Breast Cancer Risk – From Genetics to Molecular Understanding of Pathogenesis

Mammakarzinomrisiko – Genetik und molekulare Mechanismen der Pathogenese

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Abstract

Several advancements over the last decade have triggered the developments in the field of breast cancer risk research. One of them is the availability of the human genome sequence along with cheap genotyping possibilities. Another is the globalization of research, which has led to the growth of research collaboration into large international consortia that facilitate the pooling of clinical and genotype data of hundreds of thousands of patients and healthy control individuals. This review concerns with the recent developments in breast cancer risk research and focuses on the discovery of new genetic breast cancer risk factors and their meaning in the context of established non-genetic risk factors. Finally the clinical application is highly dependent on the accuracy of breast cancer risk prediction models, not only for all breast cancer patients, but also for molecular subtypes, preferably for those which are associated with an unfavorable prognosis. Recently risk prediction incorporates all possible risk factors, which include epidemiological risk factors, mammographic density and genetic risk factors.

Zusammenfassung

In den letzten Jahren sind, begünstigt durch einige Fortschritte, neue Entdeckungen auf dem Gebiet der Erforschung des Brustkrebserkrankungsrisikos gemacht worden. Zum einen stehen nach der Veröffentlichung des Referenz-Genoms preiswerte Genotypisierungsmethoden zur Verfügung und zum anderen haben sich Forschungskooperationen im Rahmen der Globalisierung in riesige Konsortien weiterentwickelt. In diesen Konsortien stehen genetische und nicht genetische Informationen von mehreren hunderttausend Brustkrebspatientinnen und gesunden Kontrollpersonen zur Verfügung. Diese Übersichtsarbeit stellt die jüngsten Entwicklungen und Entdeckungen sowohl für genetische Risikofaktoren als auch für deren Interaktion mit etablierten klinischen und epidemiologischen Risikofaktoren dar. Da die klinische Anwendung von der Genauigkeit einer Risikoprädiktion abhängig ist, versuchen Risikoprädiktionsmodelle so viele Risikofaktoren wie möglich in die Prädiktion des Erkrankungsrisikos mit einzubeziehen. Die Risikoprädiktion sollte sich nicht nur auf alle Frauen und Brustkrebspatientinnen beziehen, sondern, wenn möglich, auch das Risiko für molekulare Subtypen berücksichtigen. Insbesondere die Risikoprädiktion für molekulare Subtypen, wie das triple-negative Mammakarzinom, wären von besonderer Bedeutung.

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Bibliography
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Introduction

Advancements of breast cancer treatment and prevention have emerged over the last decade. The developments in both fields imply that both breast cancer treatment and breast cancer risk assessment have to develop towards each other.

Concerning breast cancer treatment and prognostic assessment the implementation and understanding of molecular subgroups has changed the approach how to treat breast cancer fundamentally [1–3]. It has been learnt that molecular subgroups of breast cancer represent either genetic or otherwise unique molecular patterns that determine the prognosis and seem to be the consequence of a specific pathogenesis [4].

With regard to breast cancer risk research the formation of large scale international networks with tens of thousands of breast cancer patients and controls with available genetic and non-genetic

information sheds some light on the direction into which breast cancer risk research will develop in the next years. Efforts aim at both, large scale genotyping and integrating genetic and non-genetic risk factors into risk assessment. The identification of molecular pathways of pathogenesis linked to specific risk factors might be the next steps needed to take breast cancer risk assessment into clinical practice.

Genetic Risk Factors

Since the discovery of the breast cancer genes 1 and 2 (BRCA1 and BRCA2) in 1994 and 1995 [5,6] many genetic variants have been described to contribute to breast cancer risk. After years of candidate gene research with its problems concerning false positive reporting [7] large consortia have enabled research at a genome-wide level, discovering and validating genetic variants that are associated with breast cancer risk. These genetic, inheritable variants are the reason for familial breast cancer risk. While higher penetrant loci make up for about 20% of familial breast cancer risk, about 28% are explained by newly discovered low penetrant loci, of which 14% are explained by about 70 low penetrant loci [8].

Recently more than 45 new common genetic breast cancer susceptibility loci were identified [8]. The following section will describe the discovery of those low penetrant loci, as this effort demonstrated the kind of collaborative efforts that lead to such success. In order to facilitate large scale genotyping the multicenter Collaborative Oncological Gene-environment Study (COGS) was founded aiming at the discovery of genetic factors of three hormone-related cancer types (breast, ovarian and prostate cancer), represented by several consortia, BCAC (Breast Cancer Association Consortium), CIMBA (The Consortium of Investigators of Modifiers of BRCA1/2), OCAC (Ovarian Cancer Association Consortium) and PRACTICAL (Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome). For further information see www.cogseu.org. These consortia built a custom genotyping array with more than 200 000 SNPs (iCOGS Chip), which was used for germline DNA genotyping of more than 200 000 individuals.

SNPs that were tested for breast cancer risk as part of COGS were selected from genome-wide association studies, performed in more than 10 000 breast cancer cases and more than 12 500 controls. Almost 30 000 SNPs were re-genotyped in more than 45 000 breast cancer cases and almost 42 000 healthy controls. This study identified more than 45 new breast cancer risk genetic variants [8–10] additionally to already published SNPs. An overview of validated breast cancer risk SNPs over the last decade is given in **Table 1**. Besides these validated breast cancer SNPs, that explain about 14% of familial breast cancer risk, it is suggested that about 1000 additional loci are involved in breast cancer susceptibility [8].

