Table 5

Combined *XRCC1* and *XPD* genotypes and breast cancer risk among all and ever smoking women

				All women			Ever actively smoking women		
No of at risk genotypes	*XRCC1-280*	*XRCC1-399*	*XPD-751*	Case/ Control	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]	Case/ Control	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
0	*Arg/Arg*	*Arg/Arg*	*Lys/Lys+ Lys/ Gln*	145/159	1.0	1.0	23/46	1.0	1.0
1	*Arg/Arg*	*Arg/Arg*	*Gln/Gln*	32/44	0.80 (0.48–1.33)	0.72 (0.42–1.25)	8/12	1.33 (0.48–3.72)	1.20 (0.37–3.86)
1	*Arg/Arg*	*Arg/Gln+ Gln/ Gln*	*Lys/Lys+ Lys/ Gln*	172/170	1.11 (0.81–1.51)	1.15 (0.83–1.60)	43/48	1.79 (0.94–3.43)	1.93 (0.93–4.05)
1	*Arg/His+His/ His*	*Arg/Arg*	*Lys/Lys+ Lys/ Gln*	45/44	1.12 (0.70–1.80)	1.19 (0.72–1.97)	11/15	1.47 (0.58–3.70)	1.94 (0.69–5.44)
1 (any one at risk genotype)	-	-	-	249/258	1.06 (0.80–1.41)	1.09 (0.81–1.47)	62/75	1.65 (0.91–3.02)	1.80 (0.91–3.56)
2	*Arg/Arg*	*Arg/Gln+ Gln/ Gln*	*Gln/Gln*	46/32	1.58 (0.95–2.61)	1.80 (1.05–3.08)	19/5	7.60 (2.52–22.0)	12.1 (3.52–41.5)
2	*Arg/His+ His/ His*	*Arg/Gln+ Gln/ Gln*	*Lys/Lys+ Lys/ Gln*	19/18	1.16 (0.59–2.29)	1.28 (0.62–2.64)	3/0	-	-
2	*Arg/His+ His/ His*	*Arg/Arg*	*Gln/Gln*	13/9	1.58 (0.66–3.82)	1.36 (0.52–3.59)	3/2	3.00 (0.47–19.2)	3.47 (0.44–27.1)
2 (any two at risk genotypes)	-	-	-	78/59	1.45 (0.97–2.18)	1.54 (1.00–2.37)	25/7	7.14 (2.69–19.0)	10.7 (3.62–31.6)
3	*Arg/His+His/ His*	*Arg/Gln+ Gln/ Gln*	*Gln/Gln*	4/1	4.39 (0.49–39.7)	4.76 (0.48–47.8)[b]	1/0	-	-

[a]Odds ratios (ORs) and confidence intervals (CIs) adjusted for age, first degree family history of breast cancer, age at menarche, number of children, age at first full term pregnancy, history of benign breast disease, weist-to-hip ratio and use of alcohol. [b]*p* for trend of having 1, 2 or 3 at-risk genotypes 0.042.

only 67% for the *XRCC1-280 His* allele containing genotypes. As the *XRCC1-194 Trp* variant allele is even less frequent among Finns (approximately 0.03) [45] compared to other Caucasians, and as the amino acid change has not been shown to affect protein function [16], we decided not to include this polymorphism in our study.

The *XPD Lys751Gln* polymorphism has been suggested to be the most important functional polymorphism in the gene due to major change in the electronic configuration of the respective amino acid in an important interaction domain of the protein [53]. However, no significant overall association with breast cancer was seen in our study for the *XPD Lys751Gln* genotypes. This was in agreement with the other five studies on the *XPD Lys751Gln* polymorphism and breast cancer risk including one in Finnish [45], one in Danish [46], one in German [47], and two in US Caucasian women [11,40]. In contrast, a significant association between the *XPD-751 Gln* allele and breast cancer risk was seen in a recent study among American women [44]. Moreover, the *XPD Asp312Asn* polymorphism was recently shown to be associated with breast cancer risk in a German population [47]. We decided not to analyse the *XPD Asp312Asn* polymorphism as it has been shown to be strictly linked with the *Lys751Gln* polymorphism [12,38].

When the present study subjects were stratified by stage of disease, the *XRCC1-399 Gln* allele posed an elevated risk for more advanced stage breast cancer. A similar tendency of increased risk for more advanced stage breast cancer was also seen for the *Arg280His* polymorphism. It can be hypothesized that defective DNA repair leads to more aggressive and, therefore, more advanced tumours at the time of diagnosis. This was also supported by the association of the *XRCC1-399 Gln* allele with higher grade tumours. However, as earlier studies on breast cancer have not evaluated the genotype effects by the stage of the disease or tumour grade, these findings remain to be confirmed in future studies.

Smoking alone did not significantly affect breast cancer risk in the present study. This is in agreement with the majority of epidemiological studies on smoking and breast cancer risk, as well as with a recent report of the Collaborative Group on Hormonal Factors in Breast cancer, which concluded that cigarette smoking has little or no effect on the risk of developing breast cancer [3]. There are, however, some studies reporting increased risk in special subgroups, such as women who started to smoke at an early age or before first pregnancy, women smoking high intensity or long duration, passively smoking women, and women with specific genotypes (reviewed in [4]). In our study, a significant interaction was seen between smoking habits and the *XRCC1 Arg399Gln* ($p = 0.025$) or *XPD Lys751Gln* ($p = 0.011$) genotypes. Subjects with the variant *Gln/Gln* genotypes were at increased risk of developing breast cancer if they had ever smoked. Furthermore, a gene-dosage effect was seen for the *XRCC1 Arg399Gln* genotype; the increased risk was higher for sub-