidence rate was 0.59 per 1000 woman-years in the tamoxifen group, compared with 0.38 per 1000 woman-years in the placebo group. Twelve of the endometrial cancers in the tamoxifen group but only three in the placebo group were detected during the active treatment period (P = .02). The majority of the endometrial cancers were International Federation of Obstetrics and Gynecology (13) stage 1 adenocarcinomas that were diagnosed in women aged 50 years or older (Table 5). The two endometrial sarcomas were both in the placebo group. More of the women with endometrial cancer in the tamoxifen group than in the placebo group had never used HRT, but the difference was not statistically significant (10 versus 5, P = .21). All but one of the HRT preparations used by the women who developed endometrial cancer was a combined medication, reflecting the preference for this type of medication for all women in this trial with an intact uterus (87%).

Thromboembolic and Cardiovascular Events

Overall, thromboembolic events were statistically significantly higher in the tamoxifen group than in the placebo group (117 versus 68 events, RR = 1.72, 95% CI = 1.27 to 2.36) (Table 6). The incidence rates were 4.10 per 1000 woman-years in the tamoxifen group and 2.38 per 1000 woman-years in the placebo group. Women in the tamoxifen group had an almost twofold excess of deep-vein thrombosis, pulmonary embolism, or retinal vein thrombosis (68 versus 37 events, RR = 1.84, 95% CI = 1.21 to 2.82) than women in the placebo group and a nearly threefold excess of superficial thrombophlebitis (23 versus 8 events, RR = 2.88, 95% CI = 1.24 to 7.44), but they had only a slight increase in other, nonspecific thrombotic events (26 versus 23 events, RR = 1.13, 95% CI = 0.62 to 2.08). The excess of thromboembolic events was found only in the active treatment phase. There were no statistically significant differences between treatment groups in the rates of any cerebrovascular events or cardiovascular events, although myocardial infarction incidence appeared to be non–statistically significantly reduced in the tamoxifen arm during the active treatment phase. However, deaths from myocardial infarction were not reduced (Table 4).

Side Effects

Although large numbers of side effects were reported in both treatment arms, the only major differences between treatment arms were observed for gynecologic or vasomotor and breast complaints (Table 7). Overall, statistically significantly more women in the tamoxifen group than in the placebo group reported gynecologic or vasomotor side effects. The increase was observed only in the active treatment phase (RR = 1.20, 95% CI = 1.16 to 1.25) and not in the subsequent period (RR = 1.06, 95% CI = 0.99 to 1.12). In addition, overall, statistically significantly fewer women in the tamoxifen group than in the placebo group reported any breast complaint (693 versus 903, RR = 0.77, 95% CI = 0.70 to 0.84). In this case, reductions were seen in both the active treatment phase and the subsequent period. The incidence of multiple cysts showed the greatest reduction with tamoxifen both during the active treatment phase (RR = 0.29, 95% CI = 0.19 to 0.44) and in the posttreatment period (RR = 0.61, 95% CI = 0.40 to 0.94). Tamoxifen had little effect on bone fractures, either overall or for sites linked with osteoporosis (hip, spine, wrist, and forearm). Small but statistically significant reductions in headaches were reported in the tamoxifen arm across the entire period of analysis (32.7% versus 35.3%, RR = 0.93, 95% CI = 0.87 to 0.99, P = .02). Again, these reductions were apparent only during the active treatment phase (24.5%

Table 3. Risk of breast cancer by treatment arm according to hormone replacement therapy (HRT) use and estrogen receptor (ER) status*

HRT use	No. of women with breast cancer: Placebo (N = 3575)	No. of women with breast cancer: Tamoxifen (N = 3579)	Rate per 1000 woman-years: Placebo	Rate per 1000 woman-years: Tamoxifen	RR (95% CI)
During trial					
All (including DCIS)	69	66	6.00	5.52	0.92 (0.65 to 1.31)
ER-positive	43	40	3.73	3.34	0.89 (0.57 to 1.41)
ER-negative	9	11	0.78	0.92	1.18 (0.44 to 3.21)
Only before or never					
All (including DCIS)	126	76	7.38	4.58	0.62 (0.46 to 0.83)
ER-positive	77	37	4.51	2.23	0.49 (0.32 to 0.74)
ER-negative	25	21	1.46	1.27	0.86 (0.46 to 1.61)

