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Second non-breast primary cancer following adjuvant therapy for early breast cancer: A report from the International Breast Cancer Study Group

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ABSTRACT

The incidence of second non-breast primary cancer following adjuvant treatment was evaluated using data from patients enrolled from 1978 to 1999 in four International Breast Cancer Study Group (IBCSG) trials. The occurrence of these tumours as sites of the first failure was assessed separately for two treatment comparisons: toremifene versus tamoxifen for 5 years in 1035 patients in IBCSG Trials 12-93 and 14-93 with a median follow-up of 8 years and endocrine therapy (toremifene or tamoxifen) versus chemo-endocrine therapy (CMF or AC plus toremifene or tamoxifen) in 1731 patients from IBCSG Trials III, VII and 12-93, with a combined median follow-up of 14 years. No significant differences in second non-breast primary tumours were observed in either comparison. In particular, the incidences of second primary uterine tumours with toremifene and tamoxifen were similar and no

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significant increase of secondary leukaemias was observed with chemo-endocrine therapy compared with endocrine therapy.

1. Introduction

Breast cancer mortality is decreasing as a result of earlier diagnosis and more effective adjuvant treatment.[1] As an increasing number of patients die of other causes, side-effects from adjuvant treatments become more relevant.[2] Late side-effects of such treatments represent a unique challenge because they may take years or even decades to develop, and as time passes it is less obvious whether adjuvant treatment is the cause. Together with cardiovascular and degenerative diseases, second non-breast primary cancers are probably the most relevant events other than breast cancer recurrence in the long-term follow-up of breast cancer patients.

Epidemiologic evidence suggests that the risk of second primary cancer is increased amongst women with early breast cancer.[3,4] Even if this risk is rather small (18% increase over the general population risk),[3] it should be addressed when adjuvant treatment and follow-up programmes are considered for patients with early breast cancer. This increased risk may be the result of individual predisposition to specific types of tumours, but adjuvant treatments may also exert carcinogenic effects.[4,5]

The impact of therapy may be influenced by treatment doses and duration of exposure, the use of supportive therapies,[6–8] and host factors such as age and individual predisposition.[5] This risk should be weighed against the hazard of recurrence and the expected benefit of adjuvant therapies. Early disclosure of results from adjuvant randomised clinical trials leads to a more rapid introduction of new therapies and new standards of treatment in clinical practice. Long-term results of clinical trials (both in terms of efficacy and safety) can provide valuable information on the risk of second primary cancer. The aim of this report is to evaluate the risk of second non-breast primary cancer in two cohorts of patients from four International Breast Cancer Study Group (IBCSG) adjuvant trials with long-term follow-up.

2. Patients and methods

Patients were selected from four IBCSG adjuvant trials which enrolled patients from 1978 to 1999: Trials III, VII, 12-93 and 14-93 (Table 1). The first analysis evaluated whether there was a difference in the cumulative incidence of second non-breast primary cancer according to the type of selective oestrogen receptor modulator (SERM), toremifene or tamoxifen. This evaluation was based on the 1035 patients from IBCSG Trials 12-93 and 14-93 randomised to the SERM comparison. Since toremifene was not available in all countries, only 391 patients in Trial 12 and 644 in Trial 14 were evaluable for this question. Countries without access to toremifene only participated in the chemotherapy questions in these trials. The second analysis addressed the difference in the cumulative incidence of second non-breast primary cancer between endocrine therapy only (pooling results for toremifene and tamoxifen) and chemo-endocrine adjuvant therapy in a population of patients from IBCSG Trials III and VII and in the first 212 patients from Trial 12-93 (Table 2). Patients in Trial III randomised to observation were excluded from this comparison.

Trial III enrolled patients between July 1978 and August 1981, and all patients underwent mastectomy and axillary dissection, and received no radiotherapy. In Trial III,[9] postmenopausal patients aged 65 years or less with axillary lymph node-positive disease were randomly assigned to observation, to tamoxifen plus low-dose prednisone for 1 year or to 12 28-day courses of CMF plus low-dose prednisone and tamoxifen for 1 year.

