original article

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Hormonal therapy for oestrogen receptor-negative breast cancer is associated with higher disease-specific mortality

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Background: Tamoxifen has a remarkable impact on the outcome of oestrogen receptor (ER)-positive breast cancer. Without proven benefits, tamoxifen is occasionally prescribed for women with ER-negative disease. This population-based study aims to estimate the impact of tamoxifen on the outcome of ER-negative disease.
Methods: We identified all women (n = 528) diagnosed with ER-negative invasive breast cancer between 1995 and 2005. With Cox regression analysis, we calculated breast cancer mortality risks of patients treated with tamoxifen compared with those treated without tamoxifen. We adjusted these risks for the individual probabilities (propensity scores) of having received tamoxifen.
Results: Sixty-nine patients (13%) with ER-negative disease were treated with tamoxifen. Five-year disease-specific survival for women treated with versus without tamoxifen were 62% [95% confidence interval (CI) 48% to 76%] and 79% (95% CI 75% to 83%), respectively ($P_{\text{Log-rank}} < 0.001$). For ER-negative patients, risk of death from breast cancer was significantly increased in those treated with tamoxifen compared with patients treated without tamoxifen (adjusted hazard ratio = 1.7, 95% CI 1.1–2.9, $P = 0.031$).
Conclusion: Our results show that patients with ER-negative breast cancer treated with tamoxifen have an increased risk of death from their disease. Tamoxifen use should be avoided for these patients.
Key words: breast cancer, cancer registry, hormonal therapy, oestrogen receptor status, survival

original article

introduction

The introduction of adjuvant hormonal therapy, in particular tamoxifen, has been one of the major breakthroughs in the fight against breast cancer mortality. For women with oestrogen receptor (ER)-positive breast cancer, 5 years of tamoxifen in an adjuvant setting decreases the risk of death from the disease by 31% [1]. In addition, tamoxifen reduces the risk of contralateral breast cancer by almost 50% [2].

According to the results of the first meta-analysis of the Early Breast Cancer Trialists' Collaborative Group, use of tamoxifen seemed to have a small beneficial effect in patients with ER-negative tumours (i.e. tumours with low or no expression of ER) [2]. A more recent overview of randomised trials showed a nonsignificantly 4% increased risk of death from breast cancer in ER-negative patients treated with tamoxifen during 5 years [1].

Still, over the last years, it is estimated that >10% of patients with ER-negative disease were treated with tamoxifen, either to reduce the risk of contralateral disease or because of a small proportion (1–9%) of tumour cells expressing ER [3].

In this study, we aimed to evaluate the effect of tamoxifen on the outcome of ER-negative breast cancer outside the context of clinical trials.

methods

We used data from the Geneva Cancer Registry, which records all incident cancer cases occurring in the population of the canton (~447 000 inhabitants in 2007). The registry collects information from various sources and the percentage of patients recorded from death certificates only is low (<2%). All hospitals, pathology laboratories, and practitioners are requested to report every cancer case. Trained registrars systematically abstract data from medical and laboratory records. Physicians regularly receive questionnaires to secure missing clinical and therapeutic data.

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Recorded data include sociodemographic information, method of detection, tumour characteristics, stage of disease at diagnosis, treatment, survival status, and cause of death.

The registry regularly assesses survival. The index date refers to the date of confirmation of diagnosis or the date of hospitalisation if it preceded the diagnosis and was related to the disease. Active follow-up is carried out yearly using the files of the Cantonal Population Office, which is in charge of the registration of the resident population. Cause of death is established from clinical records and coded according to the World Health Organisation classification [4]. Follow-up was completed on 31 December 2006.

We identified all patients diagnosed with invasive ER-negative breast cancer from 1 January 1995 to 31 December 2005. We defined tumours as ER negative when <10% of the tumour cells expressed ER by immunohistochemical assay.

