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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 polymorphisms 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 designated 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 life 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.

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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.

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Table 1. Frequencies and estimated risks of stressful life events as well as combined *UGT1A1* and *UGT1A6*^a genotypes in breast cancer cases and controls

Variables	Cases n (%)	Controls n (%)	OR ^b (95% CI)
Life event			
unmated	50 (5.0)	56 (5.6)	1.00 ^c
married/living with partner	692 (69.2)	665 (66.7)	1.18 (0.79-1.77)
divorce/separation/death of husband	258 (25.8)	276 (27.7)	1.07 (0.70-1.64)

UGT combined				
	+	303 (73.2)	351 (80.0)	1.00 ^c
	-	111 (26.8)	88 (20.0)	1.51 (1.10-2.09) ^d
Life event		UGT combined		
unmated	+	17 (81.0)	15 (78.9)	1.00 ^c
unmated	-	4 (19.0)	4 (21.1)	0.56 (0.04-8.72)
married/living with partner	+	216 (73.7)	228 (77.3)	1.00 ^c
married/living with partner	-	77 (26.3)	67 (22.7)	1.21 (0.83-1.77)
divorce/separation/death of husband	+	70 (70.7)	108 (86.4)	1.00 ^c
divorce/separation/death of husband	-	29 (29.3)	17 (13.6)	2.61 (1.29-5.29) ^e

^a*UGT1A1**1/*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 *UGT*_541_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