SNPs and Disease Risk Modification in BCRA Mutation Carriers

The same collaborative group was used to discover and validate genetic risk modifiers for individuals with a BRCA mutation [11]. The CIMBA within COGS used a genome-wide association study in more than 2700 *BRCA1* mutation carriers and selected about 32 000 SNPs to be genotyped with the iCOGS chip. A total of

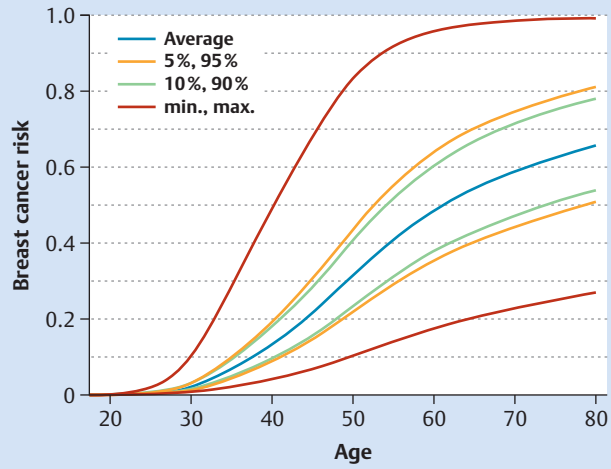

Fig. 1 Predicted breast and ovarian cancer absolute risks for BRCA1 mutation carriers at the 5th, 10th, 90th, and 95th percentiles of the combined SNP profile distributions. The minimum, maximum and average risks are also shown. Predicted cancer risks are based on the associations of known breast cancer susceptibility loci (identified through GWAS) with cancer risk for BRCA1 mutation carriers and loci identified through the present study. Breast cancer risks based on the associations with: 1q32, 10q25.3, 19p13, 6q25.1, 12p11, TOX3, 2q35, LSP1, RAD51L1 TERT (figure and figure legend from [11]).

11 705 *BRCA1* mutation carriers were genotyped with the iCOGS chip. This analysis gave indication that 17 SNPs were of interest and were genotyped in further about 2500 *BRCA1* mutation carriers [11]. After analysis for breast and ovarian cancer risk in this specific population, a novel breast cancer risk modifier locus at 1q32 for *BRCA1* mutation carriers was described (rs2290854, HR = 1.14, 95% CI: 1.09, 1.20). Two further SNPs were associated with ovarian cancer risk, one locus at 17q21.31 (rs17631303, HR = 1.27, 95% CI: 1.17, 1.38) and one at 4q32.3 (rs4691139, HR = 1.20, 95% CI: 1.17–1.38). Previously described risk modifiers and this new locus are summarized in **Table 2**.

When modeling breast cancer lifetime risk for *BRCA1* mutation carriers it becomes clear that additional loci can help to estimate different lifetime risks substantially more accurate. In this model *BRCA1* mutation carriers have an average lifetime risk of about 65% (**Fig. 1** from [11]). When incorporating genetic variants from 10 additional genes into the lifetime risk calculation of *BRCA1* mutation carriers [9,11] it can be seen that at the 5% and 95% percentiles of the population, lifetime risks of about 80% and 50% can be calculated. At the rare maximum and minimum level risks, even almost 100% and about 30% lifetime risk are calculated, however these constellations are very rare.

Pathways for triple negative breast cancers

It has been known already for some time, that *BRCA* mutations occur more frequently in patients with triple negative breast cancer tumors. This implies that the missing function of *BRCA* during the pathogenesis of breast cancer ultimatively leads to a triple negative breast cancer. In unselected cases the frequency of *BRCA* mutations among triple negative breast cancer patients has been reported to range between 4 and 21% (**Table 3**), however all populations were rather small and the study with the highest reported BRCA mutation prevalence included some familial cases. Other rare and medium to high penetrant mutations are dis-

Table 1 Validated single nucleotide polymorphisms (SNPs) for sporadic breast cancer (Chr: Chromosome; SNP: Single Nucleotid Polymorphism; OR: Odds Ratio; CI: Confidence Interval).

