was 2.9 kb in the *ATM* gene, 4.0 kb in the *CHEK2* gene and 2.8 kb in the *ERBB2* gene. We detected strong LD across all three genes [supplementary Figure 1, Figure 1 in Einarsdóttir and colleagues [56] and supplementary figure 2, respectively]. Using the SNP dropping method [47], we found that the tagSNPs selected from the SNPs included in our study could capture nongenotyped SNPs as efficiently as the SNPs included in our study (supplementary Table 1).

Breast cancer survival

Table 2 summarizes the information on the tagSNPs in the *ATM, CHEK2* and *ERBB2* genes that we genotyped in breast cancer cases and controls. All of the tagSNPs in the *CHEK2* and *ERBB2* genes and two of the tagSNPs in the *ATM* gene were not only genotyped in breast cancer cases and controls who participated through blood sample donation, but were also genotyped in breast cancer cases who participated through tissue sample donation. None of the tagSNPs deviated significantly from HWE among the controls or showed a meaningful association with known breast cancer risk factors. Only one of the tagSNPs – TAG5 (also named I655V) in the *ERBB2* gene – conferred an amino acid change in the protein product.

We estimated the risk of death from breast cancer associated with the tagSNPs (Table 2) in the *ATM*, *CHEK2* and *ERBB2* genes or their haplotypes (Table 3). We found a decreased risk of death from breast cancer associated with each addition of the rare TAG2 allele in the *CHEK2* gene ($P = 0.026$) and an elevated risk of death from breast cancer associated with the rare TAG6 allele in the *CHEK2* gene ($P = 0.03$), compared with homozygotes of the common allele for each variant. The associations did not, however, withstand Bonferroni correction. Carriers of haplotype 2 in the *CHEK2* gene seemed to have a decreased risk of death from breast cancer ($P = 0.038$) compared with haplotype 1 carriers, whereas carriers of the rare *ERBB2* haplotypes seemed to have an increased risk of death from breast cancer ($P = 0.009$). Neither association carried over to the global test ($P = 0.15$ and $P = 0.45$, respectively).

We noticed in Table 3 that all of the *ATM* haplotypes conferred a decrease in risk of death from breast cancer compared with haplotype 1. We therefore assessed the association of haplotype 1 with the risk of death from breast cancer and found a nonsignificantly elevated risk compared with noncarriers [odds ratio (OR), 1.13; 95% confidence interval (CI), 0.92–1.40].

Tumour characteristics

We calculated global *P* values for the association between the tagSNP haplotypes in the *ATM*, *CHEK2* and *ERBB2* genes and the risk of tumour-characteristic-defined breast cancer from logistic regression models. Cases were divided into groups according to their tumour characteristics and each group contrasted against all controls. Each logistic regression model included the common haplotypes and the combined group of rare haplotypes, with the most common haplotype used as a reference standard. None of the global *P* values reached significance (supplementary Table 4), which indicates that none of the individual haplotypes affected the risk of developing tumours with certain characteristics.

We genotyped the *CHEK2 1100delC* gene mutation in our study population and have previously reported its effect on the overall risk of breast cancer [56]. The deletion was very rare in our study population, with a frequency of 0.7% among the cases and 0.4% among the controls. We could therefore not perform a meaningful analysis of the association between the deletion and breast cancer characteristics or survival in the current study.

Overall risk of breast cancer: the *ATM* and *ERBB2* genes

We found no effect of the *ATM* or *ERBB2* tagSNPs (supplementary Table 5) or haplotypes (supplementary Table 6) on the overall risk of breast cancer, which was not altered after conditioning on the selection variables (menopausal hormone therapy and diabetes mellitus) or restricting the analyses to the randomly selected cases and controls. Stratifying the haplotype results by known breast cancer risk factors did not yield any additional compelling findings (supplementary Table 7).

We genotyped two mis-sense mutations in the *ATM* gene in the complete sample set: 4258 C→T (rs1800058; L1420F) and 2572 T→C (rs1800056; F858L). Neither mutation deviated significantly from HWE in controls. They were both rare in our study population, with a minor allele frequency of 1.9% for 4258 C→T and 1.4% for 2527 T→C in the controls. In exploring the change in the risk of breast cancer with each addition of the rare allele compared with noncarriers (assuming co-dominance), an elevated – but not significant – risk for the 4258 C→T (OR, 1.36; 95% CI, 0.91–2.04) was found, but no association emerged between the 2527 T→C and the risk of breast cancer (OR, 1.05; 95% CI, 0.65–1.71).

Discussion

Although the gene products of *ATM, CHEK2* and *ERBB2* are involved in various aspects of breast cancer development and progression, our results suggest that common variation in these genes does not affect survival, tumour-characteristic-defined risk or the overall risk of breast cancer. We carefully studied these associations, both overall and in subgroups of known nongenetic breast cancer risk factors, using large population-based case–control material, and conclude that on the population level, common genetic variation in these genes is not of great importance for these outcomes. This does not preclude the possibility that more crucial – and rare – variation is influential in selected patient groups.