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CARCINOGENIC EFFECTS OF ADJUVANT TAMOXIFEN TREATMENT AND RADIOTHERAPY FOR EARLY BREAST CANCER

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The occurrence of new primary tumours among postmenopausal patients with primary breast cancer subsequent to adjuvant treatment in Denmark was assessed by linkage to the cancer registry. Following primary surgery, patients in low risk of recurrence (n = 1 828) received no further treatment while patients in high risk randomly received either adjuvant radiotherapy alone (n = 846) or radiotherapy + tamoxifen 30 mg daily for 48 weeks (n = 864). With a median follow-up of 8 years, the incidence of tumours in the contralateral breast was similar among tamoxifen-treated, and non-treated high-risk patients even after adjusting for tumours arising within the first year. The standardized incidence ratio for endometrial cancer was 1.9 (95% confidence interval 0.8–3.9) among tamoxifen treated, the cumulative incidence 1% compared to 0.3% among non-treated patients (p = 0.11). The cumulative risk of non-lymphocytic leukaemia was 0.9% and 0.1% among irradiated and non-irradiated patients respectively (p = 0.4). Prolonged follow-up of tamoxifen-treated patients with regard to new tumours is recommended.

Key words: Breast cancer, adjuvant radiotherapy, adjuvant tamoxifen, secondary cancers.

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Tamoxifen (TMX), an antioestrogenic compound, is effective both by inducing remission in disseminated breast cancer (1) and by prolonging recurrence-free survival and total survival when given adjuvantly to postmenopausal women with early breast cancer (2). From three major adjuvant trials indications further exist that TMX may reduce the incidence of new primary tumours in the opposite breast (3–5). This, together with experiences from animal experiments where TMX prevents or postpones the development of breast tumours, has stimulated interest in trials of long-term TMX prophylaxis in healthy women belonging to breast cancer high-risk groups (6–7).

The potential long-term effects of TMX, including carcinogenesis, are, however, not fully elucidated. TMX in humans, beside being anti-oestrogenic on the breast, also acts as a partial oestrogenic agonist on the endometrium and might increase the incidence of endometrial carcinoma. This has in fact been observed in the Stockholm adjuvant trial (3), but not in others (8).

We recently reported on the incidence of new primary tumours in Danish patients with early breast cancer given adjuvant treatment with TMX and radiation (RT) based on cancer registry data (9). The major findings were a significantly increased risk of non-lymphocytic leukaemia (NLL) among patients given RT, a non-significantly increased risk of endometrial carcinoma (EC) among

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patients given TMX, and no indications of a protective effect of TMX with regard to tumour development in the opposite breast. Further details on these findings are given in the present paper.

Material and Methods

From 1977 to 1982, most postmenopausal early breast cancer patients in Denmark were enrolled in protocols organized by the Danish Breast Cancer Cooperative Group (DBCG). Details on study design and preliminary results have been reported earlier (10, 11). In short, patients with low risk of recurrence (LR-group) were those with no axillary lymph node metastases and primary tumours smaller than 5 cm without involvement of skin or fascia. All others were considered to be at high risk of recurrence. All patients had a modified radical mastectomy. Patients in LR-group received no further treatment (n = 1 828), while high-risk patients all received RT against the chest wall and regional lymph nodes and, by randomization, no further treatment (HR RT-group, n = 846) or TMX 30 mg daily for 48 weeks (HR RT + TMX-group, n = 864). Patients were followed up regularly by medical examination, and clinical data, including data on first recurrence of breast cancer, were reported to the DBCG database. New primary tumours among patients in the protocol, were identified by computerized linkage with the Danish Cancer Registry. Standardized incidence ratios (SIR) for site specific new tumours were computed based on the incidence rates of the general population and 95% confidence intervals (95% CI) calculated assuming a Poisson distribution. Cumulative incidences were analyzed by Kaplan-Meier estimates and log-rank test and differences between means by t-test.

