Meta-analysis of CYP2D6 impairment and tamoxifen failure

Background

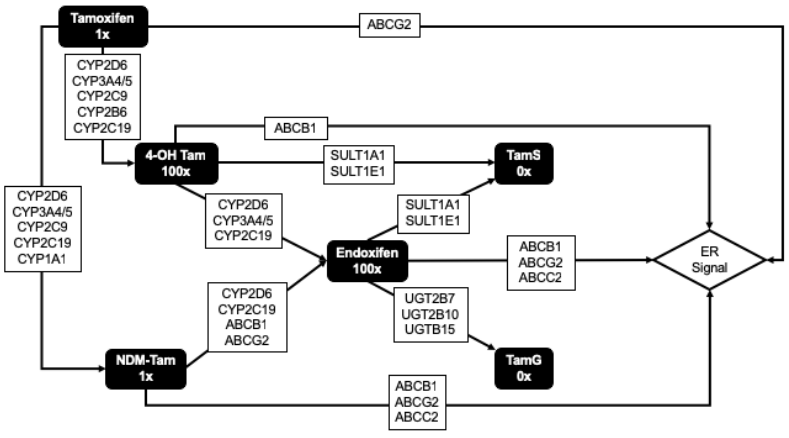
Tamoxifen resistance in breast cancer

About three quarters of breast tumors express the estrogen receptor (ER).[1] When estrogens bind to ER in breast cancer cells the receptor complex interacts with the genome to promote transcription of genes that drive cell survival and proliferation.[2] The drug tamoxifen and its metabolites compete with estrogens for binding to ER, but instead neutralize the receptor, preventing breast cancer cell growth.[3] Five years of tamoxifen treatment approximately halves the risk of breast cancer recurrence in patients with ER-positive breast tumors.[4] Unfortunately, response to tamoxifen therapy varies between women with otherwise similar prognostic profiles, and some tamoxifen-treated women experience a recurrence of their breast cancer. This variation in response suggests that patient characteristics other than tumor ER expression can also influence drug response.

Tamoxifen metabolic pathway

Tamoxifen has relatively low affinity for the ER in its administered form.[5] Its pharmacologic activity is potentiated by *in vivo* production of higher-affinity metabolites.[5,6] Pathways of tamoxifen metabolism and transport are summarized in Figure 1. In the figure, tamoxifen and its metabolites appear as black boxes, with arrows denoting transitions from one compound to another. Boxes overlying the arrows show the metabolic enzymes and transporter proteins that contribute to each transition. Effects of these tamoxifen metabolites are ultimately mediated by their actions at the ER, which is denoted by the diamond shape at the right side of the figure.

The metabolites 4-hydroxy tamoxifen (4-OH Tam) and 4-hydroxy-N-desmethyl tamoxifen (endoxifen) bind ER with about 100-fold higher affinity than native tamoxifen.[7] The phase I cytochrome P450 enzymes (CYP1A1, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) catalyze the oxidation and demethylation reactions that form these metabolites.[8] Sulfonated and glucuronidated metabolites (Tam-S and Tam-G) are formed by phase II reactions catalyzed by sulfotransferases (SULT1A1 and SULT1E1) and UDP-glucuronosyl transferases (UGT2B15 and UGT2B7), respectively.[9–11] Tam-S and Tam-G have little or no ER binding affinity and are rapidly eliminated.[12,13]



Genetic variation in the tamoxifen pathway

The genes encoding tamoxifen metabolic enzymes harbor functional polymorphisms, which may affect formation and clearance of active metabolites and access to tumor ER—and hence patient response to therapy. These relatively common germline genetic variants are promising candidates for predicting patient response before initiation of tamoxifen therapy.

Goal of the meta-analysis

Much of the research on this topic has focused on high-prevalence variants in the CYP2D6 enzyme, which is thought to be the chief activity responsible for the formation of active oxidized tamoxifen metabolites. In Caucasian populations, the *CYP2D6**4 allele (rs3892097) encodes a nonfunctional enzyme. In Asian populations, the *CYP2D6**10 allele (rs1065852) encodes a reduced-function enzyme. Our goal was to summarize the evidence pertaining to the role of these genetic variants in tamoxifen treatment failure, defined as a breast cancer recurrence or a breast cancer death during or following adjuvant treatment of ER-positive breast patients with tamoxifen.