* ER status was evaluated only for invasive tumors. RR = risk ratio; CI = confidence interval; DCIS = ductal carcinoma in situ.

versus 28.8%, RR = 0.85, 95% CI = 0.79 to 0.92, $P<.0001$). A small and not statistically significant increase in cataracts was seen in the tamoxifen group (1.9% versus 1.5%) that appeared only after the completion of treatment (Table 7). A fuller description of the timing and severity of side effects will be reported elsewhere.

Discussion

These updated results from the IBIS-I trial provide further confirmation that tamoxifen reduces the risk of ER-positive breast cancers in high-risk women. More importantly, they provide the first randomized evidence that the benefits of tamoxifen extend beyond the active treatment period, but the side effects largely do not. Tamoxifen reduced the incidence of invasive ER-positive cancers by 44% in the period after the active treatment phase, in addition to the 26% reduction achieved during the active treatment phase. The NSABP P-1 study (8) also found that the incidence rates remained low for at least 2 years after completion of treatment, but rates in the placebo group were also reduced, possibly because of crossover.

A key issue for long-term follow-up of clinical trials is the completeness of the database. For our study, information was obtained from three sources—regular clinic visits, which were maintained in Australia and New Zealand for 10 years; annual questionnaires which were used in the United Kingdom and Europe and had a response rate of about 85% (85.9% in the tamoxifen arm and 84.6% in the placebo arm) for returning at least one questionnaire; and a national registration system for the United Kingdom. In addition, most breast cancers were diagnosed in the same hospital through which the women participated in IBIS-I. Because the amount of code breaking was low, with blinding being maintained in almost 90% of the women who have not developed breast cancer, any unreported cancers are like to be equally divided between treatment groups. Women wishing to know which treatment they were on were encouraged to wait until at least year 6 to see if any potentially treatment-related side effects persisted. Clinic reports and annual questionnaires indicated that use of tamoxifen or raloxifene after completion of IBIS-I was very low. All major side effects or endpoints reported on questionnaires were verified from medical records, but minor side effects were not pursued as fully on the follow-up questionnaires, and are likely to have been

Table 4. Specific causes of death by treatment arm*

Cause of death	Placebo (N = 3575)	Tamoxifen (N = 3579)
Total	55	65
Breast cancer	13	11
Endometrial cancer	0	1
Colon cancer	5	4
Lung cancer	6	5
Ovarian cancer	4	2
Other cancer	6	13
Myocardial infarction	0	4
Other cardiac	2	2
DVT/PE	2	3
Stroke or CVA	1	1
Other	16	19

* DVT = deep-vein thrombosis; PE = pulmonary embolism; CVA = cerebrovascular accident.

Table 5. Endometrial cancers according to treatment arm*

Characteristics	Placebo (N = 3575)	Tamoxifen (N = 3579)
Total	11	17
During treatment	3	12
After treatment	8	5
Grade		
1	5	5
2	2	7
3	4	4
FIGO stage†		
1	9	14
2	2	1
3/4	0	2
Histology		
Adenocarcinoma	5	14
Endometroid carcinoma	3	2
Sarcoma	2	0
Clear cell carcinoma	0	1
Age at diagnosis, y		
≤50	2	1
51–60	5	8
>60	4	8
HRT use		
Never	5	10
During trial	6	3
Before trial	0	4

* FIGO = International Federation of Obstetrics and Gynecology; HRT = hormone replacement therapy.

† (13).