Results

Contralateral breast cancer. Table 1 shows the number of cancers of the opposite breast reported to the cancer registry and the corresponding SIRs. The SIR did not differ between the HR RT- and the HR RT + TMX-groups (SIR = 4.2 and 4.4) but was significantly higher than that of the LR-group (SIR = 1.4). However, a large proportion of the cancers, especially in the HR-groups, was diagnosed shortly after diagnosis of the primary cancer. If only those arising more than one year after the first cancer were considered no difference between any group with regard to SIR (Table 1) or cumulative frequency (Fig. 1) was observed.

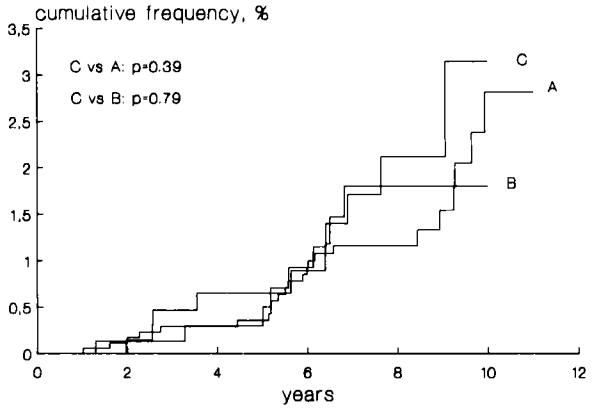

Fig. 1. Cumulative frequency of contralateral breast cancer occurring more than 1 year after diagnosis of the primary breast cancer. A = LR group, B = HR RT-group, C = HR RT + TMX-group.

Endometrial carcinoma. All cases of EC were histologically verified as adenocarcinomas. Eleven cases occurred in the LR-group, SIR = 1.1 (95% CI = 0.6–2.0), 2 cases in the HR RT-group, SIR = 0.6 (95% CI = 0.1–2.1), and 7 cases in the HR RT + TMX-group, SIR = 1.9 (95% CI = 0.8–3.9). The SIR was thus 3.3 times (95% CI = 0.6–31) higher for TMX-treated high-risk patients than for high-risk patients not receiving TMX. The cumulative frequency after 10 years (Fig. 2) was 0.8% in the LR-group, 0.3% in the HR RT-group, and 1.0% in the HR RT + TMX-group. No statistically significant differences

Table 1

Number of cancers (n) in the opposite breast and standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) among patients with early breast cancer as reported to the Danish Cancer Registry

Treatment group	All tumours			Cancers occurring more than one year after the primary		
	n	SIR	(95% CI)	n	SIR	(95% CI)
LR*)	44	1.4	(1.0–1.8)	23(4)**)	0.9	(0.6–1.4)
HR RT	47	4.2	(3.1–5.6)	8(0)	1.0	(0.4–1.9)
HR RT + TMX	52	4.4	(3.3–5.8)	10(1)	1.1	(0.5–2.1)

*) Abbreviations: See text.

**) Numbers within parentheses indicate cases where contralateral breast cancer was preceded by recurrence of primary breast cancer.

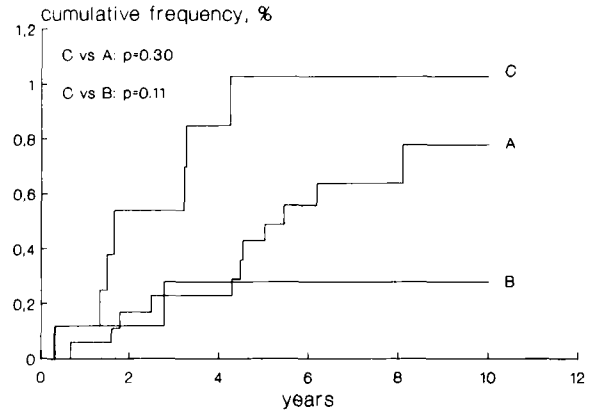

Fig. 2. Cumulative frequency of endometrial cancer subsequent to breast cancer. A = LR-group, B = HR RT-group, C = HR RT + TMX-group.

