LUND UNIVERSITY

No association found between CYP2D6 genotype and early breast cancer events in tamoxifen-treated patients.

Markkula, Andrea; Hjertberg, Maria; Rose, Carsten; Ingvar, Christian; Jernström, Helena

Published in:
Acta Oncologica

DOI:
10.3109/0284186X.2013.840739

2014

Link to publication

Citation for published version (APA):
Markkula, A., Hjertberg, M., Rose, C., Ingvar, C., & Jernström, H. (2014). No association found between CYP2D6 genotype and early breast cancer events in tamoxifen-treated patients. *Acta Oncologica*, *53*(2), 195-200. https://doi.org/10.3109/0284186X.2013.840739

Total number of authors:
5

General rights
Unless other specific re-use rights are stated the following general rights apply:
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.
• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: https://creativecommons.org/licenses/

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

No association found between *CYP2D6* genotype and early breast cancer events in tamoxifen-treated patients

Andrea Markkula*[1], Maria Hjertberg*[1,2], Carsten Rose[3], Christian Ingvar[4], Helena Jernström[1]**

1) Division of Oncology, Department of Clinical Sciences, Lund, Lund University, Sweden
2) Vrinnevi Hospital, Norrköping, Sweden
3) CREATE Health and Department of Immunotechnology, Lund University, Medicon Village, Building 406, Lund, Sweden
4) Division of Surgery, Department of Clinical Sciences, Lund, Lund University and Department of Surgery, Skåne University Hospital, Lund, Sweden

*) Shared first authorship

**) Address for correspondence and reprints:

Helena Jernström, Division of Oncology, Department of Clinical Sciences, Lund, Lund University, Barngatan 2B, SE- 221 85 Lund, Sweden

Telephone: + 46 – 46 – 17 76 19   Fax: + 46 – 46 – 14 73 27

E-mail: helena.jernstrom@med.lu.se

Running title: *CYP2D6* genotype in tamoxifen-treated breast cancer patients

Key Words: *CYP2D6* genotype, CYP2D6 inhibitor, tamoxifen, breast cancer, drug interactions

Abstract

Background. CYP2D6 is considered the key enzyme in tamoxifen metabolism. Several studies have investigated the relationship between the *CYP2D6* genotype and tamoxifen treatment outcome, with discrepant results. CYP2D6 inhibitor use, aromatase inhibitor use, and chemotherapy may account for some of the discrepancies. We examined the association between *CYP2D6* genotype and early breast cancer events in tamoxifen-treated breast cancer patients, in relation to CYP2D6 inhibitor use, aromatase inhibitor use, and chemotherapy. *Materials and Methods* Pre- and postoperative questionnaires on lifestyle and concomitant medications were completed by 634 primary breast cancer patients between 2002 and 2008, among whom 333 patients had ER-positive tumors and received tamoxifen. *CYP2D6**3, *4, *6, *10 and *41 were genotyped. Information on clinical data, breast cancer events, and tumor characteristics was obtained from patients' charts, population registries, the Regional Tumor Registry, and pathology reports. *Results* Median follow-up was 4.9 years. Neither poor metabolizers (adjusted HR 0.50; 95% CI 0.07-3.82) nor intermediate metabolizers (adjusted HR 1.00; 95% CI 0.47-2.11) had an increased risk of early breast cancer events when compared with extensive metabolizers. CYP2D6 activity score (taking into account genotype and CYP2D6 inhibitor use) was not associated with early breast cancer events (LogRank, P_{trend}=0.44). *Conclusions CYP2D6* genotype was not associated with tamoxifen treatment outcome, even when CYP2D6 inhibitor use, aromatase inhibitor use, or chemotherapy was taken into account. *CYP2D6* genotype may be of minor importance for tamoxifen-treated patients in Scandinavia.

Introduction

Breast cancer is the most common cancer among women (1). Despite an overall 5-year relative survival rate of almost 90% for breast cancer patients in Sweden (2), it remains the primary cause of cancer death among women world-wide (1). Though tamoxifen is an effective anti-estrogen treatment for breast cancer patients with estrogen receptor (ER) positive tumors, around 30% of tamoxifen-treated women relapse despite five-years of tamoxifen treatment (3). Markers of tamoxifen treatment-resistance could allow for more personalized treatment, improving the prognosis for many women (4).