Chr	Gene name or Chr Region	SNP	MAF	OR (95 % CI)	Reference
1	1p11.2	rs11249433	0.40	1.09 (1.07, 1.11)	[8, 51]
1	1p13.2	rs11552449	0.17	1.07 (1.04, 1.10)	[8]
1	*LGR6*	rs6678914	0.41	1.00 (0.98, 1.02)	[10]
1	*MDM4*	rs4245739	0.26	1.02 (1.00, 1.04)	[10]
1	*PEX14*	rs616488	0.33	0.94 (0.92, 0.96)	[8]
2	2p24.1	rs12710696	0.36	1.04 (1.01, 1.06)	[10]
2	2q14.2	rs4849887	0.098	0.91 (0.88, 0.94)	[8]
2	2q31.1	rs2016394	0.48	0.95 (0.93, 0.97)	[8]
2	2q35	rs13387042	0.47	0.88 (0.86, 0.90)	[8, 49, 52]
2	2q35	rs16857609	0.26	1.08 (1.06, 1.10)	[8]
2	*CASP8*	rs1045485	0.13	0.97 (0.94, 1.00)	[8, 53]
2	*CDCA7*	rs1550623	0.16	0.94 (0.92, 0.97)	[8]
3	3p26.2	rs6762644	0.40	1.07 (1.04, 1.09)	[8]
3	*SLC4A7*	rs4973768	0.47	1.10 (1.08, 1.12)	[8, 54]
3	*TGFBR2*	rs12493607	0.35	1.06 (1.03, 1.08)	[8]
4	*ADAM29*	rs6828523	0.13	0.90 (0.87, 0.92)	[8]
4	*TET2*	rs9790517	0.23	1.05 (1.03, 1.08)	[8]
5	5p12	rs10941679	0.25	1.13 (1.10, 1.15)	[8, 55]
5	*EBF1*	rs1432679	0.43	1.07 (1.05, 1.09)	[8]
5	*MAP3K1*	rs889312	0.28	1.12 (1.10, 1.15)	[8, 56]
5	*PDE4D*	rs1353747	0.095	0.92 (0.89, 0.95)	[8]
5	*RAB3C*	rs10472076	0.38	1.05 (1.03, 1.07)	[8]
5	*TERT*	rs10069690	0.26	1.06 (1.04, 1.09)	[8, 15]
5	*TERT*	rs2736108	0.29	0.94 (0.92, 0.95)	[9]
6	6q14.1	rs17529111	0.22	1.05 (1.03, 1.08)	[8]
6	*ESR1*	rs2046210	0.34	1.08 (1.06, 1.10)	[8, 57]
6	*ESR1*	rs3757318	0.07	1.16 (1.12, 1.21)	[8, 58]
6	*FOXQ1*	rs11242675	0.39	0.94 (0.92, 0.96)	[8]
6	*RANBP1*	rs204247	0.43	1.05 (1.03, 1.07)	[8]
7	7q35	rs720475	0.25	0.94 (0.92, 0.96)	[8]
8	8p21.1	rs9693444	0.32	1.07 (1.05, 1.09)	[8]
8	8q21.11	rs6472903	0.18	0.91 (0.89, 0.93)	[8]
8	8q24	rs13281615	0.41	1.09 (1.07, 1.12)	[8, 56]
8	8q24.21	rs11780156	0.16	1.07 (1.04, 1.10)	[8]
8	*HNF4 G*	rs2943559	0.07	1.13 (1.09, 1.17)	[8]
9	9q31	rs865686	0.38	0.89 (0.88, 0.91)	[8, 59]
9	9q31.2	rs10759243	0.39	1.06 (1.03, 1.08)	[8]
9	*CDKN2A/B*	rs1011970	0.17	1.06 (1.03, 1.08)	[8, 58]
10	10q26.12	rs11199914	0.32	0.95 (0.93, 0.96)	[8]
10	*ANKRD16*	rs2380205	0.44	0.98 (0.96, 1.00)	[8, 58]
10	*DNAJC1*	rs7072776	0.29	1.07 (1.05, 1.09)	[8]
10	*DNAJC1*	rs11814448	0.02	1.26 (1.18, 1.35)	[8]
10	*FGFR2*	rs2981579	0.40	1.27 (1.24, 1.29)	[8, 58]
10	*FGFR2*	rs2981582	0.40	1.27 (1.24, 1.29)	[8, 56]
10	*TCF7L2*	rs7904519	0.46	1.06 (1.04, 1.08)	[8]
10	*ZMIZ1*	rs704010	0.38	1.08 (1.06, 1.10)	[8, 58]
10	*ZNF365*	rs10995190	0.16	0.86 (0.84, 0.88)	[8, 58]
11	11q13.1	rs3903072	0.47	0.95 (0.93, 0.96)	[8]
11	11q24.3	rs11820646	0.41	0.95 (0.93, 0.97)	[8]
11	*CCDN1*	rs614367	0.15	1.21 (1.18, 1.24)	[8, 58]
11	*CCND1*	rs554219	0.12	1.33 (1.28, 1.37	[60]
11	*CCND1*	rs75915166	0.06	1.38 (1.32, 1.44)	[60]
11	*LSP1*	rs3817198	0.31	1.07 (1.05, 1.09)	[8, 56]
12	12p13.1	rs12422552	0.26	1.05 (1.03, 1.07)	[8]
12	12q24	rs1292011	0.42	0.92 (0.90, 0.94)	[8, 61]
12	*NTN4*	rs17356907	0.30	0.91 (0.89, 0.93)	[8]
12	*PTHLH*	rs10771399	0.12	0.86 (0.83, 0.88)	[8, 61]
13	*BRCA2*	rs11571833	0.008	1.26 (1.14, 1.39)	[8]
14	*CCDC88C*	rs941764	0.34	1.06 (1.04, 1.09)	[8]
14	*PAX9*	rs2236007	0.21	0.93 (0.91, 0.95)	[8]
14	*RAD51L1*	rs999737	0.23	0.92 (0.90, 0.94)	[8, 51]
14	*RAD51L1*	rs2588809	0.16	1.08 (1.05, 1.11)	[8]
16	*CDYL2*	rs13329835	0.22	1.08 (1.05, 1.10)	[8]

Table 1 Validated single nucleotide polymorphisms (SNPs) for sporadic breast cancer (Chr: Chromosome; SNP: Single Nucleotid Polymorphism; OR: Odds Ratio; CI: Confidence Interval). *(continued)*