Variables of interest were age, social class (high, middle, low, unknown), sector of care (private, public), and period of diagnosis. For staging, we used the pathological tumour–node–metastasis classification system or, when not available, the clinical tumour–node–metastasis classification [5]. Tumour differentiation (grade) was classified as good (grade 1), moderate (grade 2), poor (grade 3), or unknown. Progesterone receptor (PgR) status was considered negative when <10% of the tumour cells expressed PgR.

Locoregional therapy was categorised as breast-conserving surgery followed by radiotherapy, mastectomy with or without radiotherapy, and other (i.e. tumourectomy without radiotherapy). Use of chemotherapy was categorised as yes versus no. Except for the last year of the study period when antiaromatase was introduced in routine care practice, hormonal therapy consisted in tamoxifen only and was classified as tamoxifen yes versus no.

We compared patients treated with tamoxifen with those treated without tamoxifen. For both groups, we calculated disease-specific survival rates using Kaplan–Meier analysis and tested survival differences with log-rank test. With chi-square test, we identified all sociodemographic, tumour, and treatment characteristics that were significantly different between the two groups. We calculated the probability of having received tamoxifen for each patient, including in the logistic regression model all variables univariately associated with the administration of tamoxifen (propensity score) [6]. With Cox regression analysis, we calculated the risk [hazard ratio (HR)] of death from breast cancer for patients treated with versus without tamoxifen. We adjusted these risks for the predicted probabilities of tamoxifen.

Table 1. Patient and tumour characteristics by use of tamoxifen for 528 patients with oestrogen receptor-negative breast cancer (Geneva Cancer Registry, 1995–2005)

	Tamoxifen		Chi-square test
	Yes, $n = 69$ (%)	No, $n = 459$ (%)	
Age (years)			$P = 0.0110$
<50	20 (10)	159 (89)	
50–69	25 (11)	213 (90)	
70+	24 (22)	87 (78)	
Method of detection			$P = 0.0274$
Breast self-examination	27 (10)	253 (90)	
Clinical examination or screening	20 (15)	114 (85)	
Symptoms/fortuitous	22 (19)	92 (81)	
Stage			$P = 0.0114$
I	12 (8)	136 (92)	
II	27 (12)	202 (88)	
III	13 (15)	71 (85)	
IV	10 (24)	31 (76)	
Unknown	7 (27)	19 (73)	
Differentiation			$P = 0.0002$
Good	7 (23)	24 (77)	
Moderate	24 (16)	129 (84)	
Poor	24 (8)	270 (92)	
Unknown	14 (28)	36 (72)	
Progesterone receptor status			$P < 0.0001$
Positive	20 (40)	30 (60)	
Negative	49 (10)	429 (90)	
Locoregional therapy			$P = 0.0012$
Standard[a]	51 (11)	405 (89)	
Other	18 (25)	54 (75)	
Chemotherapy			$P = 0.0025$
No	30 (20)	119 (80)	
Yes	39 (10)	340 (90)	

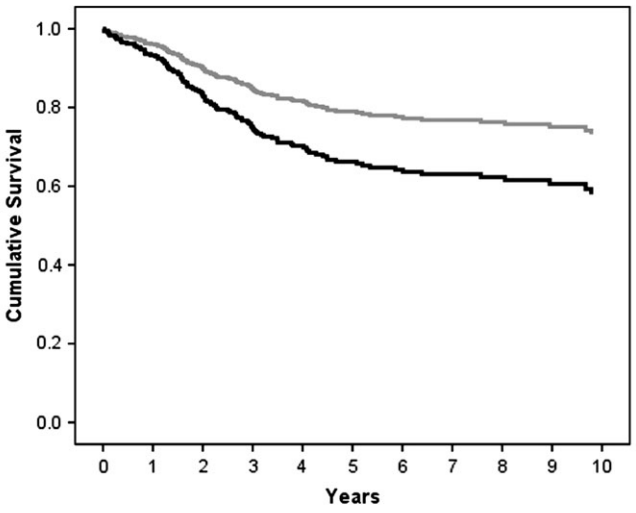
[a]Standard locoregional therapy: breast-conserving surgery associated with radiotherapy and mastectomy with or without radiotherapy.

