

Endometrial and other primary cancers after tamoxifen treatment of breast cancer — results of retrospective cohort study

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Abstract

Objectives: The aim of the retrospective cohort study was to evaluate the relationship between the influence of tamoxifen on the development of endometrial and other second primary cancers in the patients with invasive breast cancer. **Study Design:** A cohort of 630 women diagnosed with breast cancer from 1987 to 1994 was selected from a population-based registry; 440 patients were treated with tamoxifen and 190 patients without it. The observation period was 8.5 years (range 5–12 years). The data were analysed by the relative risk (RR) calculation at a confidence interval (CI) of 95%, using a Mantel–Haenszel χ^2 -test and Fisher's *p*-test to evaluate statistical significance. **Results:** There were no statistically significant differences between the group of breast cancer patients treated with tamoxifen and without it as regards the age at the breast cancer diagnosis, family medical histories, body mass, age at menopause, fertility, diabetes, hormone replacement therapy and oestrogen-hormone replacement therapy. In 41/440 (9.3%) tamoxifen-treated patients and in 8/190 (4.2%) non-users of tamoxifen, diagnostic curettage was performed due to benign endometrial changes and endometrial cancer (EC). The difference in the proportions of patients with diagnostic curettage in both group was statistically significant ($\chi^2=4.45$, $p=0.03$). In the group of patients treated with tamoxifen, with the median treatment duration of 40 months (range 1–97 months) and in the group of patients without tamoxifen, EC was diagnosed in 11 and in two patients, respectively. The evaluated RR was 2.38 (0.53–10.61, 95% CI). The second primary cancer, excluding contralateral breast cancer and EC, was diagnosed in the group of breast cancer patients treated with tamoxifen and without it in almost the same percentage, i.e. in 12 patients (3%) in the group of patients who were treated with tamoxifen and in 10 patients (5%) in the group of patients without tamoxifen treatment. **Conclusion:** Despite the fact that the calculated RR of EC in our study (2.4) was not statistically significant, due to a small number of patients, our results support the IARC evaluation that tamoxifen is carcinogenic to humans. Our data also suggest that tamoxifen does not increase the risk of other second primary cancers. However, the risk of individual second primary cancers cannot be reliably assessed due to a limited number of patients. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Endometrial cancer; Breast cancer; Tamoxifen

1. Introduction

Tamoxifen (Nolvadex) or ICI 46.474 was discovered in the research laboratory of ICI Pharmaceuticals in Cheshire (UK) [1]. Tamoxifen (TAM) is a synthetic, non-steroid, *trans*-isomeric derivative of triphenyl ethylene, similar to diethylstilbestrol. It is an anti-oestrogen with oestrogen-like activity in different tissues of some species. Undoubtedly, tamoxifen is the most important and successful hormonal drug in breast cancer treatment and one of the most widely prescribed drugs in the world today. Tamoxifen, one of the

most important selective oestrogen receptor modulators (SERMs), reacts through the oestrogen receptors, inhibits the growth promoting effects of oestrogens in the breast tissue and blocks a number of growth factor pathways that are critically involved in cell proliferation. Tamoxifen has a favourable influence upon the cells in the other breast and reduces the risk of carcinoma three to four times [2]. Women on tamoxifen had fewer contralateral breast cancers. Hence, tamoxifen is now undergoing clinical trials in order to prove its potential as preventive agent in women at high risk of breast cancer [3–5]. In addition to its anti-oestrogenic effect in the breast, tamoxifen is also gaining in importance for its oestrogenic-positive side effects. Tamoxifen increases the bone density and, consequently, decreases the osteoporosis [6], and reduces the risk of cardiovascular diseases with at

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least 5-year therapy [7]. In general, in spite of some negative side effects presumably caused by tamoxifen in women who have already been treated for breast cancer, the positive side effects of tamoxifen always far outweigh any eventual negative effects [6]. According to WHO classification, tamoxifen is one of the most important breast cancer drug.

Tamoxifen is well-tolerated, with only 5% of patients having discontinued the therapy because of its side effects [8]. Among its side effects, the following, though non-malignant, should be mentioned: toxic effect on the endometrium [9], inducing a variety of senile cystic endometrial atrophias, hyperplasia, endometrial polyps and uterine fibroids, and some fairly expressed climacteric disorders, such as periodic fever episodes, sweating, dyspareunia and mental disorders [9]. Sight problems, though rare, due to the reversible damages of the retina, macular oedema or optic neuritis could be observed, too [8]. There is experimental evidence that the drug may induce cataract formation [10]. Tamoxifen slightly increases the risk of thromboembolic diseases [7] and, presumably, also the risk of ovarian cyst formation in pre-menopausal patients [11].