Chr	Gene name or Chr Region	SNP	MAF	OR (95% CI)	Reference
16	*FTO*	rs11075995	0.24	1.04 (1.02, 1.06)	[10]
16	*FTO*	rs17817449	0.40	0.93 (0.91, 0.95)	[8]
16	*TOX3*	rs3803662	0.26	1.24 (1.21, 1.27)	[8, 56]
17	*COX11*	rs6504950	0.28	0.94 (0.92, 0.96)	[8, 54]
18	18q11.2	rs527616	0.38	0.95 (0.93, 0.97)	[8]
18	*CHST9*	rs1436904	0.40	0.96 (0.94, 0.98)	[8]
19	19q13.31	rs3760982	0.46	1.06 (1.04, 1.08)	[8]
19	*MERIT40*	rs8170	0.19	1.04 (1.01, 1.06)	[8, 46]
19	*MERIT40*	rs2363956	0.50	1.01 (0.98–1.04)	[16]
19	*SSBP4*	rs4808801	0.35	0.93 (0.91, 0.95)	[8]
21	*NRIP1*	rs2823093	0.27	0.92 (0.90, 0.94)	[8, 61]
22	22q12.2	rs132390	0.036	1.12 (1.07, 1.18)	[8]
22	*MKL1*	rs6001930	0.11	1.12 (1.09, 1.16)	[8]

Table 2 Single nucleotide polymorphisms (SNPs) as modifiers of lifetime risk in *BRCA* mutation carriers (adapted from [11, 50, 62]).

		BRCA1 mutation carriers		*BRCA2* mutation carriers		
SNP	Gene/region	HR (95% CI)	p value	HR (95% CI)	p value	Reference
rs1801320	*RAD51*	1.59 (0.96 to 2.63)	0.07	3.18 (1.39 to 7.27)	< 0.001	[63]
rs1045485	*CASP8*	0.85 (0.76 to 0.97)	0.01	1.06 (0.88 to 1.27)	0.60	[64]
rs2981522	*FGFR2*	1.02 (0.95 to 1.09)	0.60	1.32 (0.20 to 1.45)	$< 10^{-7}$	[65]
rs3803662	*TOX3*	1.11 (1.03 to 1.19)	< 0.01	1.15 (1.03 to 1.27)	< 0.01	[65]
rs889312	*MAPK3K1*	0.99 (0.93 to 1.06)	0.90	1.12 (1.02 to 1.24)	0.02	[65]
rs3817198	*LSP1*	1.05 (0.99 to 1.11)	0.90	1.16 (1.07 to 1.25)	< 0.001	[66]
rs13387042	2q35	1.14 (1.04 to 1.25)	< 0.01	1.18 (1.04 to 1.33)	< 0.01	[66]
rs13281615	8q24	1.00 (0.94 to 1.05)	0.90	1.06 (0.98 to 1.14)	0.20	[66]
rs8170	*MERIT40*	1.26 (1.17 to 1.35)	$< 10^{-8}$	0.90 (0.77 to 1.05)	0.20	[46]
rs2363956	MERIT40	0.84 (0.80 to 0.89)	$< 10^{-8}$	1.12 (0.99 to 1.27)	0.07	[46]
rs2046210	6q25.1	1.17 (1.11 to 1.23)	$< 10^{-8}$	1.06 (0.99 to 1.14)	0.09	[67]
rs9397435	6q25.1	1.28 (1.18 to 1.40)	$< 10^{-7}$	1.14 (1.01 to1.28)	0.03	[67]
rs11249433	1p11.2	0.97 (0.92 to 1.02)	0.2	1.09 (1.02 to 1.17)	0.015	[67]
rs2290854	1q32	1.14 (1.09 to 1.20)	$< 10^{-7}$			[11]

CI: confidence intervals; HR: hazard ratio; SNP: single nucleotide polymorphism

Table 3 BRCA somatic mutation frequencies in unselected triple negative breast cancer patients.

Country	Population	Genotype method	Number of triple negatives	Number of BRCA2 mutations	Number of all BRCA mutations	Number of BRCA mutations (%)	Reference
China	unselected	PCR-DHPLC	79	3 (3.8)	6 (7.6)	3 (**3.8**)	[68]
USA	unselected	Myriad	199	13 (6.6)	8 (4.0)	21 (**10.6**)	[69]
USA	unselected	Myriad	77	11 (14.3)	3 (3.9)	14 (**18.2**)	[70]
Netherlands	unselected and familial	Sanger, MLPA	199	36 (18.1)	6 (3)	42 (**21.1**)	[71]

cussed to be associated with triple negative breast cancers such as *RAD51, TP53, BRAF, KRAS* and others [12, 13].

Besides these high penetrant genes there are several common variants that have been associated with a triple negative pathogenesis of breast cancer [14]. There have been reports about genetic variants in the following genes or regions to be associated with triple negative breast cancer risk: *TERT, MDM4*, 19p13.1 [10, 15, 16]. Additionally some loci were specific for estrogen receptor negative tumors and not estrogen receptor positive tumors. These loci are *FTO, LGR6, RALY* and 2p24.1 [10, 17].

Non-Genetic Risk Factors and Molecular Mechanism of Pathogenesis

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Only few non-genetic risk factors can be linked to a specific mechanism of action, such as DNA damage by radiation or some chemicals. For most non-genetic risk factors the molecular mechanism of action is unclear. However during the last years some studies have been published that shed some light on the pathogenesis of non-genetic risk factors. These studies explore whether breast cancer risk factors are specifically modifying the risk for intrinsic subtypes of breast cancer. Others studies inves-

tigate the interaction between molecular mechanisms of pathogenesis and risk factors. Finally interactions between commonly established risk factors and genetic risk factors could help as well to acquire knowledge about the molecular pathogenesis of non-genetic risk factors.

