

**Supplemental Table 1.** The risk of breast cancer associated with gene-gene interactions previously reported in the literature.

Genotypes		# High Risk Genotypes <sup>1</sup>	Case n (%)	Control n (%)	OR <sup>2</sup>	95% CI	
<i>GSTMI</i>	<i>GSTTI</i>						
present	present	0	340 (38.3)	348 (39.8)	1.0 (ref)		
null	present	1	81 (9.1)	67 (7.7)	1.1	0.9	1.3
present	null	1	401 (45.2)	389 (44.5)	1.2	0.9	1.8
null	null	2	66 (7.4)	71 (8.1)	0.9	0.6	1.4
					$p_{\text{int}} = 0.20$		
<i>COMT</i>	<i>GSTPI</i>						
GG	AG/GG	0	128 (14.4)	125 (14.3)	1.0 (ref)		
GG	AA	1	96 (10.8)	86 (9.8)	1.1	0.7	1.6
GA/AA	AG/GG	1	381 (42.8)	383 (43.8)	1.0	0.7	1.3
GA/AA	AA	2	286 (32.1)	281 (32.1)	1.0	0.7	1.3
					$p_{\text{int}} = 0.21$		
<i>COMT</i>	<i>GSTTI</i>						
GG	present	0	191 (21.4)	178 (20.3)	1.0 (ref)		
GG	null	1	33 (3.7)	32 (3.7)	0.9	0.6	1.6
GA/AA	present	1	553 (62.1)	560 (63.9)	0.9	0.7	1.2
GA/AA	null	2	114 (12.8)	106 (12.1)	1.0	0.7	1.4
					$p_{\text{int}} = 0.61$		
<i>COMT</i>	<i>GSTMI</i>						
GG	present	0	109 (12.3)	98 (11.2)	1.0 (ref)		
GG	null	1	115 (12.9)	112 (12.8)	0.9	0.6	1.3
GA/AA	present	1	312 (35.1)	317 (36.2)	0.8	0.6	1.3
GA/AA	null	2	352 (39.6)	348 (39.8)	0.9	0.6	1.4
					$p_{\text{int}} = 0.58$		
<i>COMT</i>	<i>GSTMI</i>	<i>GSTTI</i>					
GG	present	present	0	89 (10.0)	82 (4.6)	1.0 (ref)	
GG	null	present	1	102 (11.5)	96 (11.0)	1.0	0.6
GG	present	null	1	20 (2.2)	16 (1.8)	1.2	0.6
GG	null	null	2	13 (1.5)	16 (1.8)	0.7	0.3
GA/AA	present	present	1	251 (28.3)	266 (30.4)	0.8	0.5
GA/AA	null	present	2	299 (33.7)	293 (33.5)	0.9	0.6
GA/AA	present	null	2	61 (6.9)	51 (5.8)	1.1	0.6
GA/AA	null	null	3	53 (6.0)	55 (6.3)	0.8	0.5
					$p_{\text{int}} = 0.58$		
<i>GSTPI</i>	<i>GSTMI</i>	<i>GSTTI</i>					
AG/GG	present	present	0	201 (22.6)	202 (23.2)	1.0 (ref)	
AG/GG	null	present	1	218 (24.6)	223 (25.6)	1.0	0.7
AG/GG	present	null	1	48 (5.4)	43 (4.9)	1.1	0.7
AG/GG	null	null	2	40 (4.5)	38 (4.4)	1.0	0.6
AA	present	present	1	139 (15.6)	145 (16.6)	0.6	0.3
AA	null	present	2	183 (20.6)	164 (18.8)	0.7	0.4
AA	present	null	2	33 (3.7)	24 (2.8)	0.9	0.4
AA	null	null	3	26 (2.9)	33 (3.8)	0.5	0.3
					$p_{\text{int}} = 0.06$		

1. Based on the risk estimates determined in the main analyses, which also align with the previous reports in the literature
2. Adjusted for age and year of diagnosis (reference date for controls)

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**Supplemental Table 2.** The risk of breast cancer associated with EPT-combined gene interactions previously reported in the literature.