results

Of the 528 ER-negative breast cancer patients included in this study, 69 women (13%) were treated with tamoxifen. ER-negative patients aged ≥70 years were more likely to receive tamoxifen, as were patients detected fortuitously or following symptoms, patients with advanced stage at diagnosis, unknown tumour differentiation, or tumours expressing PgR. Patients treated with tamoxifen were less likely to receive locoregional treatment according to the standard guidelines (i.e. mastectomy or breast-conserving surgery followed by breast irradiation) and chemotherapy (Table 1). All these factors were included in the logistic model to calculate the individual probabilities of having received tamoxifen.

The median follow-up was 47 months. Five- and 10-year disease-specific survival rates were 62% (95% confidence interval (CI) 48% to 76%) and 47% (95% CI 27% to 67%), respectively, for women treated with tamoxifen, and 79% (95% CI 75% to 83%) and 74% (95% CI 68% to 80%), respectively, for women treated without tamoxifen (Figure 1). These differences were highly, statistically significant with *P*-value log-rank tests <0.001.

In the unadjusted analysis, patients who received tamoxifen had a more than two-fold increased risk of death from breast cancer compared with those who did not (HR 2.2, 95% CI 1.4–3.4). This result remained similar after adjustment for propensity scores to have received tamoxifen. Additional adjustment for all other prognostic factors did not modify the HR value, but results were no longer significant. HRs did not change after excluding women with distant metastases and women who did not undergo surgery for their breast cancer (Table 2). The increased mortality risk linked to use of tamoxifen was limited to patients with PgR-negative tumours ($n = 478$, HR 2.6, 95% CI 1.6–4.3) while in the subgroup of women with PgR-positive tumours ($n = 50$), use of tamoxifen was not significantly associated with an increased breast cancer-specific mortality risk (HR 1.4, 95% CI 0.4–4.7). The



Grey line: treatment without tamoxifen, black line: treatment with tamoxifen.

Number of patients at risk at the beginning of each year following diagnosis

Year	1	2	3	4	5	6	7	8	9	10
Tamoxifen no	459	431	366	281	224	192	166	139	118	91
Tamoxifen yes	69	60	43	36	29	23	15	11	9	8

[1] Survival curves are derived from Cox model adjusted for propensity scores. Only death from breast cancer was considered.

Figure 1. Disease-specific survival[1] according to treatment with or without tamoxifen among 528 women with oestrogen receptor-negative breast cancer.

Table 2. Risk (HR)[a] of death from oestrogen receptor-negative breast cancer for women treated with tamoxifen compared with those treated without tamoxifen (Geneva Cancer Registry, 1995–2005)

Tamoxifen use	*n*	Deaths	Unadjusted HR	PS-adjusted HR
All breast cancers ($n = 528$)				
No	459	88	1	1
Yes	69	24	2.2 (1.4–3.4) $P = 0.0007$	1.7 (1.1–2.9) $P = 0.0305$
Stages I–III breast cancer only ($n = 461$)				
No	409	63	1	1
Yes	52	13	1.9 (1.1–3.5) $P = 0.0306$	2.0 (1.0–3.7) $P = 0.0362$
Operated breast cancer only ($n = 484$)				
No	430	72	1	1
Yes	54	15	1.9 (1.1–3.3) $P = 0.0227$	1.8 (1.0–3.2) $P = 0.0629$
PgR-positive breast cancer only ($n = 50$)				
No	30	6	1	1
Yes	20	5	1.4 (0.4–4.7) $P = 0.5616$	1.1 (0.3–3.8) $P = 0.8995$
PgR-negative breast cancer only ($n = 478$)				
No	429	19	1	1
Yes	49	82	2.6 (1.6–4.3) $P = 0.0001$	1.8 (1.0–3.1) $P = 0.0482$

[a]HRs were derived from Cox model adjusted for the individual probabilities (propensity scores) to have received tamoxifen; only death from breast cancer was considered.