Table 6. Thromboembolic, cerebrovascular, and cardiac events according to treatment arm and follow-up period*

	Entire period			During active treatment			After active treatment		
Side effect	**Placebo**	**Tamoxifen**	**RR (95% CI)**	**Placebo**	**Tamoxifen**	**RR (95% CI)**	**Placebo**	**Tamoxifen**	**RR (95% CI)**
All VTE	68 (2.38)	117 (4.10)	1.72 (1.27 to 2.36)	42 (2.35)	85 (4.76)	2.03 (1.38 to 3.01)	26 (2.43)	32 (2.99)	1.23 (0.71 to 2.15)
DVT/PE	37 (1.29)	68 (2.38)	1.84 (1.21 to 2.82)	23 (1.29)	52 (2.91)	2.26 (1.36 to 3.87)	14 (1.31)	16 (1.49)	1.14 (0.52 to 2.53)
Superficial thrombophlebitis	8 (0.28)	23 (0.81)	2.88 (1.24 to 7.44)	6 (0.34)	17 (0.95)	2.84 (1.07 to 8.78)	2 (0.19)	6 (0.56)	3.00 (0.54 to 30.41)
Other thrombosis	23 (0.81)	26 (0.91)	1.13 (0.62 to 2.08)	13 (0.73)	16 (0.90)	1.23 (0.56 to 2.78)	10 (0.93)	10 (0.93)	1.00 (0.37 to 2.68)
All cerebrovascular	34 (1.19)	32 (1.12)	0.94 (0.56 to 1.57)	17 (0.95)	12 (0.67)	0.71 (0.31 to 1.57)	17 (1.59)	20 (1.87)	1.18 (0.59 to 2.39)
Stroke/CVA	12 (0.42)	15 (0.53)	1.25 (0.55 to 2.93)	8 (0.45)	8 (0.45)	1.00 (0.33 to 3.06)	4 (0.37)	7 (0.65)	1.75 (0.45 to 8.16)
TIA	22 (0.77)	17 (0.60)	0.77 (0.39 to 1.52)	9 (0.50)	4 (0.22)	0.44 (0.10 to 1.59)	13 (1.21)	13 (1.21)	1.00 (0.43 to 2.34)
All cardiac	123 (4.30)	122 (4.27)	0.99 (0.77 to 1.29)	71 (3.98)	64 (3.59)	0.90 (0.63 to 1.28)	52 (4.85)	58 (5.42)	1.12 (0.75 to 1.66)
Myocardial infarction	15 (0.53)	9 (0.32)	0.60 (0.23 to 1.46)	7 (0.39)	2 (0.11)	0.29 (0.03 to 1.50)	8 (0.75)	7 (0.65)	0.88 (0.27 to 2.76)
Angina	51 (1.78)	60 (2.10)	1.18 (0.80 to 1.74)	32 (1.79)	31 (1.74)	0.97 (0.57 to 1.64)	19 (1.77)	29 (2.71)	1.53 (0.83 to 2.88)
Other cardiac	57 (1.99)	53 (1.86)	0.93 (0.63 to 1.38)	32 (1.79)	31 (1.74)	0.97 (0.57 to 1.64)	25 (2.33)	22 (2.05)	0.88 (0.47 to 1.63)

* Data are given as numbers of events, with rate per 1000 woman-years in parentheses. RR = risk ratio; CI = confidence interval; VTE = venous thrombolic events; DVT = deep-vein thrombosis; PE = pulmonary embolism; CVA = cerebrovascular accident; TIA = transient ischemic attack.

reported differently than during the active treatment period. Thus, the absolute numbers of events cannot be compared directly between periods. However, because blinding was largely maintained, the risk ratios between treatment arms for the proportions of side effect reports within each period are still informative.

The effect of HRT on the risk-reducing properties of tamoxifen is a controversial issue. The NSABP P-1 trial (12) did not allow HRT use, whereas the IBIS-I trial (10) and other European trials (14,15) permitted limited use. There is little doubt that HRT preparations containing both estrogen and progestin increase the risk of breast cancer (16,17), and the Italian trial of tamoxifen in high-risk women who had had a hysterectomy (18) found that tamoxifen was particularly effective in preventing breast cancer in women receiving concurrent HRT, although the numbers in this subgroup were small. These data led to the initiation of the HRT Opposed to Low-Dose Tamoxifen (HOT) study, in which HRT users are being randomized to low-dose tamoxifen or placebo and the incidence of breast cancer is compared (19). In this report from the IBIS-I study, the risk-reducing benefits of tamoxifen prophylaxis were clear only in never and previous users of HRT, with little or no benefit seen in concurrent users. This finding was unexpected, and because the interaction between treatment and HRT use was not statistically significant and because the confidence intervals for effect size in the different HRT groups overlap, the finding must be regarded as hypothesis generating. It also conflicts with the calculation that tamoxifen fully saturates the ER in postmenopausal women (20) and with the lack of efficacy of HRT on tamoxifen-induced vasomotor symptoms previously reported in IBIS-I (21), both of which would suggest that adding back low levels of estrogen should not influence the effects of tamoxifen.