Pregnancies and breastfeeding

Pregnancies and breastfeeding are thought to have two effects on a woman's breast cancer risk. During and shortly after pregnancy, women have an increased risk of breast cancer, but later in life the breast cancer risk is lower in comparison with women who have never given birth to a child [18]. Most studies use a design that examines women at a later stage of their life cycle and provides data on the risk-reducing effect. Women with no live deliveries have a lifetime risk of about 6.3% up to the age of 70 [19]. The risk decreases with each pregnancy. The relative risk of breast cancer decreases by 4.3% (95% CI, 2.9 to 5.8) for every 12 months of breastfeeding, in addition to a decrease of 7.0% (95% CI, 5.0 to 9.0) for each birth [19].

There is some evidence that nulliparity and increasing age at first birth are associated with an increased risk for estrogen receptor positive breast cancer as well as progesterone receptor positive breast cancer, but not for triple negative breast cancer [20]. Similar associations are seen in case-case analyses. Patients with ER negative tumors are more likely to be nulliparous or having a high age at first birth [20].

The molecular mechanisms that link non-genetic risk factors to the pathogenesis of breast cancer are mainly unknown, however some first insights have been found in studies that look at the interaction between non-genetic and genetic risk factors with regard to breast cancer risk. A study within the COGS examined the interaction between 10 established environmental risk factors and 23 SNPs [21]. This study could show that the effect of rs3817198 in *LSP1* (Lymphocyte-specific protein 1) is greater in women with more births [21]. LSP1 is expressed in white blood cells and has been described to regulate neutrophil motility and adhesion to extracellular matrix proteins [22].

However it has to be pointed out that these kind of interaction analyses require really large sample sizes and a well-performed quality control of genotype and clinical data, as earlier studies with a smaller sample size (26 000 cases and 32 000 controls) were not able to show this LSP1-association after adjustment for multiple testing, although the nominal p-value for this association was 0.002 [23].

Mammographic density

Mammographic density (MD) is one of the most important risk factors for breast cancer. Women with a high MD have an up to fivefold increase in the risk for breast cancer [24–26]. Because of its importance, knowledge about the molecular mechanisms, and how mammographic density is linked to breast cancer pathogenesis, could be of special use for breast cancer prevention.

Some studies investigated whether mammographic density is a risk factor for a certain type of cancer. Early studies have shown that, for example, tumor histology was associated with breast cancer risk [27]. In a recent case-control study mammographic density seemed to be a stronger risk factor for cancer with a higher grading and estrogen receptor negative breast cancer. These results were confirmed in a case-case analysis associating a higher mammographic density with a lower percentage of estrogen receptor positive tumors [28]. The same study implied that the association with progesterone receptor positivity was inverse to that with the estrogen receptor. The authors concluded that mammographic density could specifically increase breast cancer risk through the progesterone receptor pathway, possibly involving RANK and RANKL [28].

The same case-case study did not see an association between mammographic density and tumor proliferation as assessed by Ki-67, however the association of commonly known breast cancer risk factors with mammographic density was different in patients with a high and a low proliferative tumor [29], suggesting that there might be a more complex relation between several risk factors and breast cancer pathogenesis.

Recently it could be shown on the protein level that the surface protein CD36 might be the mediator, which is responsible for high mammographic density in both healthy breast tissue and breast tumors [30]. It was shown that CD36 induces the transformation of stromal cells to adipocytes and that it suppressed the expression of extracellular matrix proteins. This was seen in both healthy breast tissue and tumor tissue [30]. This work is one of the first to shed light on the molecular background of breast density regulation in healthy and malignant tissue.

Finally there have been genetic risk factors that could be associated with several risk factors for breast cancer and breast cancer risk itself. One of these examples is the SNP rs3817198 in the gene *LSP1*. The rare allele was associated with both, a higher breast cancer risk and a higher mammographic density [31]. The same was seen for rs10483813 in *RAD51L1* [31]. The SNP in *LSP1* seems to be of special interest for breast cancer as it does not only alter breast cancer risk, is interacting with parity and mammographic density as breast cancer risk factors, but has been described as a prognostic factor in hormone receptor breast cancer patients as well [32].

These findings are some of the first examples that can help to understand through which molecular pathways breast density is linked to the pathogenesis of breast cancer. It will need more comprehensive analyses to identify further molecules and pathways that help to understand those connections.

Breast Cancer Assessment in Practice

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The information available about breast cancer risk has now become truly comprehensive. It has been applied in practice in the large breast cancer prevention trials, selecting for women with an increased risk for breast cancer, but the use of breast cancer risk assessment tools in clinical practice appears to be limited with regard to all aspects of prevention, intensified early detection, prophylactic medication, and prophylactic surgery.

Several tools have been developed for assessing breast cancer risk; some of the most frequently used are summarized in ▶ **Table 4** in relation to their use of risk factor information [33–43]. Some have been in use for decades already, such the Gail model [41]. More recently developed risk models aim at the combination of several risk factors, specifically mammographic density and genetic risk factors. The Tice model was one of the first to include mammographic density [44]. Together with genetic risk factors these models will possibly improve with regard to clinical utility. A case-control study has already combined breast density, breast cancer risk SNPs and clinical risk factors for the prediction of breast cancer risk [43].