between the groups were observed, but the risk of EC among TMX-treated patients was consistently elevated relative to the general population, to patients in the LR-group, and to patients in the HR RT-group. There was a tendency (Table 2) for patients with EC in the HR RT + TMX-group to be older at diagnosis of breast cancer than patients in the LR-group (mean 68.6 vs 65.4 years), and to have a shorter interval from breast cancer diagnosis to EC (mean 2.4 vs 4.3 years) and a shorter total survival time after diagnosis of EC (2.2 vs 4.2 + years). None of these differences, however, was statistically significant.

Leukaemia. Eight cases of NLL were diagnosed (Table 3). All of them were acute myelogenous leukaemia except one in the HR RT + TMX-group, which was chronic myelogenous leukaemia. Knowing that ionizing radiation of the bone marrow has been shown to induce NLL, the incidence of NLL in patients given RT (i.e. HR RT- and HR RT + TMX-groups) was compared with that of patients not receiving RT (i.e. LR-group). The mean age at diagnosis of breast cancer and the interval from diagnosis of breast cancer to leukaemia was similar in 6 irradiated and 2 non-irradiated patients with leukaemia (67.7 vs 66.0 years and 4.8 vs 4.5 years). Two cases of NLL among irradiated and one case among non-irradiated patients were preceded by recurrence of the breast cancer. SIR of NLL was 5.2 (95% CI = 1.4–13) in the HR RT-group (n = 4), 2.5 (95% CI = 0.3–9.0) in the HR RT + TMX-group (n = 2), and 0.8 (95% CI = 0.1–3.0) in the LR-group (n = 2), and the quotient between the SIR of irradiated and non-irradiated patients was thus 4.7 (95% CI = 0.8–46). The cumulative risk of NLL after 9 years was significantly increased among irradiated patients compared to non-irradiated (0.9% vs 0.1%, p = 0.04) (Fig. 3).

Table 2

Characteristics of patients with endometrial cancer (EC) occurring after diagnosis of breast cancer

Treatment group	Age at breast cancer operation, years	Time from breast cancer operation to EC, years	Survival after EC, years	Breast cancer recurrence before EC
LR*)				
	70	1.8	4.7	No
	64	4.6	6.0 +	No
	59	8.1	0.8	Regionally, 1.1 year after breast cancer operation
	72	1.5	3.3	No
	75	0.7	4.8	No
	69	4.5	7.0 +	No
	60	4.3	6.8 +	No
	62	5.0	0.7	No
	65	5.5	2.7	No
	58	6.5	4.7 +	No
	64	4.5	5.0	No
HR RT				
	55	2.8	3.0	No
	66	0.3	120 +	No
HR RT + TAM				
	76	1.5	3.6	No
	67	3.2	0.8	No
	51	1.7	0	No
	69	2.2	8.2	No
	70	4.3	0.4	No
	77	3.3	0	Bones, 1.3 years after breast cancer operation
	70	0.3	2.3	No

*) Abbreviations: See text.

Table 3

Characteristics of patients with non-lymphocytic leukaemia occurring after diagnosis of breast cancer

Treatment group	Age at breast cancer operation, years	Time from breast cancer operation to leukaemia, years	Survival after leukaemia, years	Breast cancer recurrence before leukaemia	Leukaemia type
LR*)					
	73	3.2	0.3	No	AML
	59	5.8	0	Pleura 4.1 years after breast cancer operation	AML
HR RT					
	78	7.0	0.1	No	AML
	55	3.3	1.3	Bones 2.6 years after breast cancer operation	AML
	55	6.7	0.1	Chest wall 3.7 years after breast cancer operation	AML
	67	2.3	1.0	No	AML
HR RT + TMX					
	75	4.2	0	No	AML
	76	4.5	0	No	CML

*) Abbrevations: See text.

