GCRI INTERVIEW

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Could you please describe your research focus?

As head of the familial breast and ovarian cancer center at the University Hospital of Cologne and coordinator of the 15 centers for familial breast and ovarian cancer that constitute the German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC), my research focus lies on the genetic causes of breast cancer. On a practitioner level, our work focuses on interdisciplinary counseling of at-risk patients and the evaluation of appropriate preventive measures, such as intensified surveillance and prophylactic surgery. In the laboratory, our research aims to identify new predisposing genes and risk alleles, modifying genes in *BRCA 1* or *BRCA2* mutation carriers, and genotype-/phenotype correlations.

What are the indicators of a genetic predisposition to breast cancer?

Within the GC-HBOC we established inclusion criteria for genetic testing, which show a mutation detection rate of at least 10%. The following familial risk constellations serve as inclusion criteria:

Familial risk constellation
≥ 3 breast cancer cases
≥ 2 breast cancer cases, 1 case < 51 years
≥ 1 breast cancer case and ≥ 1 ovarian cancer case (in two women)
≥ 1 breast cancer case and ≥ 1 ovarian cancer case (in two women)
≥ 2 ovarian cancer cases
≥ 1 male breast cancer case and ≥1 breast cancer or 1 ovarian cancer case
> 1 breast cancer case < 36 years
1 bil. breast cancer case, first < 51 years

BRCA1 and BRCA2 are well-known high-risk genes for breast and ovarian cancer. How many other high-risk genes have been discovered? How many do you believe to actually be involved in causing these specific cancer types?

Besides *BRCA1* and *BRCA2,* several low, moderate, and high risk genes have already been detected. Recent data suggest that the still missing genetic predispositions result from an oligo- or polygenetic trait, in which several moderate

and low risk genes frequently interact. It is very likely that latest activities of the large international consortia, the *Breast Cancer Association Consortium* (BCAC) and *The Consortium of Investigators of Modifiers of BRCA1/2* (CIMBA), will discover the remaining risk genes and variants in the near future. However, it will be a challenge to identify the interactions between these risk genes and establish a risk prediction score that will allow more precise risk calculations and, therefore, a better foundation for the decision-making on the uptake of preventive measures.

What preventive care advice do you offer women who have a family history of breast cancer?

The preventive care advice greatly depends on factors, such as the defective gene, the age, and the concrete familial constellation. We offer women from a high-risk constellation the possibility to participate in an intensified surveillance program. In case of a deleterious *BRCA1* or *BRCA2* mutation, we advise their patients to undergo a prophylactic salpingo**-**oophorectomy after having completed their family planning around the age of forty. For carriers of a mutated *BRCA1* or *BRCA2* gene a prophylactic mastectomy is a further option that we propose non-directively.

Are there any discernible differences between genetically triggered and spontaneous breast cancer during the course of the disease?

While *BRCA1*-associated breast cancers present a specific phenotype, i.e. high-grade, fast growth and triple negativity, *BRCA2*-associated breast cancers resemble the spontaneous form of breast cancer. As both genes are involved in DNA repair by homologous recombination of DNA double-strand breaks, the associated tumors are likely to be more sensitive to DNA intercalating chemotherapeutic compounds. In vitro and retrospective analyses suggest this hypothesis, although level 1 evidence by RCTs is still missing. A compound suitable for targeted therapy in *BRCA1* and *BRCA2* mutation carriers, the PARP inhibitors, already exists. PARP inhibitors target the base excision repair that interacts with the homologous recombination repair pathway, thereby killing *BRCA1*-associated tumor cells by the concept of synthetic lethality. Therefore, upcoming Phase III studies with PARP inhibitors in *BRCA1/BRCA2* mutation carriers are awaited with great interest.