Models for breast cancer risk prediction do not at present distinguish between distinct molecular subtypes, although subtype-specific risk factors have already been identified [20,45–49].

Table 4 Breast cancer risk assessment tools (adapted from [50]).

Risk factor	NCI model	Claus model	BRCAPro	Tyrer et al.	BOADICEA	Tice et al.	Darabi et al.
Reference	[40, 41]	[42]	[33–35]	[38]	[36, 37, 39]	[44]	[43]
Age	+	+	+	+	+	+	+
Age at menarche	+			+			+
Age at menopause				+			
BMI				+			+
Age at first birth	+			+			+
History of breast biopsies	+			+		+	+
History of premalignant lesions	+			+			+
HRT				+			
Family history of breast cancer	+	+	+	+	+		+
Family history of ovarian cancer			+	+	+		
Family history of other cancers					+		
Contralateral breast cancer			+	+	+		
Male breast cancer			+				
BRCA mutation			(+)		+		
Low penetrant genetic variants							+
Ethnicity	+					+	+
Mammographic density						+	+

BMI: body mass index; BOADICEA: Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; HRT: hormone replacement therapy; NCI: National Cancer Institute

However, predicting breast cancer and assessing specific risks can only make sense if they address women who have a high likelihood of developing a cancer with an unfavorable prognosis [50]. As early detection and cancer treatment also have an impact on survival, studies would ideally have to be designed in order to predict which women are likely to have an aggressive tumor that can be detected early [50].

Conclusions

Large international consortia and large scale genotyping studies can help to systematically work on the molecular background of breast cancer etiology and ultimately shed light on how these risk factors are connected to the pathogenesis on the molecular level. Over the last few years, very first insights have been described how non-genetic risk factors are linked to breast cancer risk on the molecular level. The scarceness of data that link breast cancer risk factors to molecular pathways of the pathogenesis makes clear that many more efforts have to be made in the future to elucidate these important causal links. However the plenty of new risk factors on the genetic side promise the discovery of new connections in the network of breast cancer risk factors.

Conflict of Interest

The authors declare that they have no conflict of interest.

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References

1 *Melcher C, Scholz C, Jager B et al.* Breast cancer: state of the art and new findings. Geburtsh Frauenheilk 2012; 72: 215–224
2 *Kolberg HC, Luftner D, Lux MP et al.* Breast cancer 2012 – new aspects. Geburtsh Frauenheilk 2012; 72: 602–615
3 *Kummel S, Kolberg HC, Luftner D et al.* Breast cancer 2011 – new aspects. Geburtsh Frauenheilk 2011; 71: 939–953
4 *Schmidt M, Fasching PA, Beckmann MW et al.* Biomarkers in breast cancer – an update. Geburtsh Frauenheilk 2012; 72: 819–832
5 *Miki Y, Swensen J, Shattuck-Eidens D et al.* A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994; 266: 66–71
6 *Wooster R, Bignell G, Lancaster J et al.* Identification of the breast cancer susceptibility gene BRCA2. Nature 1995; 378: 789–792
7 *Fasching PA, Gayther S, Pearce L et al.* Role of genetic polymorphisms and ovarian cancer susceptibility. Mol Oncol 2009; 3: 171–181
8 *Michailidou K, Hall P, Gonzalez-Neira A et al.* Large-scale genotyping identifies 41 new loci associated with breast cancer risk. Nat Genet 2013; 45: 353–361
9 *Bojesen SE, Pooley KA, Johnatty SE et al.* Multiple independent variants at the TERT locus are associated with telomere length and risks of breast and ovarian cancer. Nat Genet 2013; 45: 371–384
10 *Garcia-Closas M, Couch FJ, Lindstrom S et al.* Genome-wide association studies identify four ER negative-specific breast cancer risk loci. Nat Genet 2013; 45: 392–398
11 *Couch FJ, Wang X, McGuffog L et al.* Genome-wide association study in BRCA1 mutation carriers identifies novel loci associated with breast and ovarian cancer risk. PLoS Genetics 2013; 9: e1003212
12 *Kim Y, Kim J, Lee HD et al.* Spectrum of EGFR gene copy number changes and KRAS gene mutation status in Korean triple negative breast cancer patients. PLoS One 2013; 8: e79014
13 *Smolarz B, Zadrozny M, Duda-Szymanska J et al.* RAD51 genotype and triple-negative breast cancer (TNBC) risk in Polish women. Pol J Pathol 2013; 64: 39–43