EPT Use <sup>1</sup>	Genotypes		# High Risk Genotypes	Case n (%)	Control n (%)	OR <sup>2</sup>	95% CI	
<i>&gt; 30 months</i>	<i>COMT</i>	<i>GSTP1</i>						
	GG	AG/GG	0	29 (15.3)	10 (9.3)	1.0 (ref)		
	GG	AA	1	8 (4.2)	16 (14.8)	0.1	0.02	0.3
	GA/AA	AG/GG	1	86 (45.5)	44 (40.7)	0.5	0.2	1.5
	GA/AA	AA	2	66 (34.9)	38 (35.2)	0.2	0.04	0.8
<i>1- 30 months</i>	GG	AG/GG	0	6 (11.8)	16 (23.5)	1.0 (ref)		
	GG	AA	1	4 (7.8)	5 (7.4)	0.5	0.02	7.1
	GA/AA	AG/GG	1	22 (43.1)	26 (38.2)	7.7	1.3	44.1
	GA/AA	AA	2	19 (37.2)	21 (30.9)	1.2	0.1	22.3
<i>Never use</i>	GG	AG/GG	0	91 (14.0)	99 (14.3)	1.0 (ref)		
	GG	AA	1	84 (13.0)	65 (9.4)	1.0	0.5	1.9
	GA/AA	AG/GG	1	273 (42.1)	310 (44.7)	0.9	0.5	1.4
	GA/AA	AA	2	200 (30.8)	220 (31.7)	0.7	0.3	1.3
						p <sub>int</sub> = 0.09		
<i>&gt; 30 months</i>	<i>COMT</i>	<i>GSTT1</i>						
	GG	present	0	30 (15.9)	21 (19.6)	1.0 (ref)		
	GG	null	1	7 (3.7)	5 (4.7)	1.0	0.3	3.5
	GA/AA	present	1	126 (66.7)	64 (59.8)	1.0	0.4	2.7
	GA/AA	null	2	26 (13.8)	17 (15.9)	0.8	0.3	2.4
<i>1- 30 months</i>	GG	present	0	7 (13.7)	18 (26.5)	1.0 (ref)		
	GG	null	1	3 (5.9)	3 (4.4)	2.4	0.4	15.4
	GA/AA	present	1	32 (62.7)	42 (61.8)	7.1	1.4	35.7
	GA/AA	null	2	9 (17.6)	5 (7.4)	24.4	3.0	200.2
<i>Never use</i>	GG	present	0	153 (23.6)	139 (20.0)	1.0 (ref)		
	GG	null	1	22 (3.4)	24 (3.4)	0.8	0.4	1.5
	GA/AA	present	1	394 (60.8)	450 (64.7)	0.7	0.5	1.2
	GA/AA	null	2	79 (12.2)	83 (11.9)	0.8	0.5	1.4
						p <sub>int</sub> = 0.004		
<i>&gt; 30 months</i>	<i>COMT</i>	<i>GSTM1</i>						
	GG	present	0	17 (9.0)	14 (13.1)	1.0 (ref)		
	GG	null	1	20 (10.6)	12 (11.2)	1.4	0.5	3.8
	GA/AA	present	1	73 (38.8)	45 (42.1)	1.0	0.3	2.9
	GA/AA	null	2	78 (41.5)	36 (33.6)	1.3	0.7	2.3
<i>1- 30 months</i>	GG	present	0	4 (7.8)	10 (14.7)	1.0 (ref)		
	GG	null	1	6 (11.8)	11 (16.2)	1.4	0.3	6.0
	GA/AA	present	1	18 (35.3)	27 (39.7)	1.3	0.7	29.8
	GA/AA	null	2	23 (45.1)	20 (29.4)	8.5	1.4	52.4
<i>Never use</i>	GG	present	0	86 (13.3)	74 (10.6)	1.0 (ref)		
	GG	null	1	89 (13.8)	89 (12.8)	0.9	0.6	1.3
	GA/AA	present	1	221 (34.2)	242 (34.8)	0.7	0.4	1.2
	GA/AA	null	2	250 (38.7)	290 (41.7)	0.7	0.4	1.1
						p <sub>int</sub> = 0.001		

1. Based on the cutpoints for EPT used in the report by Mitrunen, et al<sup>22</sup>

2. Adjusted for age and year of diagnosis (reference date for controls)