

Letter to the Editors

CYP2D6 genotyping and tamoxifen in the treatment of post-menopausal breast cancer

Per Damkier

Clinical Pharmacology, Department of Clinical Chemistry and Pharmacology, Odense University Hospital, Denmark

I appreciate the review on the ongoing controversial subject of tamoxifen treatment of post-menopausal breast cancer and CYP2D6 genotyping by Brauch & Schwab [1]. However, I am somewhat surprised that on at least two central issues the authors do not discuss original findings that fail to support their position.

- a) While I do not claim that there is *no* issue with tumour-line derived genotyping as opposed to germ-line genotyping, at least two different studies have been published that suggest a high degree of concordance [2, 3]. I believe such data and positions warrant discussion in the context of the present review.
- b) On the issue of concomitant treatment with tamoxifen and CYP2D6 inhibitors for support of the biological rationale as suggested by the authors, one study demonstrated an effect of paroxetine, but an interaction effect could not be demonstrated for fluoxetine, a very potent and effective inhibitor of CYP2D6 [4]. Another study did not confirm an interaction between CYP2D6 inhibitors and breast cancer recurrence in tamoxifen treated patients [5].

Additionally, despite the determined opinion of the authors on the Hardy–Weinberg equilibrium (HWE) issue as related to various clinical sets of data, this may not be as clear as they would like it to be [6, 7]. In fact, the publication highlighted by the authors for credibility on this matter [8], itself contains a sample violating the HWE [9].

Despite the authors' introductory acknowledgement of an ongoing controversy, the uninitiated reader is left with the impression that the *pro et contra* of CYP2D6 genotyping prior to tamoxifen treatment in postmenopausal breast cancer, is now settled once and for all in favour of the *pro*. The conclusion of the meta-analysis recently published by the International Tamoxifen Pharmacogenomics Consortium [10], to which the two authors themselves belong, appears more balanced.

Competing Interests

The author has completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request) and declares no support from any organization for the submitted work.

REFERENCES

- 1 Brauch H, Schwab M. Prediction of tamoxifen outcome by genetic variation of CYP2D6 in post-menopausal women with early breast cancer. *Br J Clin Pharmacol* 2014; 77: 695–703.
- 2 Rae JM, Regan MM, Thibert JN, Gersch C, Thomas D, Leyland-Jones B, Viale G, Pusztai L, Hayes DF, Skaar T, Van Poznak C. Concordance between CYP2D6 genotypes obtained from tumor-derived and germ-line DNA. *J Natl Cancer Inst* 2013; 105: 1332–4.
- 3 Ahern TP, Christensen M, Cronin-Fenton DP, Lunetta KL, Rosenberg CL, Sørensen HT, Lash TL, Hamilton-Dutoit S. Concordance of metabolic enzyme genotypes assayed from paraffin-embedded, formalin-fixed breast tumors and normal lymphatic tissue. *Clin Epidemiol* 2012; 2: 241–6.
- 4 Kelly CM, Juurlink DN, Gomes T, Duong-Hua M, Pritchard KI, Austin PC, Paszat LF. Selective serotonin reuptake inhibitors and breast cancer mortality in patients receiving tamoxifen: a population based cohort study. *BMJ* 2010; 340: c693.
- 5 Lash TL, Cronin-Fenton D, Ahern TP, Rosenberg CL, Lunetta KL, Silliman RA, Garne JP, Sørensen HT, Hellberg Y, Christensen M, Pedersen L, Hamilton-Dutoit S. CYP2D6 inhibition and breast cancer recurrence in a population-based study in Denmark. *J Natl Cancer Inst* 2011; 103: 489–500.
- 6 Berry B. CYP2D6 genotyping and the use of tamoxifen in breast cancer. *J Natl Cancer Inst* 2013; 105: 1267–9.
- 7 Rae JM. CYP2D6 genotype should not be used to determine endocrine therapy in postmenopausal breast cancer patients. *Clin Pharmacol Ther* 2013; 94: 183–5.

8 Schroth W, Goetz MP, Hamann U, Fasching PA, Schmidt M, Winter S, Fritz P, Simon W, Suman VJ, Ames MM, Safgren SL, Kuffel MJ, Ulmer HU, Boländer J, Strick R, Beckmann MW, Koelbl H, Weinshilboum RM, Ingle JN, Eichelbaum M, Schwab M, Brauch H. Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. *JAMA* 2009; 302: 1429–36.

9 Goetz MP, Rae JM, Suman VJ, Safgren SL, Ames MM, Visscher DW, Reynolds C, Couch FJ, Lingle WL, Flockhart DA, Desta Z, Perez EA, Ingle JN. Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. *J Clin Oncol* 2005; 23: 9312–8.

10 Province MA, Goetz MP, Brauch H, Flockhart DA, Hebert JM, Whaley R, Suman VJ, Schroth W, Winter S, Zembutsu H, Mushiroda T, Newman WG, Michael Lee MT, Ambrosone CB, Beckmann MW, Choi JY, Dieudonné AS, Fasching PA, Ferraldeschi R, Gong L, Haschke-Becher E, Howell A, Jordan LB, Hamann U, Kiyotani K, Krippel P, Lambrechts D, Latif A, Langsenlehner U, Lorzio W, Neven P, Nguyen AT, Park BW, Purdie CA, Quinlan P, Renner W, Schmidt M, Schwab M, Shin JG, Stingl JC, Wegman P, Wingren S, Wu AH, Ziv E, Zirpoli G,

Thompson AM, Jordan VC, Nakamura Y, Altman RB, Ames MM, Weinshilboum RM, Eichelbaum M, Ingle JN, Klein TE. CYP2D6 genotype and adjuvant tamoxifen tamoxifen. Meta-analysis of heterogeneous study populations. *Clin Pharmacol Ther* 2013; 95: 216–27.

RECEIVED

27 September 2013

ACCEPTED

31 October 2013

ACCEPTED ARTICLE PUBLISHED ONLINE

22 January 2014

CORRESPONDENCE

Dr Per Damkier MD, PhD, Department of Clinical Chemistry and Pharmacology, Odense University Hospital, DK-5000 Odense C, Denmark.

Tel.: +45 6550 3790

E-mail: pdamkier@health.sdu.dk