Methods

Search strategy and selection criteria

For our review of the association between genetic inhibition of CYP2D6 and tamoxifen effectiveness, we searched the OVID database using the search parameters outlined below. All papers published or presented as abstracts through 31 January 2020 regarding the association between *CYP2D6* gene variants and the risk of breast cancer recurrence or breast cancer-specific mortality were reviewed to determine whether their results should be included. Citations included within the selected scientific papers or other reference sources were used to locate additional sources of evidence (*e.g.*, conference abstracts).

OVID search parameters

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1     tamoxifen.mp. or exp Tamoxifen/ (29293)
2     nolvadex.mp. (140)
3     1 or 2 (29294)
4     CYP2D6.mp. or exp Cytochrome P-450 CYP2D6/ (7257)
5     3 and 4 (525)
6     breast neoplasms.mp. or exp Breast Neoplasms/ (287287)
7     breast cancer.mp. (264559)
8     6 or 7 (361189)
9     (pharmacogen* or genetic* or genom* or gene varia* or genotype* or polymorphism*).mp. (4059641)
10    3 and 5 and 8 and 9 (384)
11    (comment or letter or review or systematic review or meta-analysis).pt. (4100663)
12    10 not 11 (262)
13    limit 12 to english language (261)
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Systematic review

The OVID search returned 261 results for title and abstract review. Citations were added to a Zotero database, which was sorted alphabetically by last author's name. Two reviewers then independently reviewed the first 50 records, applying the following inclusion checklist in their evaluation of each paper:

1. Does the paper report original research (not a commentary, letter to the editor, meta analysis, literature review, etc.). Yes=include, No=exclude
2. Is the original research human subjects research (not reporting results in animals, *in vitro* studies, analytic chemistry, etc.). Yes=include, No=exclude

3. Are the human subjects breast cancer patients (diagnosed with breast cancer as an inclusion criterion for the research)? Yes=include, No=exclude
4. Are the human subjects divided into exposure groups on the basis of *CYP2D6* genotype (*e.g., *4, *1, *10,* etc) or on the basis of CYP2D6 phenotype (*e.g.,* extensive metabolizer, intermediate metabolizer, poor metabolizer, etc.)? Yes=include, No=exclude
5. Are the phenotypes determined on the basis of genetics (*e.g., *4, *1, *10,* etc.) and not solely on the basis of use of CYP2D6 inhibiting drugs (*e.g.,* SSRI)? Yes=include, No=exclude
6. Is an outcome in the study breast cancer recurrence, death from breast cancer, death from any cause, or breast cancer progression? Yes=include, No=exclude

Papers meeting all of these review criteria were assigned a tag of "include" in the Zotero library. A single reviewer completed evaluation of papers remaining after the duplicated set of 50, as concordance in that set of 50 showed perfect agreement between two reviewers.

Of the 261 citations returned by the OVID search, 176 were excluded based on review of titles and abstracts. A further 14 papers were excluded after full-text review. This left 71 eligible papers. For the meta-analysis, we included only those papers that reported associations comparing recurrence or breast cancer specific mortality rates between women with homozygous variant genotypes and women with homozygous wild-type genotype at *CYP2D6*. We included only the most recently published result when a set of papers reported findings from duplicated study samples. After applying all of these criteria, 35 studies were included in the meta-analysis.

Statistical methods in the web application

The web application offers both conventional and Bayesian meta-analysis methods. For conventional models, studies can be summarized with either a fixed effects model or a random effects model. Random effects models are fit with the DerSimonian and Laird estimator.[14] Conventional meta-analyses are performed with the 'metafor' package for R, version 2.1-0.[15] Documentation for the 'metafor' package is available here. Bayesian meta-analyses are performed with the 'bayesmeta' package for R, version 2.4.[16] Documentation for the 'bayesmeta' package is available here.

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