The studies on tamoxifen carcinogenicity and tumour promotion fall into the following four categories; studies on chemical analysis, studies on experimental animals, analysis of the oestrogenic effects of tamoxifen on healthy endometrial tissue, and clinical data on the incidence of the second cancers [12–14].

The present retrospective cohort study is aimed to evaluate the influence of tamoxifen on the development of endometrial cancer (EC) and other second primary cancers in breast cancer patients.

2. Material and methods

This retrospective study included 630 patients with invasive breast cancer, aged 55 years and more, who were treated at the Institute of Oncology, Ljubljana, in the period from 1987 to 1994. The patients who had hysterectomy or were not followed up at the Institute, were not included in the study. The patients were divided into two groups: the first group comprised tamoxifen-treated patients and the second group consisted of the patients without tamoxifen treatment. We compared the risk factors of EC of both groups of patients, i.e. the family medical history, particularly with reference to breast and gynaecological cancers, age, body mass, age at menopause, fertility, diabetes, hypertension, hormone replacement therapy (HRT) and oestrogen hormone replacement therapy (E-HRT). The body mass calculation was made according to Quetelet's rule (body mass index (BMI)), based upon the body weight and height. The patients were categorised by Quetelet's index into five classes, with the most lean patients in the Class 1 and the most obese ones in Class 5.

The diagnostic criteria of the second primary cancer included only primary malignancies detected 1 month after the breast cancer diagnosis. The patients with a history of

cancer or with synchronous bilateral breast cancer or other synchronous malignancies were excluded. The diagnosis of the second primary malignancy in breast cancer patients was registered by Cancer Registry of Slovenia. Only those cases with the histologically confirmed second primary malignancy were analysed in detail. All other cases were excluded. As it is in the majority of breast cancer patients with the carcinoma in the contralateral breast almost impossible to distinguish between the progress of the disease and the second primary tumour, these patients were excluded from our analyses.

Observation period was 8.5 years (range 5–12 years). The data were analysed by the relative risk (RR) calculation at a confidence interval (CI) of 95%, with Mantel–Haenszel χ^2 and Fischer's *p*-tests used to evaluate statistical significance.

3. Results

A total of 630 patients were included into the study. Of these, 440 were treated with tamoxifen and 190 without it. Median age of the tamoxifen-users and non-users was 65 years, viz. 55–88 and 55–87 years, respectively. The patients were classified into five classes by the age at the time of the diagnosis. The comparison of the two groups, the users and non-user of tamoxifen, showed no statistically significant differences as regards the age of the patients (Table 1). The comparison of the two groups in view of family medical histories, body mass, age at menopause, fertility, diabetes, HRT and E-HRT showed no statistically significant differences, either (Table 2). Each tamoxifen user's daily dose was 20 mg, median treatment duration was 40 months (1–97). Total duration of tamoxifen treatment was 17,541 patient-months or 1462 patient-years. In 56 patients (9%), side effects, which were supposed to be associated with the use of tamoxifen, occurred on an average 28 months after the beginning of the therapy. Among them, the most common were uterine bleeding or discharge (72%). In 41/440 (9%) tamoxifen-treated patients, diagnostic curettage was performed. In 11/41 patients, the EC was detected, while in the rest of them, many cases of polypous changes in the endometrium and cystic hyperplasia were found. Diagnostic

Table 1
Age distribution of patients at breast cancer diagnosis, treated with tamoxifen or without it

Age (in years)	Tamoxifen+ (%)	Tamoxifen– (%)	χ^2	<i>p</i>
55–59	25	23	0.48	0.48
60–64	27	27	0.01	0.91
65–69	25	23	0.12	0.72
70–74	13	14	0.06	0.80
75–79	7	10	1.33	0.24
80–84	2	2	0.77	0.38
85 and more	1	1	0.02	0.87
Total	100	100		

Table 2

Characteristics of breast cancer patients, treated with tamoxifen or without it

Characteristic	Tamoxifen+ (%)	Tamoxifen- (%)	χ^2	<i>p</i>
Family medical history	24	24	0.01	0.94
BMI — (4 and 5)	58	65	0.89	0.34
Pre-menopause	0	1	2.33	0.12
Nullipara	16	17	0.08	0.77
Diabetes	11	8	1.55	0.21
Hypertension	20	22	0.19	0.66
HRT	0.7	1	0.24	0.62
E-HRT	0.5	0	0.86	0.35

curettage due to uterine bleeding was performed in eight out of 190 non-users of tamoxifen. In two of these cases, the curettage was required because of EC. The difference between the two groups of patients in view of diagnostic curettage was within the limits of statistical significance ($\chi^2=4.45$, $p=0.03$).