HR, hazard ratio; PS, propensity scores; PgR, progesterone receptor.

number of patients with low expression of ER (1%–9% of tumour cells expressing ER) was low ($n = 29$); therefore, we could not carry out a meaningful subgroup analysis.

discussion

The results of this study show that the use of tamoxifen in women with ER-negative breast cancer is associated with an increased risk of death from the disease. The deleterious effect of tamoxifen was limited to patients with ER- and PgR-negative tumours.

Our results are in contrast with those reported in the first meta-analysis by the Early Breast Cancer Trialists' Collaborative Group [2]. The results of this study showed that use of adjuvant tamoxifen seemed to have a small benefit in patients with ER-negative tumours (low or no ER). Use of tamoxifen reduced the risk of recurrent disease by 9% ($P = 0.03$) and the mortality risk by 6% (not statistically significant). However, the investigators were uncertain whether this represented a real benefit of tamoxifen in truly ER-negative women or only in women whose tumours would have had a low, but detectable level of ER by current methods.

Several years later, the same Early Breast Cancer Trialists' Collaborative Group published an updated overview of randomised trials on the effects of chemotherapy and hormonal therapy on long-term recurrence and survival after early breast cancer [1]. They analysed 12 trials including 15 017 women and compared the effect of 5 years of adjuvant tamoxifen use versus no hormonal treatment. This time the authors found that 1- to 2-year use of tamoxifen in ER-poor disease was associated with a nonsignificant 9% reduced risk of death from breast cancer, while 5-year use of adjuvant tamoxifen was associated with a nonsignificantly 4% increased risk of death from breast cancer. The authors stratified by PgR status (PgR-positive versus PgR-poor breast cancer) and observed that tamoxifen was associated with a 13% nonsignificantly increased risk of local recurrence and mortality in ER/PgR-negative disease.

This meta-analysis included one trial which specifically investigated the effect of tamoxifen in patients with ER-negative breast cancer [7]. In premenopausal women, survival of patients treated with chemotherapy and tamoxifen was significantly lower than that of patients treated with chemotherapy alone.

More recently, Hutchins et al. [8] investigated the impact of adjuvant chemotherapy with and without tamoxifen in node-negative high-risk breast cancer and found that the effect of tamoxifen was modified by the hormone receptor status. For hormone (ER and PgR) receptor-positive breast cancer patients, tamoxifen was beneficial, but for ER- and PgR-negative breast cancer patients, tamoxifen was deleterious (HR for disease-free survival 0.81, 95% CI 0.64–1.03).

In the German Adjuvant Breast Cancer Group trial IV D-93, postmenopausal patients with ER- and PgR-negative disease were randomly assigned to 5 years of tamoxifen versus no tamoxifen following chemotherapy. The risk of recurrence among patients in the tamoxifen group was increased by 13% (HR 1.13, 95% CI 0.87–1.48, $P = 0.34$) [9].

In a study from the International Breast Cancer Study Group Trial, premenopausal women with node-positive disease who

received chemotherapy were randomly assigned to receive further adjuvant tamoxifen during 5 years versus no additional treatment. Tamoxifen had a detrimental effect on disease-free survival in patients with ER-negative tumours compared with no tamoxifen (HR 2.10, 95% CI 1.03–4.29, $P = 0.04$) [10].

A pooled analysis of two British randomised trials, which included ER-negative node-positive and node-negative postmenopausal patients and ER-negative node-negative premenopausal patients, showed that 2 years of tamoxifen (versus no adjuvant treatment) was beneficial only in patients whose tumours expressed PgR [11].

In our study, tamoxifen did not have a detrimental effect in the small group of patients with PgR-positive disease, which is in accordance with previous studies [1, 11].

