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Letter to the Editor

Combined UGT1A1 and UGT1A6 genotypes together with a stressful life event increase breast cancer risk

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To the Editor,

Breast cancer is a multifactor disease and causative factors include genetic variations i.e. mutations and polymorphisms as well as epidemiological risks. BRCA1 and BRCA2 germline
mutations and other rare mutations at ATM, BRIP1, CHEK and PALB2 are causative for hereditary breast cancers [1-3], and among common variants the cell signaling and cell growth factor FGFR2 polymorphism rs2981582 is the most prominent genetic risk [1]. While the search for breast cancer susceptibility genes has been extended to whole genome approach and continues at fast pace, breast cancer risks remains a complex phenomenon contributed by a plethora of epidemiological factors (e.g. age, early age at menarche, family history of breast cancer) [1, 4, 5], and stressful life events are considered as a contributor[6-8]. This is plausible because stress has been appreciated as a known risk for several physical disorders including migraines, asthma, high blood pressure and cardiovascular diseases [9-11]. Whether and how stress contributes to cancer, in particularly breast cancer, remains elusive [12-14]. Moreover, whether there is an interaction of stressful life events with genetic variations in breast cancer risk has not been explored. The most suitable incisive life event is the loss of a significant other (death of a husband or divorce) rather than other events such as loss of a job, change in residence or financial problems that have been shown to be subject to selective remembering in the time of breast cancer diagnosis [7, 15]. Following the strategy of testing the association between stressful life events and other factors such as genetic variation, we employed a population-based case control study as recommended by Levav et al. [16]. We investigated a potential impact of genetic polymorphisms located in the UDP glucuronosyl transferases 1A1 and 1A6 (UGT1A1 and UGT1A6) on breast cancer risk of women who reported divorce/separation or death of a husband.

UGTs are suggested to play a critical role in breast carcinogenesis because they are key enzymes of the metabolism of endogenous and exogenous compounds including steroid hormones, xenobiotics and drugs [17, 18]. Several polymorphisms have been described in UGT genes and some genetic variations are known to affect expression and activity of the encoded enzymes [18-20]. In the present study we selected one promoter polymorphism in UGT1A1 (UGT1A1_(TA)$_n$ TAA repeat, UGT1A1*28) and two non-synonymous
polymorphisms in UGT1A6 (UGT1A6_19_T>G, UGT1A6*2, Ser7Ala, rs6759892 and UGT1A6_541_A>G, UGT1A6*2, Thr181Ala, rs2070959, UGT1A6*2). These polymorphism are linked to each other and the variant alleles are suggested to lead to a decreased expression of UGT1A1 and UGT1A6 [21-23]. Moreover, a possible reduction of side effects detoxification, increase of unwanted side effects of drugs and susceptibility of some diseases such as hepatocellular or breast carcinoma have been discussed for the variant alleles [23-25]. Accordingly, there is a possibility that these genetic variants may be involved in the metabolic dysregulation of known and putative endogenous and exogenous breast carcinogens potentially provoked by stressful events.

We analyzed the UGT1A1*28 and UGT1A6*2 polymorphisms in 1021 breast cancer cases and 1015 controls of the GENICA collection, a German age-matched population-based case control study [26, 27]. The GENICA study was approved by the Ethic’s Committee of the University of Bonn. All study participants gave written informed consent. The UGT1A1_(TA)n TAA repeat was genotyped using MegaBACE 1000 DNA Analyzer (GE Health Care Biosciences Corp. Piscata Way, NY, USA) and UGT1A6_19_T>G as well as UGT1A6_541_A>G were genotyped by matrix assisted laser desorption/ionization mass spectrometry (MALDI-TOF MS; Sequenom, San Diego, CA) as described previously [24]. In case of the UGT1A1_(TA)n TAA repeat carriers of 5/6 or 6/6 repeats were designated as homozygous *1, carriers of 5/7, 6/7 or 6/8 repeats were designated heterozygous *1/*28 as well as carriers of 7/7 or 7/8 repeats were designated homozygous *28. In case of UGT1A6 carriers of the UGT1A6_19_TT and UGT1A6_541_AA genotypes were designated homozygous *1 and carriers of the variant UGT1A6_19_GG and UGT1A6_541_GG genotypes were designates homozygous *2. All women homozygous for UGT1A1*1 and UGT1A6*1 (+) as well as all women homozygous for UGT1A1*28 and UGT1A6*2 (-) were included in the statistical analysis. The following subgroups were used in the association analysis: (i) women who reported to be unmated (never lived with a partner or husband), (ii)
women which currently live with a partner or husband, and (iii) women that reported separation/divorce/death of husband. Associations between the combined UGT1A1 and UGT1A6 genotypes and breast cancer risk were analyzed by logistic regression conditional on age (5-year groups) and adjusted for six epidemiological breast cancer risk factors (i.e. menopausal status, family history of breast cancer, use of oral contraceptives, use of hormone therapy, body mass index, and smoking). Statistical analyses were performed using SAS v9.1.3 (SAS Institute Inc., Cary, NC, USA).