In the tamoxifen-treated group, the EC was diagnosed in 11 women of median age 68 years (57–85). In the group of patients without tamoxifen, the EC was detected in two patients of median age 64.5 years (64–65). The evaluated RR 2.38 (0.53–10.61, 95% CI) was statistically insignificant ($\chi^2=1.38$, $p=0.24$) (Table 3). All cases of EC in the tamoxifen-treated breast cancer patients were detected on average 41 months (2–78) after the breast cancer had been diagnosed and 37 months (1–77) after the therapy with tamoxifen had been started. In the patients who were treated without tamoxifen, the EC was detected on average 16 months (13–18) after the breast cancer had been diagnosed. Of 11 tamoxifen-treated breast cancer patients who subsequently developed the EC, seven had the EC diagnosed during the therapy with tamoxifen and four after the therapy. The average application time of tamoxifen from the beginning of the therapy until the diagnosis of EC was 31 months (1–60). None of the patients with endometrial carcinoma had HRT or E-HRT before the diagnosis of breast cancer. In the tamoxifen-treated group, with the duration of treatment less than 12 months, two cases of EC were diagnosed, both with the differentiation grade III and depth of invasion more than one-thirds in the first case and less than one-thirds in the second case. The differentiation grades of the rest of ECs

Table 3

Number of endometrial cancer cases in the group treated with tamoxifen or without it^a

	Tamoxifen+ (%)	Tamoxifen- (%)	Total
EC	11	2	11
Without EC	429	188	619
Total	440	190	630

^a RR=2.38 (0.53–10.61); $\chi^2=1.38$; $p=0.24$.

(nine patients), diagnosed 12 months or more after the therapy with tamoxifen had been started, were as follows. The differentiation grades I and II — six cases (67%) and the differentiation grade III — three cases (33%).

In the two patients without tamoxifen treatment who developed endometrial carcinoma, the differentiation grade I was diagnosed in one case and the differentiation grade II in the second case; the difference in view of the differentiation grades of ECs between tamoxifen-treated group and the group without tamoxifen was statistically insignificant ($\chi^2=0.25$, $p=0.61$).

The depth of invasion in the tamoxifen-treated group was less than one-thirds in six cases (75%, none in three cases, less than one-thirds in three cases) and more than one-thirds in two cases (25%). In the two patients without tamoxifen treatment, one patient was not operated on and in the other, the depth of tumour invasion was more than one-thirds. In view of the depth of tumour invasion, the difference between tamoxifen-treated group and the group without tamoxifen treatment was statistically insignificant ($\chi^2=0.62$, $p=0.10$).

The second primary malignancy with the exclusion of EC was detected in 12 tamoxifen-treated breast cancer patients and in 10 patients who were treated without tamoxifen. Evaluated RR 0.52 (0.23–1.18, 95% CI) was statistically insignificant ($\chi^2=2.53$, $p=0.11$). The classification of the breast cancer patients by the second primary carcinoma with the exclusion of EC and with regard to the localisation, pathohistological diagnosis and tamoxifen treatment is presented in Table 4.

The second primary malignancy with the exclusion of the EC in 12 tamoxifen-treated breast cancer patients was detected in on average 43 months (3–110) after the breast cancer had been diagnosed and 36 months (17–60) after the tamoxifen therapy had been started. Out of 12 tamoxifen-treated breast cancer patients who subsequently developed a second primary malignancy, five were diagnosed with the second primary malignancy during the therapy with tamoxifen and seven after the completed tamoxifen therapy. The average time from the discontinuation of the tamoxifen therapy until the diagnosis of the second primary malignancy in seven tamoxifen-treated breast cancer patients was 35 months (1–85).

In the patients who were treated without tamoxifen, the second primary malignancy (with the exclusion of the EC) was detected in 10 patients on average 40 months (4–93) after the breast cancer was diagnosed.