In addition to the growing evidence that the effect of tamoxifen could be deleterious on the prognosis of ER-negative tumours, there are also data suggesting that it could influence carcinogenesis of ER-negative tumours. In particular, Esserman et al. [12] hypothesised that the preventive use of tamoxifen in high-risk women decreases the risk of ER-positive breast cancer, but may actually increase the risk of ER-negative breast cancer.

To our knowledge, this is the first study assessing the effect of tamoxifen on patients with ER-negative breast cancer in a population-based setting. Clinical trials usually involve highly specialised physicians and patients are treated according to the standard protocols under relatively optimal conditions. Therefore, it is important to confirm results of clinical trials in daily care practice. However, since our study is not a randomised trial, patients receiving tamoxifen were by no means comparable with those not receiving tamoxifen. With propensity score analysis, we calculated for each patient the individual probability of having received tamoxifen, based on demographic, tumour, and treatment characteristics. In multivariate analysis, we adjusted for propensity scores, thus rendering comparable patients treated with versus without tamoxifen. Nevertheless, there maybe other factors associated with the prescription of tamoxifen for which we did not account. However, even though some residual confounding maybe present, it is unlikely that this could explain the doubled risk of death from breast cancer in ER-negative patients treated with tamoxifen. Also, other prognostic factors, like overexpression of HER-2 and presence of vascular/lymphatic invasion, were not available for the study period. Another limitation of our study was the lack of pathological review and updated centralised assessment of steroid receptors. In particular, the possibility of misclassification of ER-positive tumours into the ER-negative tumours exists [13]. Furthermore, the immunohistochemical assay used in our patients routinely assesses ER-α but not ER-β, the latter being positive in a nonnegligible proportion of ER-α-negative tumours. ER-β expression has been recently associated with tamoxifen response in ER-α-negative breast cancer [14]. Both these biases would rather dilute the increased mortality risk observed in ER-α-negative breast cancer. Finally, a recent study on quality of ER assessment concluded that ER assay results from pathological reports are reasonable alternative to central laboratory ER testing for population-based studies [15].

The effects of oestrogen and hormonal manipulation on cancer prevention, promotion, and growth are far from being completely understood. More than 20 years ago, Fisher et al. [7] postulated that if oestrogen acted only through ER, and if the effect of tamoxifen was only to block this pathway, there would hardly be any reason to believe that tamoxifen could have an adverse effect, particularly in women with ER-negative disease. Today, we know that tamoxifen also acts on growth factor signaling pathways, including tumour growth factor α and β, insulin-like growth factor-II, and epidermal growth factor receptors (EGFRs) [16, 17]. Also, the dual mechanism of tamoxifen is well established, as it acts both as ER antagonist and ER agonist [18]. Tamoxifen has partial agonist/antagonist activity through ER-α, but a pure antagonist effect through ER-β [19]. It has been recently shown *in vitro* that the agonist activity of tamoxifen on cell proliferation was strongly increased in cells expressing high level of both HER-2 (member of the EGFR family) and ER coactivator called amplified in breast cancer-1 (AIB1). This agonist activity of tamoxifen results in important tumour growth stimulation [20]. Both HER-2 receptor and AIB1 coactivator are more frequently expressed in ER-negative disease and associated with tamoxifen resistance [11, 21, 22]. Of note, ER-positive breast tumours with amplification of HER-2 apparently may not respond favourably to tamoxifen in an adjuvant setting [23–26].

To date, aromatase inhibitors are superior to tamoxifen as adjuvant treatment of postmenopausal ER-positive breast cancer and their efficacy in a preventing setting is under study [27–30]. Since aromatase inhibitors are increasingly being favoured to tamoxifen, one could expect the number of ER-negative breast cancer patients treated with aromatase inhibitors to increase. However, the impact of aromatase inhibitors on the outcome of ER-negative disease is still unknown. This study on tamoxifen can make clinicians aware of the putative risk of overindication of antioestrogen or antiaromatase treatment. Also, a better understanding of the biological mechanism behind the detrimental effect of tamoxifen on ER- and PgR-negative breast cancer could help to better determine factors linked to growth of breast tumour cells.

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