Trial VII[10] enrolled postmenopausal patients with positive lymph nodes between July 1986 and April 1993. All patients underwent a mastectomy or a breast-conserving procedure and axillary node dissection. All patients received tamoxifen for 5 years and were randomly assigned to receive either three courses of classical CMF initially or no initial treatment. Irrespective of the first treatment, patients were also randomly assigned to receive no further treatment or three courses of classical CMF at months 9, 12 and 15 (delayed chemotherapy). Radiotherapy was mandatory in cases of breast-conserving surgery and had to be postponed until the end of the initial phase of chemotherapy. No radiotherapy was to be given after mastectomy.

Trials 12-93 and 14-93 enrolled patients between May 1993 and August 1999.[11] IBCSG Trial 12-93 was a randomised three by two factorial phase III clinical trial that compared three adjuvant systemic regimens (chemotherapy with endocrine therapy starting concurrently versus chemotherapy with endocrine therapy starting sequentially versus endocrine therapy alone) and evaluated toremifene versus tamoxifen as the endocrine agent. The trial included both post- and perimenopausal women with node-positive, oestrogen receptor (ER)-positive breast cancer who were considered suitable for endocrine therapy alone. The chemotherapy regimen consisted of four courses of AC (anthracycline (doxorubicin 60 mg/m^2 OR epirubicin 90 mg/m^2 iv day 1) plus cyclophosphamide 600 mg/m^2 iv day 1). Toremifene and tamoxifen were given, respectively, at the doses of 20 mg and 60 mg daily for 5 years. Because the accrual rate was low, in 1997 the protocol was modified to discontinue the three-arm randomisation for the chemotherapy-oriented question and continue exclusively with randomisation to toremifene versus tamoxifen; the use and type of chemotherapy prior to initiation of toremifene or tamoxifen were left to the discretion of the investigators. Thus, only the first 212 patients in Trial 12 were randomised to receive chemotherapy and were included in

Table 1 – Characteristics of IBCSG Trials III, VII, 12-93 and 14-93.

Trial	Population	Years of accrual	Treatment arms	Enrolled patients	Median Follow-up (yrs)	References
III	Postmenopausal less than 65 yrs with positive nodes	1978–1981	Observation p + Tam × 12 CMFp + Tam × 12	463	25.0	[10]
VII	Postmenopausal with positive nodes	1986–1993	Tam alone Tam + delayed CMF × 3 Tam + early CMF × 3 Tam + early CMF × 3 + delayed CMF × 3	1212	14.7	[11]
12-93	Postmenopausal with positive nodes	1993–1997	Six-arm randomisation: Concurrent AC × 4 + Tor/Tam Sequential AC × 4 + Tor/Tam Tor/Tam alone	212 (74) (68) (70)	8.0	[12]
		1997–1999	Endocrine randomisation stratified by chemotherapy (Y/N) CT → Tor/Tam Tor/Tam alone	238 (143) (95)		
14-93	Postmenopausal with positive nodes	1993–1997	AC × 4 + CMF × 3 + Tam AC × 4 + Gap + CMF × 3 + Tam AC × 4 + CMF × 3 + Tor AC × 4 + Gap + CMF × 3 + Tor	969	8.1	[12]

Abbreviations: CMF: C, cyclophosphamide 100 mg/m^2 orally (po) days 1–14 of each cycle; M, methotrexate 40 mg/m^2 intravenously (iv) days 1 and 8 of each cycle; F, 5-fluorouracil 600 mg/m^2 iv days 1 and 8 of each cycle; p, prednisone 7.5 mg/d po. Delayed CMF: three cycles of CMF 9, 12 and 15 months after randomisation. Early CMF, three cycles of CMF 1, 2 and 3 months after randomisation; Tam, tamoxifen 20 mg po once daily; Tor, toremifene 60 mg po once daily; OFS, ovarian function suppression. AC: A, doxorubicin 60 mg/m^2 or epirubicin 90 mg/m^2 iv day 1; C, cyclophosphamide 600 mg/m^2 iv day 1 for every 21 days; Gap, 16 weeks without chemo-endocrine therapy, beginning the week after the last AC dose.

Table 2 – Characteristics of patient populations according to the study question.