The cytochrome P2D6 (CYP2D6) enzyme is considered the key enzyme in transforming tamoxifen into one of its most abundant active metabolites, endoxifen (5). Patients with two non-functional *CYP2D6* alleles have lower plasma concentrations of endoxifen than patients with functioning alleles (6, 7). Hence, it has been proposed that *CYP2D6* genotype may be associated with recurrence among tamoxifen-treated breast cancer patients. Several studies have investigated the relationship between the gene encoding cytochrome P450 2D6 (CYP2D6) and tamoxifen treatment outcome, with widely heterogeneous results (4, 5, 8-10).

It has been suggested that CYP2D6 inhibitor use, aromatase inhibitor use and chemotherapy may account for some of these discrepancies (5). Therefore, we examined the association between *CYP2D6* genotype and early breast cancer events in tamoxifen-treated breast cancer patients, in relation to CYP2D6 inhibitor use, aromatase inhibitor use, and chemotherapy in a prospective cohort of tamoxifen-treated breast cancer patients in Sweden.

Materials and Methods

The design of the study has been described in detail elsewhere (11). In brief, preoperative questionnaires on lifestyle and concomitant medications were completed by 634 breast cancer patients in Sweden between 2002 and 2008, among whom 333 patients had ER-positive tumors and received tamoxifen (*Figure 1*). Follow-up questionnaires were completed up to nine years postoperatively. Information on clinical data, breast cancer events, and tumor characteristics was obtained from patients' charts, population registries, the Regional Tumor Registry, and pathology reports. ER and progesterone receptor (PR) status were obtained from each patient's pathology report. ER and PR status were determined by immunohistochemistry using the Dako LSAB™ kit system (Dako, Glostrup, Denmark) and the antibodies M7047 (ER) and M3569 (PR) (Dako, Glostrup, Denmark). Tumors with more than 10% positive nuclear staining were considered ER-positive or PR-positive (12). All tumors were analyzed at the Department of Pathology at Skåne University Hospital in Lund. Written informed consent was obtained from all patients. The study was approved by the Ethics Committee of the Lund University (Dnr 75-02 and 37-08).

*CYP2D6**3,*4,*6,*10, and *41 were analyzed using Genomic deoxyribonucleic acid (DNA) extracted from the leukocyte portion of whole blood. The SNPs were genotyped with custom TaqMan® assay (*CYP2D6**3), TaqMan® Drug Metabolism Genotyping Assays (*CYP2D6**4,*6,*10), and iPLEX reagents (*CYP2D6**41) at Region Skåne Competence Centre (RSKC Malmö), Malmö University Hospital, Malmö, Sweden, using methods previously described (11). Over 10% of the samples were run in duplicate with a concordance of 100%. CYP2D6 inhibiting drugs were classified in accordance with Flockhart *et al.* (13). Only the use of the strongest inhibitor was considered. Patients with ER-negative tumors who had received tamoxifen treatment were excluded. Each patient received a CYP2D6 genotype activity score and a CYP2D6 activity score (14, 15), and was then categorized as poor (PM), intermediate (IM), and extensive metabolizer (EM) (activity scores 0, 0.5-1.5, 2, respectively) (14).

Breast cancer-free survival was calculated from the pre-operative visit to the last follow-up visit or a non-breast cancer related death, or to a diagnosis of a breast cancer event prior to Jan 1, 2012. Survival analyses were performed using Kaplan-Meier and Cox regression models. Patients who had received pre-operative treatment (n=17), patients with carcinoma *in situ* (n=1), patients who lacked *CYP2D6* genotype information (n=7), and patients who both received pre-operative treatment and lacked *CYP2D6* genotype information (n=1) were excluded from the survival analyses. Survival in relation to combined tamoxifen and CYP2D6 inhibitor use was assessed though landmark analyses (landmark set as treatment-initiation of tamoxifen and CYP2D6 inhibitors within nine months of study entry). A *P*-value of <0.05 was taken to be significant. All *P*-values were two-sided.

