Table 3

Association between *XRCC1* and *XPD* genotypes and breast cancer risk according to smoking habits

Genotype	Never active or passive smoking			Only passive smoking			Active smoking		
	Cases (%)	Controls (%)	OR (95% CI)[a]	Cases (%)	Controls (%)	OR (95% CI)[a]	Cases (%)	Controls (%)	OR (95% CI)[a]
XRCC1-280									
Arg/Arg	177 (84.7)	154 (84.6)	1.0	120 (79.5)	140 (83.8)	1.0	94 (83.9)	111 (86.0)	1.0
Arg/His+His/His	32 (15.3)	28 (15.4)	1.09 (0.60–1.99)	31 (20.5)	27 (16.2)	1.11 (0.59–2.08)	18 (16.1)	18 (14.0)	1.41 (0.65–3.08)
XRCC1-399									
Arg/Arg	118 (56.5)	89 (48.9)	1.0	72 (47.7)	91 (54.5)	1.0	45 (40.5)	75 (58.6)	1.0
Arg/Gln	76 (36.4)	76 (41.8)	0.83 (0.53–1.31)	67 (44.4)	66 (39.5)	1.40 (0.84–2.32)	49 (44.2)	43 (33.6)	2.14 (1.15–3.97)
Gln/Gln	15 (7.2)	17 (9.3)	0.73 (0.33–1.64)	12 (7.9)	10 (6.0)	1.61 (0.61–4.23)	17 (15.3)	10 (7.8)	3.27 (1.25–8.58)[b]
Arg/Gln+Gln/Gln	91 (43.5)	93 (51.1)	0.81 (0.53–1.25)	79 (52.3)	76 (45.5)	1.42 (0.87–2.32)	66 (59.5)	53 (41.4)	2.33 (1.30–4.19)[c]
XPD-751									
Lys/Lys	66 (31.6)	58 (31.9)	1.0	40 (26.3)	56 (33.3)	1.0	40 (35.7)	40 (31.0)	1.0
Lys/Gln	109 (52.2)	91 (50.0)	1.03 (0.63–1.66)	83 (54.6)	77 (45.8)	1.35 (0.78–2.34)	40 (35.7)	77 (45.8)	0.68 (0.35–1.33)
Gln/Gln	34 (16.3)	33 (18.1)	0.78 (0.40–1.49)	29 (19.1)	35 (20.8)	0.84 (0.41–1.69)	32 (28.6)	35 (20.8)	1.96 (0.89–4.32)
Lys/Lys+Lys/Gln	175 (83.7)	149 (81.9)	1.0	123 (80.9)	133 (79.2)	1.0	80 (71.4)	109 (84.5)	1.0
Gln/Gln	34 (16.3)	33 (18.1)	0.77 (0.43–1.39)	29 (19.1)	35 (20.8)	0.70 (0.38–1.29)	32 (28.6)	20 (15.5)	2.52 (1.27–5.03)[d]

[a]Odds ratios (ORs) and confidence intervals (CIs) adjusted for age, age at menarche, age at first full term pregnancy, number of pregnancies, history of benign breast disease, first degree family history of breast cancer, weist-to-hip ratio and use of alcohol. [b]*p* for trend = 0.003. [c]Interaction between smoking habits and *XRCC1-399* genotype ($p = 0.025$). [d]Interaction between smoking habits and *XPD-751* genotype ($p = 0.011$).

95% CI 1.25–8.58, *p* for trend = 0.003) *XRCC1-399 Gln* variant alleles compared to those carrying the *Arg/Arg* genotype (*p* for interaction between smoking habits and *XRCC1-399* genotype 0.025) (Table 3). A similar increase in risk was seen for ever smoking women with the *XPD-751 Gln/Gln* genotype compared to ever smoking women without this genotype (OR 2.52, 95% CI 1.27–5.03, *p* for interaction 0.011).

When ever smoking women were further stratified by pack-years smoked (<5, ≥5 pack-years), the increase in risk was seen to be confined to those who had smoked over five pack-years and carried at least one *XRCC1-399 Gln* allele (OR 4.14, 95% CI 1.66–10.3), or the *XPD-751 Gln/Gln* genotype (OR 4.41, 95 % CI 1.62–12.0) compared to similarly smoking women without these genotypes (Table 4). Similar effects were seen for the *XRCC1 Arg399Gln* genotypes when smokers were stratified by daily tobacco consumption (<10, ≥10 cigarettes/day) or by smoking years (<15, ≥15 years). The ORs were 5.32 (95% CI 1.97–14.4) for women smoking ≥10 cigarettes/day and carrying at least one *XRCC1-399 Gln* allele, and 4.03 (95% CI 1.40–11.6) for women who had smoked ≥15 years and carried at least one *XRCC1-399 Gln* allele, compared to women with similar smoking habits but with the *XRCC1-399 Arg/Arg* genotype. For the carriers of the *XPD-751 Gln/Gln* genotype, a similar increase in the risk of breast cancer was seen for women smoking ≥10 cigarettes/day (OR 4.78, 95% CI 1.50–15.2) while no statistically significant increase was seen by smoking years (OR 2.25, 95% CI 0.85–5.96 for women smoking ≥15 years), compared to women smoking the same amount, but not carrying the homozygous variant *XPD-751 Gln/Gln* genotype.

When stratified by current use of alcohol, women who reported using alcohol weekly to daily and carried the *XPD-751 Gln/Gln* genotype were at 3.18-fold (95% CI 1.34–7.57) increased risk of breast cancer compared to similarly drinking women carrying the other genotypes (*p* for interaction 0.026). No interaction was found between *XRCC1-280* or *XRCC1-399* genotypes and current use of alcohol (data not shown).

When the joint effect of the *XRCC1-280*, *XRCC1-399*, and *XPD-751* genotypes was studied, a statistically significant increase in the risk of breast cancer was seen for subjects carrying two at-risk genotypes of these genes (OR 1.54, 95% CI 1.00–2.37) compared to subjects with the wild-type genotypes for all three polymorphic sites (Table 5). This increase was mainly due to the combined effect of *XRCC1-399* and *XPD-751* genotypes (OR 1.80, 95% CI 1.05–3.08, *p* for gene-gene interaction 0.043). A trend of increasing risk with increasing number of at-risk genotypes was seen (*p* for trend 0.042). However, this estimate did not reach statistical significance (OR 4.76, 95% CI 0.48–47.8), possibly due to the low number of subjects with all the three at-risk genotypes (four cases and one control). When the combined effects were studied among ever active smokers, women who carried any two at-risk genotypes were at remarkably increased risk of