At baseline, there was no risk association with stressful live events (Table 1). However, we observed a significantly increased breast cancer risk for women carrying the UGT1A1*28 and UGT1A6*2 variant genotype (-) as compared to women carrying the common UGT1A1*1 and UGT1A6*1 genotype (+) with an odds ratio (OR) of 1.51 (95% confidence interval [CI]: 1.10-2.09, p = 0.012; Table 1).

When we performed a combined analysis for UGT genotypes and life events we observed an elevated breast cancer risk with an OR of 2.61 (95% CI: 1.29-5.29, p = 0.008; Table 1) for women carrying the UGT variant genotype (-) and reporting separation/divorce/death of husband. Since UGTs are involved in the elimination of sex hormones from the circulation any lower activity, e.g. due to the background of UGT1A1*28 and UGT1A6*2 genotypes (-), expected to increase estrogen levels [21-23]. It is of note because elevated estrogen levels are known to be critical for carcinogenesis of breast tumors [28]. This effect can be promoted by stressful events that may further impact on the dysregulation of the metabolism of hormone related carcinogens. In the absence of a baseline risk of stress events, our results suggest, that a small breast cancer risk conveyed by UGT1A1 and UGT1A6 variants may be further amplified by the experience of persisting stressful events. To challenge this hypothesis our findings should be followed up in larger patient cohorts.

Acknowledgements
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All authors disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations.

References


Table 1. Frequencies and estimated risks of stressful life events as well as combined UGT1A1 and UGT1A6<sup>a</sup> genotypes in breast cancer cases and controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases n (%)</th>
<th>Controls n (%)</th>
<th>OR&lt;sup&gt;b&lt;/sup&gt; (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>unmated</td>
<td>50 (5.0)</td>
<td>56 (5.6)</td>
<td>1.00&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>married/living with partner</td>
<td>692 (69.2)</td>
<td>665 (66.7)</td>
<td>1.18 (0.79-1.77)</td>
</tr>
<tr>
<td>divorce/separation/death of husband</td>
<td>258 (25.8)</td>
<td>276 (27.7)</td>
<td>1.07 (0.70-1.64)</td>
</tr>
<tr>
<td>Life event</td>
<td>UGT combined</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>unmated</td>
<td>303 (73.2)</td>
<td>111 (26.8)</td>
<td></td>
</tr>
<tr>
<td>married/living with partner</td>
<td>351 (80.0)</td>
<td>88 (20.0)</td>
<td></td>
</tr>
<tr>
<td>divorce/separation/death of husband</td>
<td>1.00</td>
<td>1.51 (1.10-2.09)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>0.56 (0.04-8.72)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>1.21 (0.83-1.77)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>2.61 (1.29-5.29)</td>
<td></td>
</tr>
</tbody>
</table>

*UGT1A1*/*28, *UGT1A6*_19_T>G and *UGT1A6*_541_A>G genotypes were combined according to their known effect on gene expression, women homozygous for the reference alleles *UGT1A1*/*1/*1, *UGT1A6*_19_TT and *UGT541-AA* leading to increased gene expression are designated (+); women homozygous for the variant alleles *UGT1A1*/*28/*28, *UGT1A6*_19_GG and *UGT1A6*_541_GG leading to decreased gene expression are designated (-)

bOR conditional on age in 5-year classes, adjusted for menopausal status, family history of breast cancer, use of oral contraceptives, use of hormone therapy, body mass index, and smoking

cReference
dp = 0.012
ep = 0.008

Abbreviations: CI = confidence interval, OR = odds ratio, UGT = UDP glucuronosyltransferases