4. Discussion

Recommendations for the use of tamoxifen for prevention purposes in healthy women at risk of breast cancer are based on the data obtained from a number of research studies that confirmed the decrease in the development of cancer in the contralateral breast in tamoxifen-treated breast cancer patients [2]. With the use of tamoxifen for prevention

Table 4

Number of second primary cancers (endometrial cancer and contralateral breast cancer excluded) and RR at 95% CI (patients with tamoxifen treatment or without it)

		No. of second primary cancers		RR ^c
		Tamoxifen+ ^a (n=440)	Tamoxifen- ^b (n=190)	
Localisation	Pathohistological diagnosis			
Stomach	Adenoca tubul	2	0	–
Oral cavity	Planocelullaræ	1	0	–
	Mel malignum	1	0	–
Uterus cervix	Squamous	1	0	–
	Adenosquamous	1	0	–
Skin	Baseocelularæ	2	3	0.28 (0.05–1.71)
	Ca squamous	1	1	–
	Adenoca adnexs	0	1	–
Kidney	Hipernefroma	0	1	–
Vulva	Ca squamous	0	1	–
Ovaries	Adenocarcinoma	1	2	0.22 (0.02–2.37)
Lung	Adenocarcinoma	1	1	–
Pancreas	Adenoca tubul	1	0	–
Total		12	10	0.52 (0.23–1.18)

^a Patients with tamoxifen therapy.

^b Patients without tamoxifen therapy.

^c RR's was not calculated where no patients or less than two patients were observed.

purposes, a number of questions concerning its positive and negative side effects have emerged.

Many retrospective and prospective studies on the assumed cause and effect relation of tamoxifen and the subsequent development of EC have been published until today with the calculations of RR ranging between 0.47 and 15.2 [13,15]. With respect to the results published so far, the risk of developing endometrial carcinoma is two to three times higher with the application of tamoxifen. It is supposed that, due to the application of tamoxifen, 0.2–0.3% more ECs are detected per year in tamoxifen-treated breast cancer patients in contrast to 0.1% of ECs cases detected yearly in the breast cancer patients treated without tamoxifen [16]. However, a number of questions concerning the relation of cause and effect between tamoxifen and EC have not been answered yet. In support of the assumption that our findings speak in favour of the effect of tamoxifen on the endometrium, we are providing the data on diagnostic curettages which were carried out in the tamoxifen-treated breast cancer patients due to uterine bleeding. Statistically significant difference between the two groups of patients supports this assumption ($p=0.03$). Benign pathohistological findings, atrophic changes on the endometrium, polypoid, cystic and atypical hyperplasia, also speak in favour of the assumption. From the data of our retrospective study, the calculated RR of developing endometrial carcinoma related to the tamoxifen use was 2.38 (0.53–10.61, 95% CI). Despite the fact that the calculated RR of EC in our study was not statistically significant, due to a small number of patients (a large value of CI pointed at), the results of our study indicate that tamoxifen increases the risk of benign endometrial changes and EC, in agreement with the IARC evaluation that tamoxifen is carcinogenic to humans [17]. The results of

the present study support the results of other studies that the prolonged treatment with tamoxifen, over 2 years or more, in breast cancer patients further increases the risk of EC.

According to some authors, tamoxifen may influence the subsequent development of poorly differentiated EC [16]. The majority of authors report that the ECs in the tamoxifen-treated patients and in the remaining female population with the diagnosed endometrial carcinoma do not differ as to their differentiation grade and stage. On the basis of our findings, we were able to discover poorly differentiated endometrial carcinoma in the minority of patients using tamoxifen (33%). Moreover, it is interesting to note that the two carcinomas which were detected in the tamoxifen-treated breast cancer patients, 1 and 3 months after the beginning of the therapy, were both poorly differentiated.

The effect of tamoxifen on, as well as the risk factors for the development of other primary cancers in breast cancer patients could not have been defined due to a limited number of cases. According to the data published by Nayfield et al. on adjuvant treatment with tamoxifen of the patients with a breast cancer in its early stage, the cumulative occurrence of the second cancers (excluding the patients with contralateral breast cancer) was lower than in the group of patients without tamoxifen treatment [18]. Fornander in his article published the data on lower, statistically insignificant number of new primary cancers (breast cancer included) in the tamoxifen-treated group of patients than in the control group [19]. The results of the NSABP-14 research study showed that the occurrence of the second primary malignancies was higher, yet statistically insignificant, in the tamoxifen-treated group of patients [13]. There was no differences between the two groups in the report by Rutqvist et al. [12]. So far, no data have been known on higher occurrence of the second

cancers in women receiving tamoxifen treatment for preventive purposes. The data from the NSABP-P1 research study indicated that the number of patients with the second primary malignancy (excluding contralateral breast cancer and EC) was the same in both groups [5]. In our study, a second primary tumour, with the cases of endometrial carcinoma and contralateral breast cancer excluded, was found in both groups at almost the same percentage (3% versus 5%).