Results

Patient characteristics for all 634 patients, and for the 333 tamoxifen-treated patients with ER-positive tumors, are presented in *Table I.* The median follow-up was 4.9 years. Frequency of the *CYP2D6* genotypes, with and without stratification according to CYP2D6 genotype activity score and CYP2D6 activity score, is presented in *Table II.* Among the 307 tamoxifen-treated patients with invasive ER-positive tumors and *CYP2D6* genotype information, 31 breast cancer events were observed. There was no association between early breast cancer events and *CYP2D6* genotype metabolizer category (*Figure 2a)*. Excluding chemotherapy treated patients (*Figure 2b*) and patients who had received either chemotherapy and/or aromatase inhibitors (*Figure 2c)* generated similar results. Neither PM, nor IM were associated with early breast cancer events in a multivariable model compared to EM (adjusted Hazard Ratio (HR_{PM}) 0.50; 95% CI 0.07–3.82; *P*=0.50), (adjusted (HR_{IM}) 1.00; 95% CI 0.47–2.11; *P*=1.00), adjusting for invasive tumor size (>20mm, or muscular or skin involvement), any axillary lymph node involvement, age at diagnosis, and histological grade III.

Among the 301 genotyped tamoxifen-treated patients with invasive ER-positive tumors who had started tamoxifen-treatment within nine months of study entry, 11 also reported use of strong CYP2D6 inhibitors, and 11 reported use of intermediate CYP2D6 inhibitors within nine months of study entry. Six of the tamoxifen-treated patients commenced tamoxifen after nine months, none of which had a breast cancer event. Two patients commenced strong CYP2D6 inhibitors use, and three patients commenced intermediate CYP2D6 inhibitors use after nine months but before five years past study entry; none of these five patients had a breast cancer event.

In the landmark analyses, CYP2D6 activity score (which takes both genotype and CYP2D6 inhibitor use into account) was not associated with early breast cancer events in the univariable (LogRank, P_{trend}=0.44) or in the multivariable model. Tamoxifen treatment-duration was not associated with *CYP2D6* genotype, age, aromatase inhibitor or chemotherapy treatment.

Discussion

In this prospective cohort of tamoxifen-treated breast cancer patients in Sweden, there was no evidence that poor CYP2D6 metabolizers had an impaired tamoxifen treatment outcome. In accordance with several previous studies of breast cancer patients in Scandinavia (10, 16, 17), neither CYP2D6 genotype nor CYP2D6 inhibitor use was associated with early events.

The present study has several strengths. It is population-based (11) and uses Swedish population registries for optimal follow-up. All polymorphisms were analyzed from germline DNA, and multiple polymorphisms were included. Also, blood for genotyping was collected at study entry, and CYP2D6 inhibitor use was collected for the entire cohort of 634 patients. A total number of 38 patients (6%) used either strong or intermediate CYP2D6 inhibitors, which is comparable to a previous publication (18). The main limitation of the study is the sample size. The number of tamoxifen monotherapy treated patients was relatively small, but the lack of association between CYP2D6 genotype and disease-free survival seen in the present study has also been reported from previous studies conducted in larger cohorts (5, 19).

CYP2D6 inhibitor use, chemotherapy, or aromatase inhibitor therapy did not account for the absence of an association between *CYP2D6* genotype and tamoxifen treatment outcome in this study. Many antidepressants are metabolized by enzymes other than CYP2D6 that are involved in tamoxifen metabolism, such as CYP2C19 (20) and CYP2C8/9 (6, 21). This could in part explain the association between antidepressant use and breast cancer free survival found in previous studies (6, 22). Other genetic variants (10, 23, 24), and lifestyle factors such as a high coffee intake, (25) have been associated with survival among tamoxifen-treated breast cancer patients in Sweden. CYP2D6 may be of minor importance for prediction of tamoxifen response in Scandinavia (9, 10, 16, 17).