Table 7. Side effects and relative risk of having an event according to treatment arm and follow-up time*

	Entire period			During active treatment†			After active treatment‡		
Side effect	**Placebo (N = 3575)**	**Tamoxifen (N = 3579)**	**RR (95% CI)**	**Placebo (N = 3575)**	**Tamoxifen (N = 3579)**	**RR (95% CI)**	**Placebo (N = 3489)**	**Tamoxifen (N = 3449)**	**RR (95% CI)**
Gynecologic/ vasomotor	2922 (81.7)	3151 (88.0)	1.08 (1.06 to 1.10)	1983 (55.5)	2389 (66.8)	1.20 (1.16 to 1.25)	1438 (41.2)	1508 (43.7)	1.06 (0.99 to 1.12)
Headaches	1261 (35.3)	1169 (32.7)	0.93 (0.87 to 0.99)	1030 (28.8)	878 (24.5)	0.85 (0.79 to 0.92)	343 (9.8)	386 (11.2)	1.14 (0.99 to 1.31)
All breast complaints	903 (25.3)	693 (19.4)	0.77 (0.70 to 0.84)	833 (23.3)	612 (17.1)	0.73 (0.67 to 0.81)	676 (19.4)	554 (16.1)	0.83 (0.75 to 0.92)
Multiple breast cysts	156 (4.4)	63 (1.8)	0.40 (0.30 to 0.54)	100 (2.8)	29 (0.8)	0.29 (0.19 to 0.44)	56 (1.6)	34 (0.9)	0.61 (0.40 to 0.94)
All fractures	235 (6.6)	240 (6.7)	1.02 (0.86 to 1.21)	142 (3.9)	121 (3.4)	0.85 (0.67 to 1.08)	93 (2.67)	119 (3.5)	1.29 (0.99 to 1.69)
Osteoporotic site fracture§	76 (2.1)	91 (2.5)	1.19 (0.89 to 1.62)	44 (1.2)	45 (1.3)	1.02 (0.68 to 1.54)	32 (0.9)	46 (1.3)	1.44 (0.92 to 2.25)
Eye complaints (excluding cataracts)	934 (26.1)	947 (26.6)	1.01 (0.94 to 1.09)	896 (25.1)	901 (25.2)	1.00 (0.93 to 1.09)	597 (17.1)	622 (18.0)	1.05 (0.95 to 1.17)
Cataracts	54 (1.5)	67 (1.9)	1.24 (0.87 to 1.77)	34 (0.9)	29 (0.8)	0.85 (0.52 to 1.40)	20 (0.6)	38 (1.1)	1.92 (1.12 to 3.29)

* Data are given as number of events, with percentage of the group in parentheses. Risk ratios (RRs) are based on the number of women who ever reported the side effect in the given period. CI = confidence interval.

† Side effect evaluation based on clinic-administered questionnaire.

‡ Side effect evaluation based on postal questionnaire or clinic visit. Denominator is all women alive and without breast cancer at year 5.

§ Fractures of the hip, spine, wrist, or forearm.

It is possible that our observation of lower tamoxifen efficacy in HRT users is related to lower compliance with tamoxifen among women who took HRT during the trial, a possibility that requires further detailed investigation. However, there was no statistically significant difference in the mean number of reported months of treatment compliance in HRT users during the trial compared with never or only previous users, either in the tamoxifen arm (45.8 months in current HRT users versus 45.6 months in previous never users), or the placebo arm (50.6 months in current HRT users versus 49.9 months in previous never users). The results of the HOT study will be important for resolving the question of whether low-dose tamoxifen can prevent the breast cancers associated with HRT without reducing its efficacy.