Study questions	Trials	No. of patients	Received radiotherapy (%)	Median follow-up (years)
Toremifene versus tamoxifen	12–93	391	208 (53)	8.0
	14–93	644	275 (43)	8.1
	Cumulative	**1035**	**483 (47)**	**8.1**
Endocrine therapy versus chemo-endocrine therapy	III	307	0 (0)	25.0
	VII	1212	268 (22)	14.7
	12–93	212	91 (43)	8.0
	Cumulative	**1731**	**359 (21)**	**14.4**

the chemo-endocrine therapy versus endocrine therapy alone comparison.

IBCSG Trial 14-93 was a randomised two by two factorial phase III clinical trial that compared two ways of delivering adjuvant chemotherapy (with a 16-week gap between AC and CMF versus without the 16-week gap) and evaluated toremifene versus tamoxifen as the endocrine agent following the completion of chemotherapy. The trial included post- and perimenopausal women with node-positive disease who were considered not suitable for endocrine therapy alone. After mastectomy or breast-conserving surgery, all patients received four courses of AC followed, with or without a 16-week treatment-free interval, by three courses of classical CMF before starting endocrine therapy (toremifene 60 mg PO daily or tamoxifen 20 mg PO daily for 5 years from randomisation).

In Trials 12-93 and 14-93, radiation therapy to the conserved breast was optional for patients having breast conservation surgery. No radiotherapy was to be given after mastectomy. In Trial 14-93, radiotherapy could be given either after all chemotherapy or integrated into CMF as agreed per institution.

In Trials III and VII, follow-up visits were scheduled every 3 months for the first 2 years, 6 months for years 3–5 and yearly

thereafter. The follow-up began similarly for Trials 12-93 and 14-93, but was reduced to every 6 months during year 2 and yearly thereafter.

The majority of cases of second primary tumours had pathological confirmation of diagnosis; all case report forms with notification of second non-breast cancer were medically reviewed by oncologists, and queries were sent to investigators to clarify questionable cases. Disease-free survival (DFS) was defined as the time from the date of randomisation to any relapse (including ipsilateral or contralateral breast recurrence), the appearance of a second primary malignancy or death, whichever occurred first. Competing risk estimates with corresponding *p*-values controlling for breast cancer recurrences and deaths prior to breast cancer events were used to assess the cumulative incidences of second non-breast primaries[12]; competing risk hazard ratios and corresponding *p*-values were calculated using the method of Fine and Gray.[13] All probability values were obtained from two-sided tests.

3. Results

Tables 3 and 4 display second non-breast primaries as sites of first failure according to different treatments. Figs. 1 and 2 display the Kaplan–Meier disease-free survival plots and cumulative incidence of second primary events for the two treatment comparisons.

3.1. *Toremifene adjuvant therapy versus tamoxifen adjuvant therapy*

A total of 1035 patients (391 from Trial 12-93 and 644 from Trial 14-93) were available for this comparison. After a median follow-up of 8.1 years, no significant differences were observed between toremifene- and tamoxifen-treated patients with regard to DFS (HR (Tor/Tam) = 0.86; 95% CI = 0.71, 1.04; *p*-value = 0.11) (Fig. 1A). Fifty-five (5.3%) cases of second non-breast primary cancer were observed: 20 cases amongst the 525 (3.8%) toremifene-treated patients and 35 (6.9%) cases amongst the 510 tamoxifen-treated patients. The most frequent second primary cancers were endometrial cancer (1.1%), colon cancer (0.8%), renal cancer (0.7%) and urothelial cancers (0.5%) (Table 3). No significant difference was evident for any sites of second primary cancer according to the different SERMs. No significant differences were observed between the two differently treated groups of patients with regard to the cumulative incidence of second primary cancers considering breast cancer relapses and deaths without recurrence as competing risks of second primary cancers (Fig. 1B) (HR (Tor/Tam) = 0.67; 95% CI = 0.37,1.95; *p*-value = 0.18).

Table 3 – Toremifene versus tamoxifen: second non-breast primaries as sites of first failure.