Acknowledgements

We wish to thank our research nurses: Anette Ahlin Gullers, Monika Meszaros, Maj-Britt Hedenblad, Karin Henriksson, Anette Möller, and Linda Ågren. We thank Sol-Britt Olsson, Nils-Gunnar Lundin, and Kristina Lövgren for taking care of blood samples. We also wish to thank Erika Bågeman, Maria Simonsson, and Maria Henningson for taking care of blood samples and data entry, and Dr Eric Dryver for proofreading.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. This work was supported by grants from The Swedish Cancer Society CAN 2011/497, the Medical Research Council K2012-54X-22027-01-3 (PI H Jernström), the Medical Faculty at Lund University, the Mrs. Berta Kamprad Foundation, the Gunnar Nilsson Foundation, the Swedish Breast Cancer Group (BRO), the South Swedish Health Care Region (Region Skåne ALF), Konung Gustaf V:s Jubileumsfond, and the Lund Hospital Fund.

References

1. Youlden DR, Cramb SM, Dunn NA, Muller JM, Pyke CM, Baade PD. The descriptive epidemiology of female breast cancer: an international comparison of screening, incidence, survival and mortality. Cancer epidemiology. 2012;36(3):237-48. Epub 2012/03/31.
2. National Board of Health and Welfare. Cancer i Siffror 2009 (Information about cancer incidence and survival in Sweden). 2009. Available from: **http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/8348/2009-126-127_2009126127.pdf.**
3. Early Breast Cancer Trialists' Collaborative Group E. 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(9472):1687-717.
4. Lash TL, Lien EA, Sorensen HT, Hamilton-Dutoit S. Genotype-guided tamoxifen therapy: time to pause for reflection? Lancet Oncol. 2009;10(8):825-33. Epub 2009/08/04.
5. Hertz DL, McLeod HL, Irvin WJ, Jr. Tamoxifen and CYP2D6: a contradiction of data. Oncologist. 2012;17(5):620-30. Epub 2012/04/26.
6. Jin Y, Desta Z, Stearns V, Ward B, Ho H, Lee KH, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J Natl Cancer Inst. 2005;97(1):30-9.
7. Borges S, Desta Z, Li L, Skaar TC, Ward BA, Nguyen A, et al. Quantitative effect of CYP2D6 genotype and inhibitors on tamoxifen metabolism: implication for optimization of breast cancer treatment. Clin Pharmacol Ther. 2006;80(1):61-74.
8. Margolin S, Lindh JD, Thoren L, Xie H, Koukel L, Dahl ML, et al. CYP2D6 and adjuvant tamoxifen: possible differences of outcome in pre- and post-menopausal patients. Pharmacogenomics. 2013;14(6):613-22. Epub 2013/04/11.
9. Wegman P, Vainikka L, Stal O, Nordenskjold B, Skoog L, Rutqvist LE, et al. Genotype of metabolic enzymes and the benefit of tamoxifen in postmenopausal breast cancer patients. Breast Cancer Res. 2005;7(3):R284-90. Epub 2005/07/01.
10. Wegman P, Elingarami S, Carstensen J, Stal O, Nordenskjold B, Wingren S. Genetic variants of CYP3A5, CYP2D6, SULT1A1, UGT2B15 and tamoxifen response in postmenopausal patients with breast cancer. Breast Cancer Res. 2007;9(1):R7.
11. Lundin KB, Henningson M, Hietala M, Ingvar C, Rose C, Jernstrom H. Androgen receptor genotypes predict response to endocrine treatment in breast cancer patients. Br J Cancer. 2011;105(11):1676-83. Epub 2011/10/29.
12. Bågeman E, Ingvar C, Rose C, Jernström H. Coffee consumption and CYP1A2*1F genotype modify age at breast cancer diagnosis and estrogen receptor status. Cancer Epidemiol Biomarkers Prev. 2008;17(4):895-901. Epub 2008/04/10.
13. Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table.: Indiana University School of Medicine (2007); [updated 2012-01-25; cited 2013 2013-04-20]; Version 5.0 of the table released 2009-01-12.:[Available from: **http://medicine.iupui.edu/clinpharm/ddis/table.aspx.**
14. Blake MJ, Gaedigk A, Pearce RE, Bomgaars LR, Christensen ML, Stowe C, et al. Ontogeny of dextromethorphan O- and N-demethylation in the first year of life. Clin Pharmacol Ther. 2007;81(4):510-6. Epub 2007/02/16.
15. Rae JM, Sikora MJ, Henry NL, Li L, Kim S, Oesterreich S, et al. Cytochrome P450 2D6 activity predicts discontinuation of tamoxifen therapy in breast cancer patients. Pharmacogenomics J. 2009;9(4):258-64. Epub 2009/05/08.
16. Lash TL, Cronin-Fenton D, Ahern TP, Rosenberg CL, Lunetta KL, Silliman RA, et al. CYP2D6 inhibition and breast cancer recurrence in a population-based study in Denmark. J Natl Cancer Inst. 2011;103(6):489-500. Epub 2011/02/18.
17. Ahern TP, Pedersen L, Cronin-Fenton DP, Sorensen HT, Lash TL. No increase in breast cancer recurrence with concurrent use of tamoxifen and some CYP2D6-inhibiting medications. Cancer Epidemiol Biomarkers Prev. 2009;18(9):2562-4. Epub 2009/08/20.