Our updated analyses indicate that the excess of thromboembolic events and endometrial cancers were confined to the active treatment period. It is not surprising that venous thrombolic events would be increased only during the period of tamoxifen treatment because the agonist effect of tamoxifen on clotting is likely to occur only during treatment. However, it is more surprising that endometrial cancers were increased only during active treatment since a latent period would be expected before the development of this disease. Also, a large case–control study found that an excess risk of endometrial cancer in women with breast cancer persisted for at least 5 years after tamoxifen treatment stopped (22). However, most of the women in that study would have received tamoxifen for only 2 years.

Likewise, the increased frequency of vasomotor and gynecologic symptoms in the tamoxifen during active treatment in our study disappeared after treatment was completed. By contrast, the reduction in benign breast complaints in general, and multiple breast cysts in particular, seen during the treatment phase continued after completion of treatment. Reports of fractures, including osteoporotic fractures, were similar in both treatment arms, both during active treatment and after completion of treatment. In the post-treatment period, women in the tamoxifen group had a higher risk of cataracts than women in the placebo group, although no difference was seen during the active phase. This result is different from that seen in the NSABP P-1 (8) and P-2 (Study of Tamoxifen and Raloxifene) (23) studies, both of which found an increase in cataracts with tamoxifen, even though follow-up was confined mainly to the active treatment phase. Most other side effects and adverse events occurred at equal rates in the placebo and tamoxifen arms after the active treatment phase.

Overall, these data presented here substantially strengthen the findings from our initial report after 50 months of follow-up (10). The benefits of tamoxifen, in terms of the reduction in risk of ER-positive breast cancer appear to extend beyond the 5-year treatment period, whereas the increased risk of endometrial cancer and venous thromboembolic events and most of the other side effects do not. Thus, the risk–benefit ratio over a 10-year period is likely to be substantially better than that computed for current models that are based on a 5-year follow-up (3–7). However, no reductions in ER-negative breast cancer were observed, and the slight increase in these cancers in the post-treatment phase in IBIS-I, and also overall in the other prevention trials (2), suggests that some cancers that would appear as ER-positive tumors if left untreated might emerge later as ER-negative tumors when tamoxifen is used prophylactically. This could happen if, in some cases, early (preinvasive) estrogen-sensitive lesions are temporarily held in check by tamoxifen but develop resistance and then appear as ER-negative tumors.

Slightly larger risk reductions were observed for premenopausal women, who also have a lower rate of endometrial cancer and thromboembolic events than postmenopausal women, suggesting that tamoxifen is a particularly attractive option for these women, especially if they have a diagnosis of lobular carcinoma in situ or atypical hyperplasia (12). For postmenopausal women, these results also indicate a better risk–benefit ratio than previously calculated for tamoxifen prophylaxis. However, aromatase inhibitors, which lack the agonist properties of tamoxifen that are responsible for its lower efficacy in the adjuvant treatment of hormone-sensitive breast cancer (24–28), and the increases they cause in thromboembolic events and gynecologic side effects, offer another attractive possibility for risk reduction for postmenopausal women (29). Results based on the occurrence of contralateral tumors in these adjuvant trials suggest that these agents may reduce the incidence of new ER-positive tumors by 75% (28). Anastrozole is currently being investigated in the IBIS-II trial (30), which compares it with placebo in healthy high-risk postmenopausal women, and exemestane is being similarly investigated in the North American MAP3 study (28). More speculatively, it is possible that offering tamoxifen or other selective ER modulators in the late premenopausal years, followed by an aromatase inhibitor when women become postmenopausal, may prove to be the most effective overall strategy for preventing breast cancer in high-risk women.

References

(1) Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 365:1687–717.

(2) Cuzick J, Powles T, Veronesi U, Forbes J, Edwards R, Ashley S, et al. Overview of the main outcomes in breast-cancer prevention trials. Lancet 2003;361:296–300.

(3) Gail MH, Costantino JP, Bryant J, Croyle R, Freedman L, Helzlsouer K, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. J Natl Cancer Inst 1999;91:1829–46.

