In Germany, less than one third of familial breast cancer (BC) and/or ovarian cancer (OC) index cases carry a mutation in known high or moderately penetrant risk genes[1,2]. Hence, 70% of the familial BC and/or OC cases cannot be explained by pathogenic germline variants in the known risk genes. This leads to the assumption that there are further genetic or non-genetic factors which modify BC/OC risk. The fact that often an accumulation of BC and/or OC cases is observed within a family points more towards genetic rather than non-genetic modifiers. The search for further BC/OC-associated risk genes is challenging since the mutation prevalence is usually low (< 1%), demanding for large samples sets to achieve statistical significance[2]. In this thesis two approaches were employed in order to improve BC risk prediction in individuals with a familial background of BC and/or OC.

First, the potential association of *BARD1* (MIM*601593) gene mutations with BC risk was assessed. BARD1 interacts with the established BC/OC high risk gene product BRCA1 and plays an important role in homologous recombination upon double strand breaks[3]. Despite several studies already investigated *BARD1*, its role in BC development remained elusive[2,4-6]. Therefore, a hypothesis-driven case-control study investigating 4,469 index patients with BC and 451 OC index patients, all previously tested negative for *BRCA1/2* germline mutations, as well as 37,265 controls, including 2,767 geographically matched female control individuals, was performed. Sequencing data were screened for protein-truncating variants (PTVs) and potentially damaging missense variants in the *BARD1* gene[7]. We found a significant association between germline PTVs in *BARD1* and early-onset BC in our familial cases (odds ratio (OR): 12.04, 95% confidence interval (CI): 5.78 – 25.08, $p < 0.00001$). *BARD1* mutation carriers were statistically significantly younger at their first diagnosis compared with the overall sample (42.3 vs. 48.6 years, $p = 0.00347$). Additionally, we did not observe evidence for an association between germline PTVs in *BARD1* and OC in 451 familial OC index patients[7].

In the course of this thesis, I was also involved in studies which assessed the associations of variants in potential risk genes, such as *BRIP1*[8] (MIM*605882) and *GPRC5A*[9] (MIM**604138) with BC/OC risk. *BRIP1* was confirmed as an OC risk gene[8], while the association with BC disposition remains to be further investigated[8]. After Sokolenko et al.[10] proposed *GPRC5A* as a genetic modifier in *BRCA1*-dependent BC development, the interaction of *GPRC5A* and *BRCA1* was investigated in our study[9]. We concluded that BC risk in *BRCA1* mutation carriers is not modified by the c.183del frameshift mutation in *GPRC5A*[9]. Additionally, a case-control study by Hauke et al.[11] led to the conclusion that *NBN* (MIM**602667), a hitherto suspected BC/OC risk gene, is not associated with increased BC risk[11].

Second, the role of single nucleotide polymorphisms (SNPs or small insertions/deletions), combined to a polygenic risk score (PRS) in BC disposition was investigated. SNPs are in contrast to the known risk genes accompanied by a high allelic frequency (> 1%) and low effect sizes[12-15]. When considered individually, the identified risk loci are not useful for risk calculation[16]. However, combining the risk estimates of each SNP into a PRS can modify the relative risk (RR) to develop the disease[17,18]. The classical hypothesis that certain mutations or certain genes are the cause of the disease is abandoned and the hypothesis is put forward that combinations of certain low-risk factors also impressively change the disease risk, this represents a paradigm shift in classical genetic screening. The patient-specific calculation of the PRS aims to provide and improve personalized risk estimation. After confirmation of the clinically usefulness of PRSs for carriers of germline mutations in high risk genes such as *BRCA1/2*[16], the question arose whether PRSs are able to modify the BC risk in carriers of pathogenic variants (PVs) in moderately penetrant risk genes and whether incorporation of the PRS can improve personalized risk stratification. We therefore chose the moderately penetrant risk gene *CHEK2*, the 3rd most frequently mutated BC risk gene in Germany, and investigated a genome-wide association studies-independent sample of 760 female carriers of a PTV in the *CHEK2* gene[19]. For PRS calculations, we employed two established SNP sets: SNP set 1 (n = 77 SNPs), developed for BC risk stratification in women unselected for their *BRCA1/2* germline mutation status[20] and SNP set 2, (n = 88 SNPs), developed for BC risk stratification in female *BRCA1/2* mutation carriers[16,19]. Both SNP sets revealed concordant PRS results at the individual level. A statistically significant association of PRSs and first BC risk was revealed by weighted cohort Cox regression analysis (SNP set 1: Hazard ratio (HR): 1.71, 95% CI: 1.36 – 2.15, $p = 3.87 \times 10^{-6}$; SNP set 2: HR: 1.71, 95% CI: 1.37 – 2.13, $p = 2.25 \times 10^{-6}$)[19]. A stronger association of PRS in younger age groups was revealed. We observed a more than fivefold increase in the cumulative risk of mutation carriers between the lowest and highest decile of the PRS distribution at an age of 50 years (> 11% vs. < 2%) though this effect was attenuated by the age of 80 years (> 33% vs. < 13%)[19]. Based on the PRSs we were able to identify *CHEK2* mutation carriers with predicted lifetime risks (LTRs) for first BC, which exceeded the thresholds for intensified clinical surveillance as proposed by international guidelines[19].

Additionally, the utility of subtype-specific PRSs in a sample set of 297 female carriers of a PV in either *BRCA1* or *BRCA2* with a so-called "extreme phenotype" of disease onset (either affected by BC at a very young age (< 35 years) or BC-unaffected until the age of 60 years) was assessed. In addition to an overall BC PRS we employed two subtype-specific PRSs for estrogen receptor (ER)-negative and ER-positive (referred to as PRS_{ERpos} and PRS_{ERneg}) disease.

Across all PRSs, we observed higher mean PRSs in the subgroup of patients which were affected at young age (early diagnosis, ED) compared to those affected at older age (late diagnosis, LaD). For *BRCA1* mutation carriers the $PRS_{overall}$ showed the strongest association with the ED (OR: 1.30, 95% CI: 0.93 – 1.82, p = 0.1207). For *BRCA2* mutation carriers, the PRS_{ERneg} showed the highest association with the ED group (OR: 1.74, 95% CI: 1.16–2.60, p = 0.00814). Taken together, it may be useful to apply a subtype-specific PRSs in *BRCA1/2* mutation carriers to achieve higher and more accurate risk discrimination. Since guidelines for endocrine therapies in moderate to high-risk patients exist, which apply to ER-positive diseases[21] the incorporation of an ER-specific PRS could potentially identify women for which this treatment could be beneficial[20]. This work suggests that PRSs could be used to identify subsets of women at the extremes of the PRS distribution for which clinical management can be adapted accordingly.

Our results complement PRS studies of *BRCA1/2* mutation carriers and studies with cohorts not selected by mutation status[16,20]. Based on results from this thesis[19] and additional studies, the Center for Familial Breast and Ovarian Cancer Cologne implemented SNPs associated with BC on the TruRisk® gene panel used for routine diagnostic screening and adapted the gene selection according to our latest findings. The integration of the PRS into BC risk prediction is already implemented for healthy individuals with a familial background at the Center Familial Breast and Ovarian Cancer Cologne.