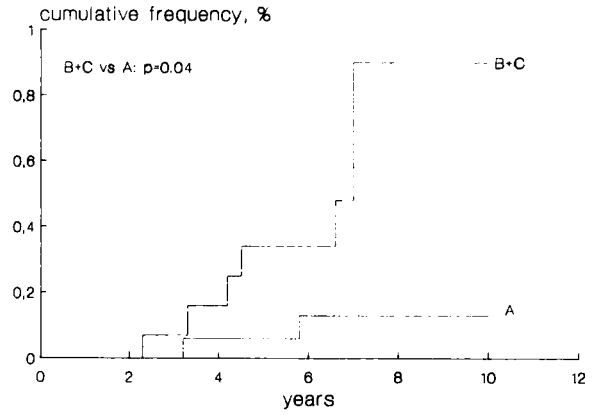

Fig. 3. Cumulative frequency of non-lymphocytic leukaemia subsequent to breast cancer. A = LR-group, B + C = HR RT and HR RT + TMX-groups combined.

Discussion

Identification of all cases of new primary tumours in this study was based on reports to the Danish Cancer Registry. The completeness of this registry is high when considering primary tumours, but completeness and accuracy might be less good when it concerns tumours arising in patients who had one cancer diagnosed already (12). It could be hypothesized that the increased medical surveillance which cancer patients enrolled in controlled trials are subjected to would result in an overestimation of the SIR and, on the other hand, that physicians in many cases might interpret new tumours as metastatic breast cancer disease (thereby underestimating the true incidence of new tumours).

This aspect is especially relevant with regard to cancers of the opposite breast where, in fact, it may be impossible, even with the most sophisticated patho-anatomical techniques to distinguish between de novo tumours and metastases. In the present study, new breast cancers were defined, pragmatically, as tumours interpreted as being primary by the reporting physicians. A large proportion of these cancers, especially among patients with high risk of recurrence, was diagnosed within one year after diagnosis of the first cancer, perhaps reflecting the high frequency of breast cancer recurrence during this period. It is, however, remarkable that no difference could be found between the incidence of cancers of the opposite breast among patients in the HR RT + TMX-group and in patients in the HR RT-group, neither when considering all cancers, nor when considering only cancers arising with a latency period of more than one year after diagnosis of the first tumour. This finding is in contrast to findings from most other major adjuvant trials with tamoxifen where the incidence of contralateral breast cancer has been significantly reduced among tamoxifen treated (3–5). Possible explanations for this discrepancy may be the relatively limited treatment period in the present study (48 weeks compared to 2 or 5 years in most other studies) and the difficulty of deciding whether the contralateral breast represented a new primary cancer or metastasis.

The observation of an increase, though not statistically significant, in the risk of endometrial carcinoma among patients given adjuvant treatment with TMX is in line with experience from the Stockholm adjuvant trial (3), which as regards study size, length of follow-up, and follow-up procedure was comparable to the present study. In the Swedish study, the cumulative risk of endometrial cancer after 8 years was approximately 0.4% among patients not

given TMX, 5.5% among patients treated for 5 years with TMX 40 mg daily ($p < 0.01$), and 1.5% among patients treated for only 2 years ($p = 0.08$). In the present study, the cumulative risk among patients treated for one year with 30 mg daily was 0.8% and among comparable controls 0.3% ($p = 0.11$) indicating the possible existence of a dose–response relation. These findings, however, have not been reproduced in other similar studies. There is obviously a need for continued, careful follow-up of patient groups treated adjuvantly with TMX for differing periods of time and with different doses, preferably within the framework of controlled trials. In the present study, the mean survival after diagnosis of endometrial cancer subsequent to TMX treatment was only 2.2 years (range 0–8.2 years) among 7 patients, of whom only one had shown signs of breast cancer recurrence before the endometrial cancer. This indicates that endometrial carcinoma following TMX treatment may not be as easily manageable as proposed (3).