(4) Hershman D, Sundararajan V, Jacobson JS, Heitjan DF, Neugut AI, Grann VR. Outcomes of tamoxifen chemoprevention for breast cancer in very high-risk women: a cost-effectiveness analysis. J Clin Oncol 2002; 20:9–16.

(5) Freedman AN, Graubard BI, Rao SR, McCaskill-Stevens W, Ballard-Barbash R, Gail MH. Estimates of the number of US women who could benefit from tamoxifen for breast cancer chemoprevention. J Natl Cancer Inst 2003;95:526–32.

(6) Eckermann SD, Martin AJ, Stockler MR, Simes RJ. The benefits and costs of tamoxifen for breast cancer prevention. Aust N Z J Public Health 2003;27:34–40.

(7) Melnikow J, Kuenneth C, Helms LJ, Barnato A, Kuppermann M, Birch S, et al. Chemoprevention: drug pricing and mortality: the case of tamoxifen. Cancer 2006;107:950–8.

(8) Fisher B, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, Robidoux A, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 2005;97:1652–62.

(9) Cuzick J, Forbes JF, Howell A. Re: Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and

Bowel Project P-1 study. J Natl Cancer Inst 2006;98:643; author reply 643–4.
(10) Cuzick J, Forbes J, Edwards R, Baum M, Cawthorn S, Coates A, et al. First results from the International Breast Cancer Intervention Study (IBIS-I): a randomised prevention trial. Lancet 2002;360:817–24.
(11) Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med 2004;23:1111–30.
(12) Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90:1371–88.
(13) Shepherd JH. Revised FIGO staging for gynaecological cancer. Br J Obstet Gynaecol 1989;96:889–92.
(14) Powles T, Eeles R, Ashley S, Easton D, Chang J, Dowsett M, et al. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. Lancet 1998;352:98–101.
(15) Veronesi U, Maisonneuve P, Costa A, Sacchini V, Maltoni C, Robertson C, et al. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. Italian Tamoxifen Prevention Study. Lancet 1998;352:93–7.
(16) Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33.
(17) Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003;362:419–27.
(18) Veronesi U, Maisonneuve P, Rotmensz N, Costa A, Sacchini V, Travaglini R, et al. Italian randomized trial among women with hysterectomy: tamoxifen and hormone-dependent breast cancer in high-risk women. J Natl Cancer Inst 2003;95:160–5.
(19) Decensi A, Galli A, Veronesi U. HRT opposed to low-dose tamoxifen (HOT study): rationale and design. Recent Results Cancer Res 2003;163:104–11; discussion 264–6.
(20) Dowsett M, Haynes BP. Hormonal effects of aromatase inhibitors: focus on premenopausal effects and interaction with tamoxifen. J Steroid Biochem Mol Biol 2003;86:255–63.
(21) Sestak I, Kealy R, Edwards R, Forbes J, Cuzick J. Influence of hormone replacement therapy on tamoxifen-induced vasomotor symptoms. J Clin Oncol 2006;24:3991–6.
(22) Swerdlow AJ, Jones ME. Tamoxifen treatment for breast cancer and risk of endometrial cancer: a case-control study. J Natl Cancer Inst 2005;97:375–84.
(23) Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial. JAMA 2006;295:2727–41.
(24) Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, et al. Results of the ATAC (arimidex, tamoxifen, alone or in combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005;365:60–2.
(25) Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003;349:1793–802.
(26) Coombes RC, Hall E, Gibson LJ, Paridaens R, Jassem J, Delozier T, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004;350:1081–92.
(27) Thurlimann B, Keshaviah A, Coates AS, Mouridsen H, Mauriac L, Forbes JF, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 2005;353:2747–57.
(28) Jakesz R, Jonat W, Gnant M, Mittlboeck M, Greil R, Tausch C, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. Lancet 2005;366:455–62.
(29) Cuzick J. Aromatase inhibitors for breast cancer prevention. J Clin Oncol 2005;23:1636–43.
(30) Cuzick J. Aromatase inhibitors in prevention—data from the ATAC (arimidex, tamoxifen alone or in combination) trial and the design of IBIS-II (the second International Breast Cancer Intervention Study). Recent Results Cancer Res 2003;163:96–103; discussion 264–6.

Appendix

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