14 *Stevens KN, Vachon CM, Couch FJ.* Genetic susceptibility to triple-negative breast cancer. Cancer Res 2013; 73: 2025–2030
15 *Haiman CA, Chen GK, Vachon CM et al.* A common variant at the TERT-CLPTM1L locus is associated with estrogen receptor-negative breast cancer. Nat Genet 2011; 43: 1210–1214
16 *Stevens KN, Fredericksen Z, Vachon CM et al.* 19p13.1 is a triple negative-specific breast cancer susceptibility locus. Cancer Res 2012; 72: 1795–1803
17 *Siddiq A, Couch FJ, Chen GK et al.* A meta-analysis of genome-wide association studies of breast cancer identifies two novel susceptibility loci at 6q14 and 20q11. Hum Mol Genet 2012; 21: 5373–5384
18 *Lambe M, Hsieh C, Trichopoulos D et al.* Transient increase in the risk of breast cancer after giving birth. N Engl J Med 1994; 331: 5–9
19 *Collaborative Group on Hormonal Factors in Breast Cancer.* Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet 2002; 360: 187–195
20 *Yang XR, Chang-Claude J, Goode EL et al.* Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. J Natl Cancer Inst 2011; 103: 250–263
21 *Nickels S, Truong T, Hein R et al.* Evidence of gene-environment interactions between common breast cancer susceptibility loci and established environmental risk factors. PLoS Genetics 2013; 9: e1003284
22 *Lanigan F, O'Connor D, Martin F et al.* Molecular links between mammary gland development and breast cancer. Cell Mol Life Sci 2007; 64: 3159–3184
23 *Milne RL, Gaudet MM, Spurdle AB et al.* Assessing interactions between the associations of common genetic susceptibility variants, reproductive history and body mass index with breast cancer risk in the breast cancer association consortium: a combined case-control study. Breast Cancer Res 2010; 12: R110
24 *McCormack VA, dos Santos Silva I.* Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2006; 15: 1159–1169
25 *Heusinger K, Loehberg CR, Haeberle L et al.* Mammographic density as a risk factor for breast cancer in a German case-control study. Eur J Cancer Prev 2011; 20: 1–8
26 *Boyd NF, Guo H, Martin LJ et al.* Mammographic density and the risk and detection of breast cancer. N Engl J Med 2007; 356: 227–236
27 *Fasching PA, Heusinger K, Loehberg CR et al.* Influence of mammographic density on the diagnostic accuracy of tumor size assessment and association with breast cancer tumor characteristics. Eur J Radiol 2006; 60: 398–404
28 *Heusinger K, Jud SM, Haberle L et al.* Association of mammographic density with hormone receptors in invasive breast cancers: results from a case-only study. Int J Cancer 2012; 131: 2643–2649
29 *Heusinger K, Jud SM, Haberle L et al.* Association of mammographic density with the proliferation marker Ki-67 in a cohort of patients with invasive breast cancer. Breast Cancer Res Treat 2012; 135: 885–892
30 *DeFilippis RA, Chang H, Dumont N et al.* CD36 repression activates a multicellular stromal program shared by high mammographic density and tumor tissues. Cancer Discov 2012; 2: 826–839
31 *Vachon CM, Scott CG, Fasching PA et al.* Common breast cancer susceptibility variants in LSP1 and RAD51L1 are associated with mammographic density measures that predict breast cancer risk. Cancer Epidemiol Biomarkers Prev 2012; 21: 1156–1166
32 *Fasching PA, Pharoah PD, Cox A et al.* The role of genetic breast cancer susceptibility variants as prognostic factors. Hum Mol Genet 2012; 21: 3926–3939
33 *Berry DA, Iversen jr. ES, Gudbjartsson DF et al.* BRCAPRO validation, sensitivity of genetic testing of BRCA1/BRCA2, and prevalence of other breast cancer susceptibility genes. J Clin Oncol 2002; 20: 2701–2712
34 *Parmigiani G, Berry D, Aguilar O.* Determining carrier probabilities for breast cancer-susceptibility genes BRCA1 and BRCA2. Am J Hum Genet 1998; 62: 145–158
35 *Parmigiani G.* BRCAPRO. 2004. Online: http://astor.som.jhmi.edu/BayesMendel/brcapro.html; last access: 01.11.2011
36 *Antoniou AC, Cunningham AP, Peto J et al.* The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. Br J Cancer 2008; 98: 1457–1466
37 *Antoniou AC, Pharoah PP, Smith P et al.* The BOADICEA model of genetic susceptibility to breast and ovarian cancer. Br J Cancer 2004; 91: 1580–1590
38 *Tyrer J, Duffy SW, Cuzick J.* A breast cancer prediction model incorporating familial and personal risk factors. Stat Med 2004; 23: 1111–1130
39 *Antoniou A.* BOADICEA. 2009. Online: http://www.srl.cam.ac.uk/genepi/boadicea/boadicea_home.html; last access: 01.11.2011
40 *National Institutes of Health.* Breast Cancer Risk Assessment Tool. 2011. Online: http://www.cancer.gov/bcrisktool/; last access: 01.11.2011
41 *Gail MH, Benichou J.* Validation studies on a model for breast cancer risk. J Natl Cancer Inst 1994; 86: 573–575
42 *Claus EB, Risch N, Thompson WD.* The calculation of breast cancer risk for women with a first degree family history of ovarian cancer. Breast Cancer Res Treat 1993; 28: 115–120
43 *Darabi H, Czene K, Zhao W et al.* Breast cancer risk prediction and individualised screening based on common genetic variation and breast density measurement. Breast Cancer Res 2012; 14: R25
44 *Tice JA, Cummings SR, Smith-Bindman R et al.* Using clinical factors and mammographic breast density to estimate breast cancer risk: development and validation of a new predictive model. Ann Intern Med 2008; 148: 337–347
45 *Azzato EM, Tyrer J, Fasching PA et al.* Association between a germline OCA2 polymorphism at chromosome 15q13.1 and estrogen receptor-negative breast cancer survival. J Natl Cancer Inst 2010; 102: 650–662
46 *Antoniou AC, Wang X, Fredericksen ZS et al.* A locus on 19p13 modifies risk of breast cancer in BRCA1 mutation carriers and is associated with hormone receptor-negative breast cancer in the general population. Nat Genet 2010; 42: 885–892
47 *Broeks A, Schmidt MK, Sherman ME et al.* Low penetrance breast cancer susceptibility loci are associated with specific breast tumor subtypes: findings from the Breast Cancer Association Consortium. Hum Mol Genet 2011; 20: 3289–3303
48 *Stevens KN, Vachon CM, Lee AM et al.* Common breast cancer susceptibility loci are associated with triple-negative breast cancer. Cancer Res 2011; 71: 6240–6249
49 *Milne RL, Benitez J, Nevanlinna H et al.* Risk of estrogen receptor-positive and -negative breast cancer and single-nucleotide polymorphism 2q35-rs13387042. J Natl Cancer Inst 2009; 101: 1012–1018
50 *Fasching PA, Ekici AB, Adamietz BR et al.* Breast cancer risk – genes, environment and clinics. Geburtsh Frauenheilk 2011; 71: 1056–1066
51 *Thomas G, Jacobs KB, Kraft P et al.* A multistage genome-wide association study in breast cancer identifies two new risk alleles at 1p11.2 and 14q24.1 (RAD51L1). Nat Genet 2009; 41: 579–584
52 *Stacey SN, Manolescu A, Sulem P et al.* Common variants on chromosomes 2q35 and 16q12 confer susceptibility to estrogen receptor-positive breast cancer. Nat Genet 2007; 39: 865–869
53 *Cox A, Dunning AM, Garcia-Closas M et al.* A common coding variant in CASP8 is associated with breast cancer risk. Nat Genet 2007; 39: 352–358
54 *Ahmed S, Thomas G, Ghoussaini M et al.* Newly discovered breast cancer susceptibility loci on 3p24 and 17q23.2. Nat Genet 2009; 41: 585–590
55 *Stacey SN, Manolescu A, Sulem P et al.* Common variants on chromosome 5p12 confer susceptibility to estrogen receptor-positive breast cancer. Nat Genet 2008; 40: 703–706
56 *Easton DF, Pooley KA, Dunning AM et al.* Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 2007; 447: 1087–1093
57 *Zheng W, Long J, Gao YT et al.* Genome-wide association study identifies a new breast cancer susceptibility locus at 6q25.1. Nat Genet 2009; 41: 324–328
58 *Turnbull C, Ahmed S, Morrison J et al.* Genome-wide association study identifies five new breast cancer susceptibility loci. Nat Genet 2010; 42: 504–507
59 *Fletcher O, Johnson N, Orr N et al.* Novel breast cancer susceptibility locus at 9q31.2: results of a genome-wide association study. J Natl Cancer Inst 2011; 103: 425–435
60 *French JD, Ghoussaini M, Edwards SL et al.* Functional variants at the 11q13 risk locus for breast cancer regulate cyclin D1 expression through long-range enhancers. Am J Hum Genet 2013; 92: 489–503
61 *Ghoussaini M, Fletcher O, Michailidou K et al.* Genome-wide association analysis identifies three new breast cancer susceptibility loci. Nat Genet 2012; 44: 312–318
62 *Milne RL, Antoniou AC.* Genetic modifiers of cancer risk for BRCA1 and BRCA2 mutation carriers. Ann Oncol 2011; 22 (Suppl. 1): i11–i17
63 *Antoniou AC, Sinilnikova OM, Simard J et al.* RAD51 135G–>C modifies breast cancer risk among BRCA2 mutation carriers: results from a combined analysis of 19 studies. Am J Hum Genet 2007; 81: 1186–1200