The finding of a significantly increased cumulative risk of NLL among patients given RT postoperatively may have been confounded by the fact that the groups which were compared with regard to NLL incidence were not defined by randomization but by stratification according to presumed risk of breast cancer recurrence. Nevertheless, a similar tendency was reported from the NSABP-trials (13) (cumulative frequency of leukaemia among patients >50 years given regional RT 1.3% after 10 years ($p = 0.16$) in comparison with patients not given RT). In a recent Danish case–control study among breast cancer patients exposure to radiation therapy gave a relative risk of 2.5 for NLL (14). This last observation could not be reproduced in a parallel American case–control study which however, only comprised half the number of cases of NLL compared to the Danish study (15).

In conclusion, the present study could not demonstrate any preventative effect of adjuvant TMX with regard to development of contralateral breast cancer. The study indicates a slightly elevated risk of endometrial carcinoma following TMX treatment and of NLL following adjuvant RT.

REFERENCES

1. Furr BJA, Jordan VC. The pharmacology and clinical uses of tamoxifen. Pharmacol Ther 1984; 25: 127–205.
2. Early Breast Cancer Trialists' Collaborative Group. Treatment of early breast cancer: worldwide evidence, 1985–1990. Oxford: Oxford University Press, 1990.
3. Fornander T, Rutqvist LE, Cedermark B, et al. Adjuvant tamoxifen in early breast cancer: Occurrence of new primary cancers. Lancet 1989; 1: 117–20.
4. Fisher B, Costantino J, Redmond C, et al. A randomized trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumours. N Engl J Med 1989; 320: 479–84.
5. CRC Adjuvant Breast Trial Working Party. Cyclophosphamide and tamoxifen as adjuvant therapies in the management of breast cancer. Br J Cancer 1988; 57: 604–7.
6. Fentiman IS. The role of tamoxifen in the prevention of breast cancer. Eur J Cancer 1990; 26: 655–6.
7. Costa A, Love RR. The Madison meetings. Eur J Cancer 1990; 26: 656–7.
8. Stewart H, Knight GM. Tamoxifen and the uterus and endometrium. Lancet 1989; 1: 375.
9. Andersson M, Storm HH. Mouridsen HT. Incidence of new primary cancers after adjuvant tamoxifen therapy and radiotherapy for early breast cancer. J Natl Cancer Inst 1991; 83: 1013–7.
10. Andersen KW, Mouridsen HT, Castberg T, et al. Organization of the Danish adjuvant trials in breast cancer. Dan Med Bull 1981; 28: 102–6.
11. Mouridsen HT, Rose C, Overgaard M, et al. Adjuvant treatment of postmenopausal patients with high risk primary breast cancer. Results from the Danish adjuvant trials DBCG 77 and DBCG 82C. Acta Oncol 1988; 27: 699–705.
12. Storm HH, Lynge E, Østerlind A, Jensen OM. Multiple primary cancers in Denmark 1943–80; influence of possible underreporting and suggested risk factors. Yale J Biol Med 1986; 59: 547–59.
13. Fisher B, Rockette H, Fisher ER, Wickerham DL, Redmond C, Brown A. Leukemia in breast cancer patients following adjuvant chemotherapy or postoperative radiation: the NSABP experience. J Clin Oncol 1985; 3: 1640–58.
14. Engholm G, Storm HH, Andersson M, Jensen OM. Leukemia following breast cancer treatment, a case–control study. Proceedings of Nordic Cancer Union Symposium: Radiation and cancer risk, 1987 December 9–10; Oslo. Nordic Cancer Union and Norwegian Cancer Society, 1987: p 18.
15. Curtis RE, Boice JD, Stovall M, Flannery JT, Maloney WC. Leukemia risk following radiotherapy for breast cancer. J Clin Oncol 1989; 7: 21–9.