rized as those who had never been exposed to either passive or active smoking, and as those exposed to passive smoking only. Ever smokers were further categorized according to the approximate median smoking years (15 years), daily consumption (10 cigarettes) and pack-years of smoking (5 pack-years) in the control population. Pack-years of cigarettes were calculated as the number of packs (20 cigarettes/pack) smoked per day multiplied by years of smoking.

Based on the prior knowledge of the functional significance or epidemiological evidence, the *XRCC1-280 Arg/Arg* and *XRCC1-399 Arg/Arg* genotypes were used as reference categories for all separate analyses. As the frequency of the *XRCC1-280 His* variant allele was low, the ORs were calculated for the combined *XRCC1-280 His* allele containing genotypes in all analyses. Similarly, in the stratified analyses, the *XRCC1-399 Gln* allele containing genotypes were combined to increase statistical power. In contrast, a recessive model was used for the *XPD Lys751Gln* polymorphism based on the observed genotype distributions and some earlier publications [42,51]. Therefore, the heterozygous *XPD-751 Lys/Gln* genotype was combined with the wild-type *Lys/Lys* genotype to serve as a reference category. Possible gene environment interactions were assessed using stratified analyses and interaction terms. Variables of interest were smoking and use of alcohol. Tests for interactions were assessed by the likelihood ratio test to compare goodness of fit of the model with the interaction term, to the reduced model including the main effect variable (genotype) and the main adjusting variables. All reported *p*-values are two-sided. No attempt was made to adjust for multiple comparisons.

Results

Characteristics of the study population are shown in Table 1. Parity was associated with decreased risk of breast cancer while higher waist-to-hip ratio, first degree family history of breast cancer and history of benign breast disease were associated with increased risk. No significant associations were seen between breast cancer risk and smoking habits. Neither were any statistically significant differences seen in the mean number of cigarettes smoked per day (mean 11.2, SD 9.2, and mean 9.5, SD 6.7, for cases and controls, respectively, $p = 0.10$), or in smoking years (16.1, SD 10.8, and 14.5, SD 10.8, for cases and controls, respectively, $p = 0.25$).

The frequencies of the *XRCC1-280 His*, *XRCC1-399 Gln*, and *XPD-751 Gln* variant alleles in controls were 0.08, 0.27, and 0.43, respectively. All the genotype distributions in the control population conformed to Hardy-Weinberg equilibrium ($p = 0.993$, $p = 0.657$, and $p = 0.876$ for *XRCC1-280*, *XRCC1-399*, and *XPD-751* locuses, respectively). No statistically significant differences were seen in the frequency of these genotypes between cases and controls (Table 2). Neither was any significant difference seen for the polymorphisms when stratified by menopausal status or age (data not shown).

Table 2

Association between *XRCC1* and *XPD* polymorphisms and breast cancer risk

Genotype	Cases (%)	Controls (%)	OR (95% CI)[a]
XRCC1-280			
Arg/Arg	399 (83.1)	406 (84.8)	1.0
Arg/His	78 (16.3)	70 (14.6)	
His/His	3 (0.6)	3 (0.6)	1.15 (0.80–1.66)[b]
XRCC1-399			
Arg/Arg	237 (49.5)	256 (53.6)	1.0
Arg/Gln	196 (40.9)	185 (38.7)	1.24 (0.93–1.65)
Gln/Gln	46 (9.6)	37 (7.7)	1.39 (0.84–2.29)[c]
Arg/Gln + Gln/Gln	242 (50.5)	222 (46.4)	1.26 (0.96–1.66)
XPD-751			
Lys/Lys	147 (30.6)	155 (32.3)	1.0
Lys/Gln	238 (49.5)	237 (49.4)	1.03 (0.76–1.40)
Gln/Gln	96 (20.0)	88 (18.3)	1.10 (0.74–1.63)
Lys/Lys+Lys/Gln	385 (80.0)	325 (81.7)	1.0
Gln/Gln	96 (20.0)	88 (18.3)	1.08 (0.77–1.53)

[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, smoking and use of alcohol. [b]OR for *Arg/His* and *His/His* genotypes combined. [c] p for trend = 0.105.

When subjects were studied by the stage of the disease at the time of diagnosis, a significant increase for advanced stage (III or IV) breast cancer was seen for women with the *XRCC1-399 Gln/Gln* genotype (OR 2.86, 95% CI 1.05–7.81) compared to those with the *Arg/Arg* genotype. No increase in risk was seen for lower stage (I or II) breast cancer (OR 1.33, 95% CI 0.79–2.26). A similar tendency of increased risk for advanced stage cancer was seen for subjects with the *XRCC1-280 Arg/His* or *His/His* genotype (OR 1.99, 95% CI 0.90–4.42) compared to subjects with the *Arg/Arg* genotype. Similarly, women with the *XRCC1-399 Gln/Gln* genotype presented with a significantly increased risk for grade II and grade III tumours (OR 1.80, 95% CI 1.06–3.07) when compared to those with the *Arg/Arg* genotype, while no increase was seen for grade I tumours (OR 1.10, 95% CI 0.75–1.62). Moreover, women who carried the *XRCC1-399 Gln/Gln* genotype and were diagnosed with early stage (I or II) breast cancer had tumours of higher grade (II or III) marginally ($p = 0.065$, one-sided) more often than those with the *Arg/Arg* genotype, 86.1% (31/36) versus 72.5 % (137/189), respectively.

When the association between *XRCC1-399* genotypes and breast cancer risk was studied according to smoking habits, increased breast cancer risk with dose-response was seen among women who had ever smoked actively and carried either one (OR 2.14, 95% CI 1.15–3.97) or two (OR 3.27,