18. Goetz MP, Knox SK, Suman VJ, Rae JM, Safgren SL, Ames MM, et al. The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. Breast Cancer Res Treat. 2007;101(1):113-21. Epub 2006/11/23.
19. Regan MM, Leyland-Jones B, Bouzyk M, Pagani O, Tang W, Kammler R, et al. CYP2D6 genotype and tamoxifen response in postmenopausal women with endocrine-responsive breast cancer: the breast international group 1-98 trial. J Natl Cancer Inst. 2012;104(6):441-51. Epub 2012/03/08.
20. Ingelman-Sundberg M, Sim SC, Gomez A, Rodriguez-Antona C. Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoepigenetic and clinical aspects. Pharmacol Ther. 2007;116(3):496-526. Epub 2007/11/16.
21. Walsky RL, Gaman EA, Obach RS. Examination of 209 drugs for inhibition of cytochrome P450 2C8. J Clin Pharmacol. 2005;45(1):68-78. Epub 2004/12/17.
22. Desmarais JE, Looper KJ. Interactions between tamoxifen and antidepressants via cytochrome P450 2D6. The Journal of clinical psychiatry. 2009;70(12):1688-97. Epub 2010/02/10.
23. Schroth W, Antoniadou L, Fritz P, Schwab M, Muerdter T, Zanger UM, et al. Breast cancer treatment outcome with adjuvant tamoxifen relative to patient CYP2D6 and CYP2C19 genotypes. J Clin Oncol. 2007;25(33):5187-93. Epub 2007/11/21.
24. Jernström H, Bågeman E, Rose C, Jönsson P-E, Ingvar C. CYP2C8 and CYP2C9 polymorphisms in relation to tumor characteristics and early breast cancer related events among 652 breast cancer patients. British Journal of Cancer. 2009;101(11):1817-23.
25. Simonsson M, Söderlind V, Henningson M, Hjertberg M, Rose C, Ingvar C, et al. Coffee prevents early events in tamoxifen-treated breast cancer patients and modulates hormone receptor status. Cancer Causes Control. 2013;24(5):929-40. Epub 2013/02/16.