	Toremifene	Tamoxifen	Total
Total patients	525 (100.0%)	510 (100.0%)	1035 (100.0%)
Total patients with second non-breast primary cancer	20 (3.8%)	35 (6.9%)	55 (5.3%)
8-year cumulative incidence of second non-breast cancer*	2.9%	4.3%	3.1%
(95% confidence interval)	(1.4%, 4.4%)	(2.4%, 6.2%)	(2.5%, 3.6%)
Types of second non-breast cancer			
Thyroid	–	1 (0.2%)	1 (<0.1%)
Lung (non-small cell)	1 (0.2%)	1 (0.2%)	2 (0.2%)
Lung (type not specified)	–	1 (0.2%)	1 (<0.1%)
Gastric	–	1 (0.2%)	1 (<0.1%)
Colon	2 (0.4%)	6 (1.2%)	8 (0.8%)
Rectal	–	1 (0.2%)	1 (<0.1%)
Pancreatic	1 (0.2%)	1 (0.2%)	2 (0.2%)
Biliary	–	1 (0.2%)	1 (<0.1%)
Renal	2 (0.4%)	5 (1.0%)	7 (0.7%)
Urothelial	2 (0.4%)	3 (0.6%)	5 (0.5%)
Ovarian	–	2 (0.4%)	2 (0.2%)
Endometrial	6 (1.1%)	5 (1.0%)	11 (1.1%)
Cervical	–	1 (0.2%)	1 (<0.1%)
Central nervous system: malignant meningioma	–	1 (0.2%)	1 (<0.1%)
Melanoma	2 (0.4%)	2 (0.4%)	4 (0.4%)
Ocular melanoma	–	1 (0.2%)	1 (<0.1%)
Skin (type not specified)	1 (0.2%)	–	1 (<0.1%)
Leiomyosarcoma	1 (0.2%)	–	1 (<0.1%)
Acute myeloid leukaemia	1 (0.2%)	1 (0.2%)	2 (0.2%)
Chronic lymphocytic leukaemia	1 (0.2%)	–	1 (<0.1%)
Non-Hodgkin's lymphoma	–	1 (0.2%)	1 (<0.1%)

* Competing risk analysis.[13]

Table 4 – Endocrine therapy versus chemo-endocrine therapy: second non-breast primaries as sites of first failure (Trials III, VII, and the first 212 patients in Trial 12).

	Endocrine therapy	Chemo-endocrine therapy	Total
Total patients	529 (100.0%)	1202 (100.0%)	1731 (100.0%)
Total patients with second non-breast primary cancer	46 (8.7%)	93 (8.0%)	139 (8.0%)
14-year cumulative incidence of second non-breast cancer*	6.5%	7.2%	7.0%
(95% confidence interval)	(4.3%, 8.6%)	(5.6%, 8.7%)	(5.7%, 8.2%)
Types of second non-breast cancer			
Head and neck	2 (0.4%)	1 (<0.1%)	3 (0.2%)
Thyroid	1 (0.2%)	3 (0.2%)	4 (0.2%)
Lung (non-small cell)	–	3 (0.2%)	3 (0.2%)
Lung (type not specified)	–	5 (0.4%)	5 (0.3%)
Lung carcinoid	1 (0.2%)	–	1 (<0.1%)
Oesophageal	–	3 (0.2%)	3 (0.2%)
Gastric	6 (1.1%)	5 (0.4%)	11 (0.6%)
Small bowel	–	1 (<0.1%)	1 (<0.1%)
Colon	5 (0.9%)	7 (0.6%)	12 (0.7%)
Rectal	4 (0.8%)	3 (0.2%)	7 (0.4%)
Pancreatic	1 (0.2%)	5 (0.4%)	6 (0.3%)
Hepatic	–	1 (<0.1%)	1 (<0.1%)
Biliary	1 (0.2%)	1 (<0.1%)	2 (0.1%)
Colorectal (type not specified)	–	1 (<0.1%)	1 (<0.1%)
Renal	1 (0.2%)	3 (0.2%)	4 (0.2%)
Urothelial	2 (0.4%)	7 (0.6%)	9 (0.5%)
Ovarian	3 (0.6%)	6 (0.5%)	9 (0.5%)
Endometrial	5 (0.9%)	16 (1.3%)	21 (1.2%)
Mixed muellerian tumour	1 (0.2%)	2 (0.2%)	3 (0.2%)
Uterine sarcoma	–	1 (<0.1%)	1 (<0.1%)
Uterine (type not specified)	–	1 (<0.1%)	1 (<0.1%)
Cervical	2 (0.4%)	2 (0.2%)	4 (0.2%)
Vulvar	–	1 (<0.1%)	1 (<0.1%)
Central nervous system (type not specified)	1 (0.2%)	–	1 (<0.1%)
Melanoma	4 (0.8%)	4 (0.3%)	8 (0.5%)
Ocular melanoma	–	1 (<0.1%)	1 (<0.1%)
Acute lymphocytic leukaemia	–	1 (<0.1%)	1 (<0.1%)
Acute myeloid leukaemia	1 (0.2%)	1 (<0.1%)	2 (0.1%)
Chronic lymphocytic leukaemia	–	2 (0.2%)	2 (0.1%)
Non-Hodgkin's lymphoma	3 (0.6%)	4 (0.3%)	7 (0.4%)
Lymphoma (type not specified)	1 (0.2%)	1 (<0.1%)	2 (0.1%)
Multiple myeloma	1 (0.2%)	–	1 (<0.1%)
Primary peritoneal	–	1 (<0.1%)	1 (<0.1%)