64 *Engel C, Versmold B, Wappenschmidt B et al.* Association of the variants CASP8 D302H and CASP10 V410I with breast and ovarian cancer risk in BRCA1 and BRCA2 mutation carriers. Cancer Epidemiol Biomarkers Prev 2010; 19: 2859–2868
65 *Antoniou AC, Spurdle AB, Sinilnikova OM et al.* Common breast cancer-predisposition alleles are associated with breast cancer risk in BRCA1 and BRCA2 mutation carriers. Am J Hum Genet 2008; 82: 937–948
66 *Antoniou AC, Sinilnikova OM, McGuffog L et al.* Common variants in LSP1, 2q35 and 8q24 and breast cancer risk for BRCA1 and BRCA2 mutation carriers. Hum Mol Genet 2009; 18: 4442–4456
67 *Antoniou AC, Kartsonaki C, Sinilnikova OM et al.* Common alleles at 6q25.1 and 1p11.2 are associated with breast cancer risk for BRCA1 and BRCA2 mutation carriers. Hum Mol Genet 2011; 20: 3304–3321
68 *Ou J, Wu T, Sijmons R et al.* Prevalence of BRCA1 and BRCA2 germline mutations in breast cancer women of multiple ethnic region in northwest China. J Breast Cancer 2013; 16: 50–54
69 *Hartman AR, Kaldate RR, Sailer LM et al.* Prevalence of BRCA mutations in an unselected population of triple-negative breast cancer. Cancer 2012; 118: 2787–2795
70 *Gonzalez-Angulo AM, Timms KM, Liu S et al.* Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. Clin Cancer Res 2011; 17: 1082–1089
71 *Lips EH, Mulder L, Oonk A et al.* Triple-negative breast cancer: BRCAness and concordance of clinical features with BRCA1-mutation carriers. Br J Cancer 2013; 108: 2172–2177