Figure 1

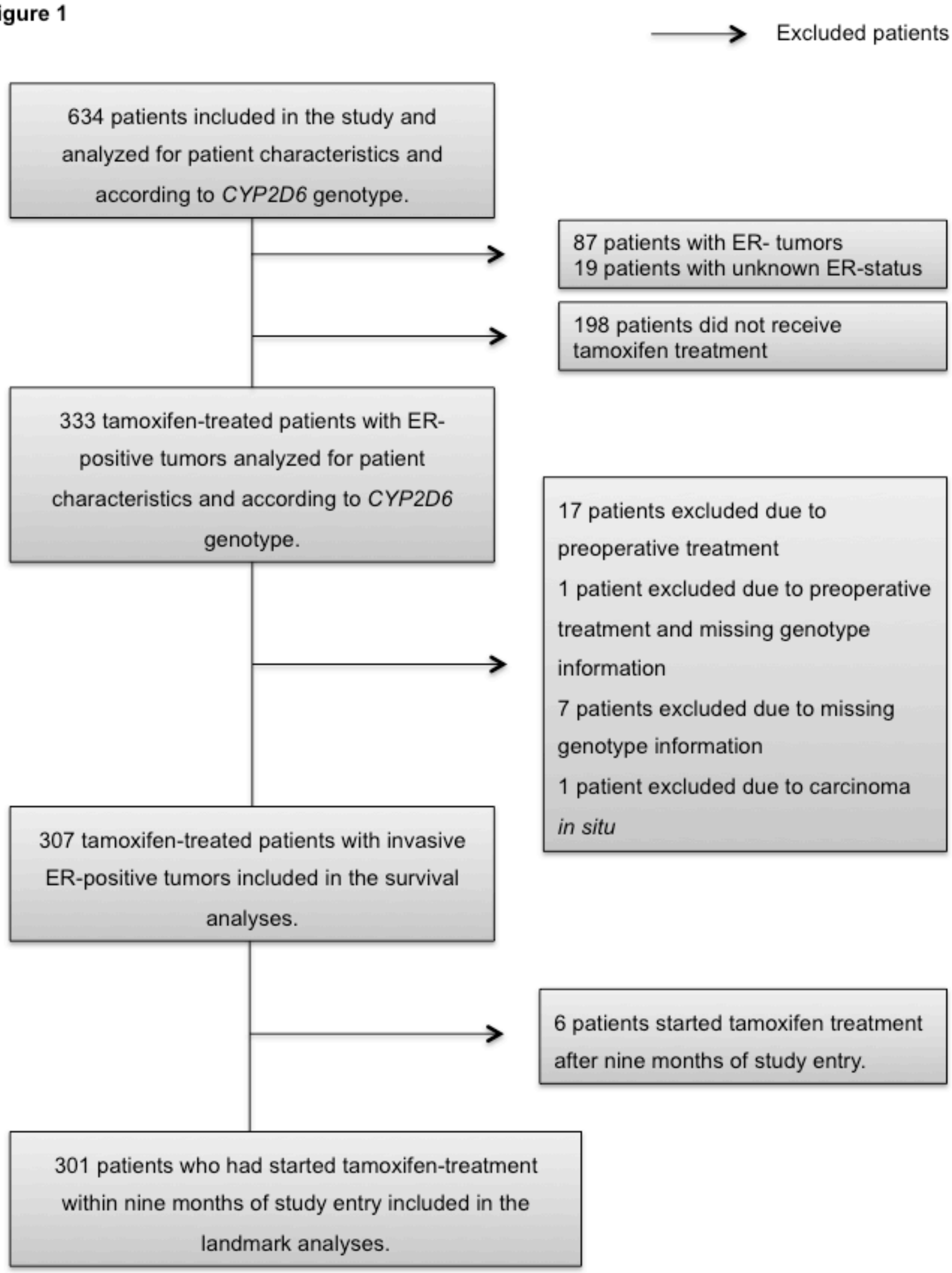

Figure 1. Flow chart of the selection process of patients.