* Competing risk analysis.[13]

3.2. *Endocrine adjuvant therapy versus chemo-endocrine adjuvant therapy*

The second comparison was based on a total of 1731 patients, 529 treated with endocrine adjuvant therapy alone and 1202 treated with a combination of chemotherapy and endocrine treatments. Median follow-up was 14.4 years and varied amongst the three clinical trials: 25 years for Trial III, 14.7 years for Trial VII and 8.0 years for Trial 12-93. The incidence of second non-breast primary cancer was 8.0% (139 cases amongst 1731 patients). Again no significant difference was evident in the incidence of different types of second primary cancers (both solid tumours and acute leukaemia or other haematological malignancies) (endocrine 8.7% (46 events/529 patients), chemo-endocrine 8.0% (93 events/1202 patients)) between the two differently treated cohorts of patients (Table 4). No significant differences were observed between the two differently treated groups of patients with regard to the cumulative incidence of second primary cancers considering breast cancer relapses and deaths without recurrence as competing risks (Fig. 2) DFS (HR (chemo-endocrine/endocrine) = 1.04; 95% CI = 0.70, 2.83; p-value = 0.84), although there was a statistically significant difference in DFS (HR (chemo-endocrine/endocrine) = 0.80; 95% CI = 0.71, 0.91; p-value = 0.0005) favouring chemo-endocrine therapy.

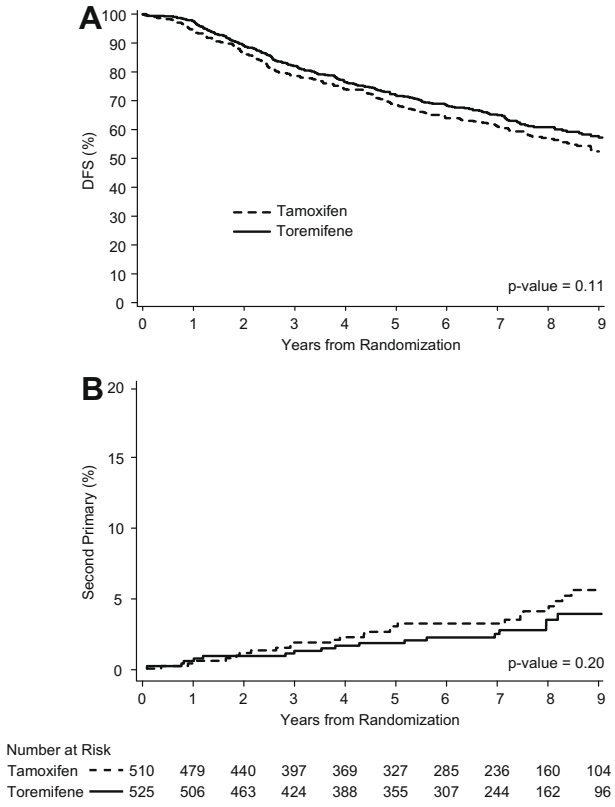

Fig. 1 – Toremifene versus tamoxifen according to disease-free survival (A) and competing risk of second non-breast primary cancer (B) amongst 1034 postmenopausal patients with node-positive early breast cancer enrolled in IBCSG Trials 12-93 and 14-93. *P*-value calculated according to Gray.[12]