The association of tamoxifen with rat hepatocarcinogenesis has increased our interest in the incidence of hepatic carcinoma in women. As the laboratory tests confirmed the toxic effect of tamoxifen upon human hepatic cells, the above laboratory test results have never been clinically confirmed [20]. Three cases of hepatic carcinoma were found in the tamoxifen-treated patients in the Stockholm trial [12] and one case of the hepatocellular carcinoma in the results of NSABP-14 protocol [13]. Rutqvist et al. observed no increased risk of hepatic carcinoma in the analysis of the three major Scandinavian trials [12]. Other randomised trials observed no increased risk of hepatocellular carcinoma after tamoxifen treatment, either. In the report of the NSABP-P1 preventive study, no case of hepatic cancer was observed [5]. In our study, no case of hepatic cancer in tamoxifen-treated patients and in patients without tamoxifen was found, either.

Rutqvist et al. observed the excess of colorectal cancers in all three major Scandinavian trials [12]. No similar results were found in other trials or the meta-analyses [2,13]. In the report of the NSABP-P1 preventive study, one excess case of stomach cancer, gallbladder cancer and three cases of pancreatic cancer were found in the placebo group. In the tamoxifen-treated patients, two excess cases of colon cancers were found [5]. In our study, two cases of stomach cancer and one case of pancreatic cancer were found in tamoxifen-treated patients and no second primary gastrointestinal cancer cases in the patients without tamoxifen treatment.

The effect of tamoxifen therapy on the post-menopausal ovary has not been clarified yet and the influence of tamoxifen on the subsequent development of ovarian cancer varies substantially [20]. The reports from randomised and non-randomised trials observed no increased risk of ovarian cancer after tamoxifen treatment. Nayfield et al. reported six primary cancers among 4028 tamoxifen-treated patients and 12 cases among 4006 controls [15]. Cook et al. reported the results of nested case-control study in which the calculated matched odds ratio for ovarian cancer was lower, with no statistically significant association [21]. A lower RR of ovarian cancer was also observed in the randomised trial reported by Fornander et al. [19]. The excess of one case of ovarian cancer was observed in the Stockholm trial, in the results of NSABP-14 protocol and NSABP-P1 preventive study [5,12,13]. In our study, only two patients were premenopausal, the rest of them were post-menopausal. One case of ovarian cancer (serous) in the tamoxifen-treated patients and two cases of ovarian cancer (serous and mucin-

nous) in the patients without tamoxifen was found. From the results of the so far published research studies, we could not draw out any data on individual pathohistological pictures of ovarian carcinoma.

The RR for some other secondary cancers (leukemias and pulmonary system, kidney, skin and other cancers) observed in the randomised trials was not increased in comparison to general population. In our study, we found no statistically significant difference in developing other primary cancers (leukemias and pulmonary system, kidney, skin and other cancers). For some other second cancers, a lower but not significant RR was also reported [13,16].

The number of second primary cancers in the group of patients with tamoxifen did not differ significantly from that without tamoxifen treatment. Though the results of this study and also of some others indicate that the risk of developing of some of the second primary cancers, with the exclusion of contralateral breast cancer and endometrial carcinoma, is smaller with tamoxifen treatment, they cannot be reliably assessed due to a limited number of patients and disrespect of some specific risk factors. Further to this observation and to the possible differences in the action of tamoxifen, found in the experimental laboratory tests, new studies will be needed in the future.

Considering the increased risk of EC and following a generally accepted recommendation, all breast cancer patients treated with tamoxifen should have annual gynaecological evaluations. Endometrial sampling should be done in the event of uterine bleeding. The guidelines for tamoxifen-treated healthy women should be determined. Until then, all tamoxifen-treated breast cancer patients and healthy women should be informed about tamoxifen side effects and aware of their symptoms.

5. Conclusion

In the retrospective study of 630 patients with breast cancer, the influence of tamoxifen on the occurrence of the endometrial and other second primary cancers was evaluated.

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