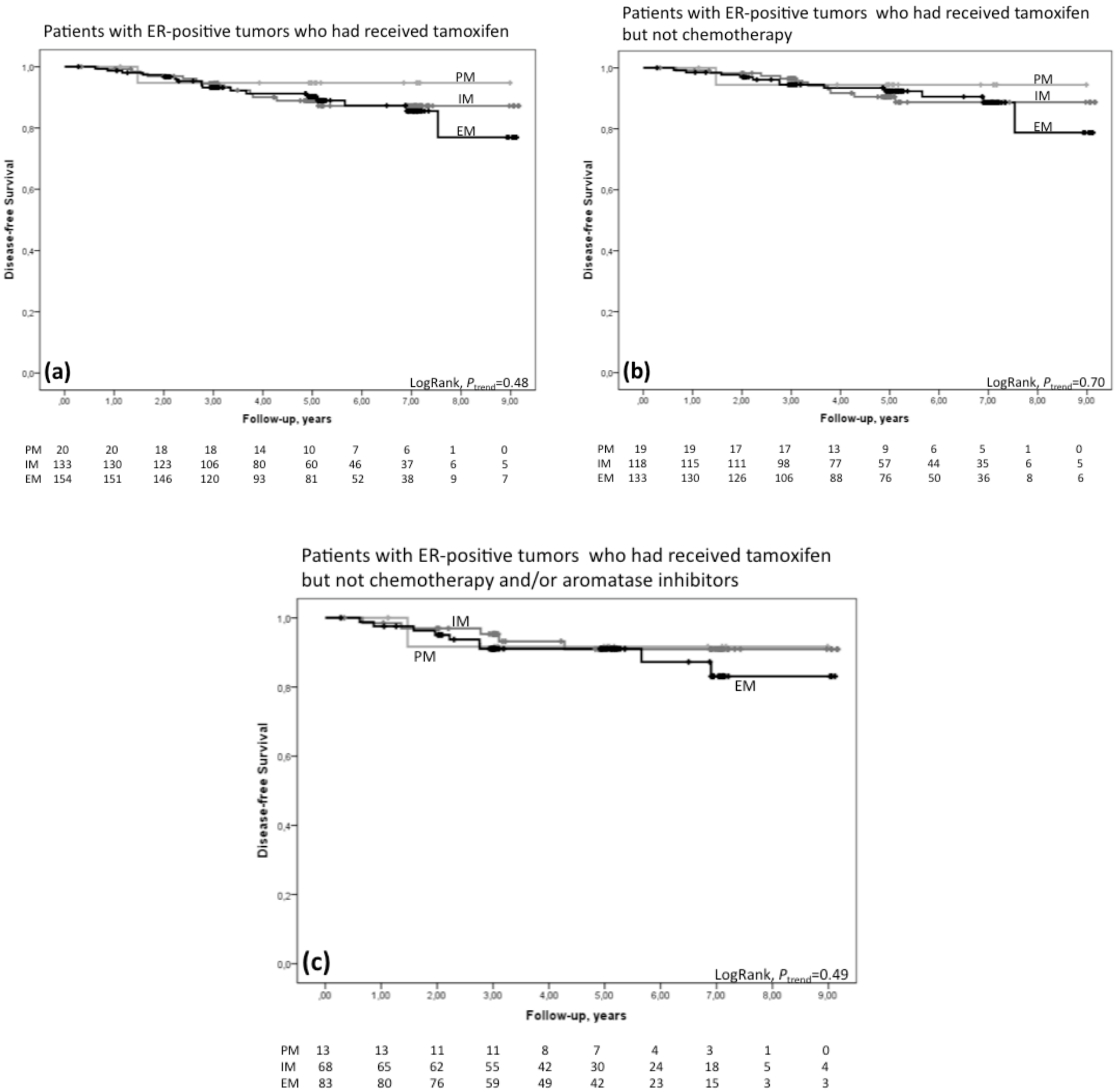

Figure 2. Kaplan-Meier estimate of breast cancer free survival in relation to *CYP2D6* genotype activity score. **a)** among tamoxifen-treated patients with invasive ER-positive tumors (LogRank, P_{trend}=0.48). Adjusted HR_{PM} (0.50; 95% CI 0.07–3.82; P=0.50) and adjusted HR_{IM} (1.00; 95% CI 0.47–2.11; P=1.00) compared with EMs.**b)** among tamoxifen-treated patients with invasive ER-positive tumors who had not received chemotherapy (LogRank, P_{trend}=0.70). **c)** among tamoxifen-treated patients with invasive ER-positive tumors who had not received chemotherapy and/or aromatase inhibitors (LogRank, P_{trend}=0.49).

Table I. Patient characteristics for all 634 patients, and for the 333 tamoxifen-treated patients with ER-positive tumors (in gray).

	All patients Median (IQR) or %		Tamoxifen treated patients Median (IQR) or %	
N=	634	Missing	333	Missing
Age at diagnosis. yrs	59.6 (51.1-66.1)	-	59.3 (50.7-65.3)	-
Weight. kgs	68 (61-76)	2	68 (62-76)	2
Height m	1.66 (1.62-1.70)	1	1.66 (1.62-1.70)	1
BMI, kgs/m²	24.6 (22.3-27.8)	3	24.5 (22.4-27.4)	3
Waist-Hip Ratio	0.84 (0.78-0.89)	4	0.84 (0.78-0.89)	2
Age at menarche, yrs	13 (12-14)	5	13 (12-14)	3
Parous, %	84.7	-	83.5	-
Smoker at baseline*, %	21.3	-	19.5	-
Ever use of HRT, %	45.3	1	45.5	1
Antidepressant use at baseline, %	10.7	-	10.8	-
Strong CYP2D6-inhibitor use**, %	2.7	1	3.9	-
Intermediate CYP2D6-inhibitor use**, %	3.3	1	3.3	-
Ever received chemotherapy, %	21.9	-	15.6	-
Ever received aromatase inhibitors, %	33.6	-	42.0	-