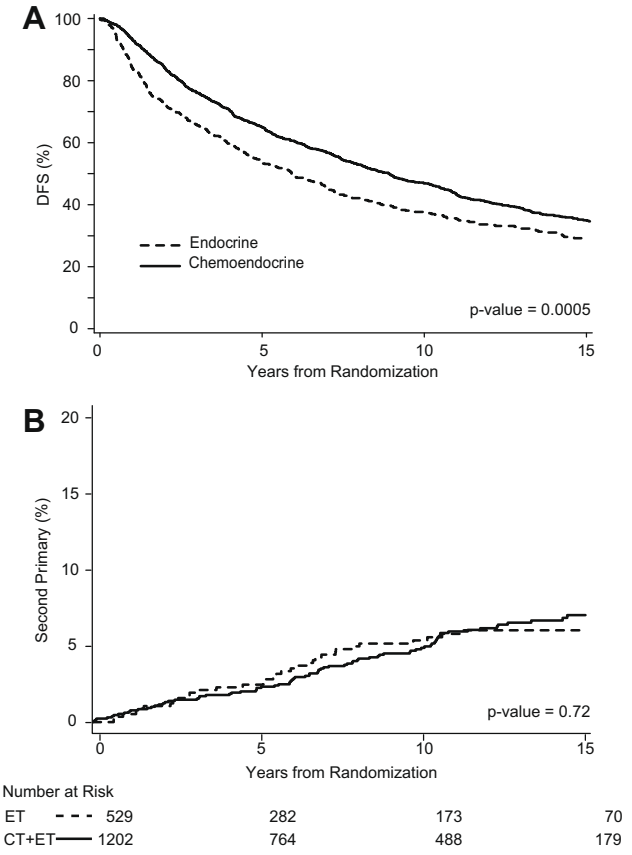

Fig. 2 – Endocrine therapy versus chemo-endocrine therapy according to disease-free survival (A) and competing risk of second non-breast primary cancer (B) amongst 1731 postmenopausal patients with node-positive early breast cancer enrolled in IBCSG Trials III, VII and 12-93. *P*-value calculated according to Gray.[12]

4. Discussion

Evidence from cancer registries and clinical studies suggests that patients with breast cancer have an increased risk of second primary cancer.[3,14–19] New primary cancers of the breast account for nearly 40% of all subsequent malignancies, but the risk of other solid tumours and of haematologic malignancies[3,14] also seems higher than in the general population. A recent large population-based cohort study from the Netherlands found that approximately one in every 20 breast cancer patients developed a second non-breast primary tumour within 10 years following a breast cancer diagnosis. Compared with the general female population, these breast cancer patients had a 22% increased relative risk in second non-breast primary cancers and an absolute excess risk of 13 cases per 10,000 women-years, and occurrence of a second non-breast cancer was associated with a decrease in overall survival.[20] This increased risk of second primary malignancies may be related to common aetiologic factors (hormonal and lifestyle), genetic predisposition[3,4] or to the adjuvant treatment.

Tamoxifen is associated with a threefold increased risk of endometrial cancer and uterine sarcoma, and with a decrease of about a third in the incidence of contralateral breast cancer.[5,15] The increased risk occurs predominantly amongst women who are 50 years or older,[15,21] and treatment duration may affect the size of risk.[4,5] An elevated risk of gastrointestinal cancer was also reported,[14,22,23] but this association remains more controversial.[5,24–26] Other SERMs such as raloxifene and toremifene may be safer for the uterus, and a lower risk of endometrial cancer has been reported.[27–34] Data from randomised adjuvant trials are conflicting. The Finnish adjuvant trial compared toremifene 40 mg/d with tamoxifen 20 mg/d given orally for 3 years in a population of postmenopausal women with lymph node-positive early breast cancer. At the first interim analysis on 899 of 1489 accrued patients after a median follow-up of 3.4 years, two cases of endometrial cancer were observed in the tamoxifen arm and none in the toremifene group.[33] On the contrary, the first IBCSG report comparing toremifene and tamoxifen (IBCSG Trials 12-93 and 14-93) as adju-