*Regular smoker or party smoker at baseline

**Use of CYP2D6 inhibitors within landmark set at nine months of study entry

Table II. Frequency of the CYP2D6 genotypes in all patients (n=634), and for the 333 tamoxifen-treated patients with ER-positive tumors (in gray) with and without stratification according to CYP2D6 genotype activity score and CYP2D6 activity score. CYP2D6 genotype was missing for 18 of the 634 patients.

CYP2D6 genotypes in the study population (n=634)	Number of patients with the *CYP2D6* genotypes (%)	CYP2D6 genotype activity score based on genotype only[1]				*CYP2D6* genotypes in the tamoxifen treated study population (n=333)	Number of tamoxifen treated patients with the *CYP2D6* genotypes (%)	CYP2D6 genotype activity score among tamoxifen treated patients based on genotype only[1]			
*1/*1	299 (47.2)	0	39 (6.2)	PM	6.3%	*1/*1	164 (49.2)	0	22 (6.6)	PM	6.6%
*1/*4	159 (25.1)	0.5	26 (4.1)			*1/*4	84 (25.2)	0.5	12 (3.6)		
*1/*41	67 (10.6)	1	180 (28.4)	IM	43.8%	*1/*41	29 (8.7)	1	95 (28.5)	IM	41.7%
*4/*4	28 (4.4)	1.5	72 (11.4)			*4/*4	16 (4.8)	1.5	32 (9.6)		
*4/*41	14 (2.2)	2	299 (47.2)	EM	47.2%	*4/*41	7 (2.1)	2	164 (49.2)	EM	49.2%
*1/*3	12 (1.9)					*1/*3	4 (1.2)				
*4/*10	6 (0.9)	Missing	18 (2.8)			*4/*10	4 (1.2)	Missing	8 (2.4)		
*3/*4	6 (0.9)					*3/*4	5 (1.5)				
*3/*41	5 (0.8)	CYP2D6 activity score based on genotype and the use of CYP2D6 inhibitors[2]				*3/*41	0	CYP2D6 activity score among tamoxifen treated patients based on genotype and the use of CYP2D6 inhibitors[2]			
*1/*6	5 (0.8)					*1/*6	4 (1.2)				
*1/*10	5 (0.8)	0	63 (9.9)	PM	9.9%	*1/*10	3 (0.9)	0	39 (11.7)	PM	11.7%
*4/*6	4 (0.6)	0.5	26 (4.1)			*4/*6	1 (0.3)	0.5	12 (3.6)		
*10/*10	2 (0.3)	1	181 (28.5)	IM	43.7%	*10/*10	1 (0.3)	1	94 (28.2)	IM	40.8%
*10/*41	2 (0.3)	1.5	70 (11.0)			*10/*41	2 (0.6)	1.5	30 (9.0)		
*6/*6	1 (0.2)	2	275 (43.4)	EM	43.4%	*6/*6	0	2	150 (45.0)	EM	45.0%
*6/*41	1 (0.2)					*6/*41	1 (0.3)				
Missing	18 (2.8)	Missing	19 (3.0)			Missing	8 (2.4)	Missing	8 (2.4)		

1) Points assigned per allele: 1 point for major alleles (*1), 0.5 points for variant alleles (*10, 41*), and 0 points for null alleles (*3, *4, *6) according to Blake et al.

2) Points deducted from the CYP2D6 genotype activity score according to Rae *et al*: -2 points for the use of strong inhibitors and 1 point for the use of moderate CYP2D6 inhibitors during at least one study visit within landmark of nine months after baseline. Zero points were deducted for the use of weak CYP2D6 inhibitors. If the patient reported use of several CYP2D6 inhibitors, only the use of the strongest inhibitor was considered.