vant hormonal treatments for early breast cancer showed after a median follow-up of 5.5 years a similar incidence of second primary cancer with the two agents and no significant difference in endometrial cancer incidence.[11] The present report provides an update of the incidence of second non-breast primary cancer in patients treated with toremifene and tamoxifen in Trials 12-93 and 14-93 with longer follow-up. The results confirm our previous findings of the lack of a significant difference in endometrial cancer incidence with 6 (1.1%) and 5 (1.0%) patients in toremifene- and tamoxifen-treated patients, respectively. Overall, second primary cancers were slightly less common amongst patients treated with toremifene, but the difference did not reach statistical significance. The issue of toremifene safety should be re-evaluated in the light of the updated reports regarding other clinical experiences with this SERM, even if the recent achievements of aromatase inhibitors in the adjuvant setting make this point less relevant.

The findings of the second comparison of this report, evaluating the impact of adding chemotherapy to endocrine treatment on the occurrence of second non-breast primary cancer, were similar to those of the first. The occurrence of second primary cancer, both solid tumours and secondary acute leukaemias, was not significantly increased in patients receiving chemo-endocrine treatment compared with patients treated with endocrine therapy alone. Patients mainly received 3–12 cycles of classical CMF (or four cycles of AC in 212 patients) in addition to SERM endocrine therapy. This observation after a long follow-up period supports previous reports which found no increase in solid tumours and only a low excess risk of leukaemia with standard intensity CMF regimens.[35,36] The risk estimate of acute myeloid leukaemia (AML) varies amongst different studies, generally ranging from 0.2% to 1.7%[36]; differences are probably in part related to different drugs used, doses, schedules, length of follow-up and possibly to some supportive therapies.[6,8,37–47]

Even if secondary AML/myelodysplastic syndrome occurs in a minority of patients who have received adjuvant chemotherapy and/or radiotherapy, and the expected gain in breast cancer mortality reduction widely exceeds risks even in the most favourable prognostic subgroup of patients,[5] the principle of caution is always required; it should be recognised that the benefit of adding chemotherapy could be very low in patients with highly endocrine-responsive disease.[48] It would therefore be advisable to tailor the selection of adjuvant therapies according to the biological characteristics of responsiveness and the risks of recurrence and toxicity.[49,50] The use of genetic testing to select patients at intermediate risk of recurrence who could benefit from adjuvant chemotherapy, as well as the identification of risk factors that may confer a higher susceptibility to the development of second non-breast primaries, such as polymorphisms in DNA repair and/or drug-metabolising enzymes, may further improve the safety of modern breast cancer adjuvant treatment.[51–54]

Radiotherapy probably accounts for the increased incidence of lung cancer reported in the literature in breast cancer patients (as well as for cancers of oesophagus, bone and soft tissue).[3] In our study, there were only fifteen cases of lung cancer (five in patients who had received radiation therapy), limiting the possibility of further analysis. Lung cancers appeared somewhat more frequently in patients treated with chemo-endocrine therapy (11 patients) than in those treated with endocrine therapy (4 patients). As all the trials selected for the present study were limited to postmenopausal patients, it is unlikely that age influenced this apparent difference.

This report, based on a substantial number of similarly treated patients with 8–14 years of accurate follow-up reporting, seems reassuring that these agents used as adjuvant treatment of breast cancer in the comparisons studied do not increase the incidence of second non-breast primary cancer . However, a control group of untreated patients was lacking in our study and it is possible that the sample size was not large enough to detect a difference in the incidence of these tumours. Finally, experience from other studies shows that cancer survivors may be at higher risk of a second primary cancer even 25–30 years after treatments,[19,54] and efforts to obtain long-term follow-up of our patients should continue.

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Conflict of interest statement

None declared.

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Appendix of participating centers that continue to follow patients on these trials

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