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Die Situation von Frauen mit einer pathogenen Variante in einem moderaten bis hoch-moderaten Risikogen für familiären Brustkrebs. Einblicke in die Erfahrungswelten und Bedürfnisse - ein qualitativer Ansatz

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Erklärung

Ich erkläre hiermit, dass ich die vorliegende Dissertationsschrift ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; die aus fremden Quellen direkt oder indirekt übernommenen Gedanken sind als solche kenntlich gemacht.[1]

Bei der Auswahl und Auswertung des Materials sowie bei der Herstellung des Manuskriptes habe ich Unterstützungsleistungen von folgenden Personen erhalten:

Frau Prof. Dr. Stephanie Stock
Frau Dr. Sibylle Kautz-Freimuth

Weitere Personen waren an der Erstellung der vorliegenden Arbeit nicht beteiligt. Insbesondere habe ich nicht die Hilfe einer Promotionsberaterin/eines Promotionsberaters in Anspruch genommen. Dritte haben von mir weder unmittelbar noch mittelbar geldwerte Leistungen für Arbeiten erhalten, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertationsschrift stehen.

Die Dissertationsschrift wurde von mir bisher weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.

Die dieser Arbeit zugrunde liegenden qualitativen Interviews wurden von Frau Dr. Sibylle Kautz- Freimuth und mir selbst im Zeitraum Februar 2017 bis Oktober 2017 durchgeführt.
Die Transkription der Interviews erfolgte durch das Schreibbüro Sabine Brinkmann.
Der Datensatz wurde von mir selbst mit Hilfe der Software MAXQDA ausgewertet. Nachdem die Hälfte des Materials gesichtet wurde, erfolgte eine interne Validierung der angewandten Methodik und der vorläufigen Auswertung durch Frau Dr. Sibylle Kautz-Freimuth und Frau Clarissa Lemmen.

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[1]Bei kumulativen Promotionen stellt nur die eigenständig verfasste Einleitung und Diskussion die Dissertationsschrift im Sinne der Erklärung gemäß dieser Erklärung dar.

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Abkürzungsverzeichnis

AGO	Arbeitsgemeinschaft Gynäkologische Onkologie
ATM	Ataxia teleangiectasia mutated
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V.
BC	Breast cancer
BRCA1	Breast cancer gene 1
BRCA2	Breast cancer gene 2
CHECK2	Checkpoint kinase 2
CRCI	Cancer-related cognitive impairments
iFE	Programm der multimodalen intensivierten Früherkennungsuntersuchung der Brust
ISCED	International Standard Classification of Education
MBCG	Moderate-risk breast cancer genes
NICE	National Institute for Health and Care Excellence
OC	Ovarian cancer
PALB2	Partner and localizer of BRCA2
PCI	Problem-centered interview
PRS	Polygener Risikoscore
PTGC	Post-test genetic counseling
RRBM	Risikoreduzierende bilaterale Mastektomie
RRKM	Risikoreduzierende kontralaterale Mastektomie
RRM	Risk-reducing mastectomy
RRSO	Risikoreduzierende Salpingo-Oophorektomie
SNP	Single nucleotide polymorphism

1. Zusammenfassung

Mit 69.000 Neuerkrankungen pro Jahr ist Brustkrebs die häufigste Krebserkrankung bei Frauen in Deutschland. Bei etwa 30 % der neu diagnostizierten Brustkrebserkrankungen liegt eine familiäre Häufung vor. Neben den Hochrisikogenen *BRCA1* und *BRCA2*, die rund 24 % der familiären Brustkrebserkrankungen zu Grunde liegen, wurden weitere Risikogene für familiären Brustkrebs identifiziert, darunter die Gene *ATM, CHEK2* und *PALB2*. Diese aktuell als moderat bis hoch-moderat eingestuften Risikogene sind mit einem Brustkrebsrisiko von 20 bis 50 % assoziiert und unterscheiden sich von den Hochrisikogenen hinsichtlich der assoziierten Erkrankungsrisiken, der betroffenen Organe und der angebotenen präventiven Optionen. Wenig ist darüber bekannt, welches medizinische Wissen Frauen mit pathogenen Varianten in moderaten bis hoch-moderaten Risikogenen für familiären Brustkrebs nach dem persönlichen ärztlichen Genbefundgespräch haben, wie sie ihre Situation wahrnehmen, wie sie mit ihrer Situation umgehen und welcher zusätzliche Informations- und Unterstützungsbedarf möglicherweise besteht. In der vorliegenden Arbeit wurden problemzentrierte, leitfadengestützte Einzelinterviews mit zwölf Frauen durchgeführt, die pathogene Varianten in moderaten bis hoch-moderaten Risikogenen für familiären Brustkrebs tragen. Die Auswertung der Interviews erfolgte gemäß der qualitativen Inhaltsanalyse nach Mayring. Die Frauen waren zwischen 29 und 59 Jahre alt und trugen pathogene Varianten in den Risikogenen *CHEK2* (n=8), *ATM* (n=1) und *PALB2* (n=3). Bezüglich folgender Aspekte konnten medizinische Unklarheiten und Informationsbedürfnisse identifiziert werden: a) medizinische Fachbegriffe, b) Risikowahrnehmung, c) Vererbungswahrscheinlichkeit, d) Brustkrebstherapie bei familiärem Brustkrebs, e) Lebensstil und Risikofaktoren und f) Familienplanung und risikoreduzierende Mastektomie. Die Frauen berichteten zudem über ein breites Spektrum an Gefühlen, sowohl positive (Erleichterung, Gelassenheit) als auch negative (Überwältigung, Angst, Trauer, Schuldgefühle), die unmittelbar durch das Genbefundgespräch oder durch die mit der pathogenen Variante verbundene Allgemeinsituation hervorgerufen wurden. Alle Frauen wandten Strategien des emotionsorientierten Copings an, um mit dieser lebenslangen Situation umzugehen. Die Einschätzung und Bewertung der Bewältigungsstrategien erkrankter Mütter oder erkrankter Familienmitglieder kann das eigene Verhalten und die eigenen Bewältigungsmechanismen der Frauen beeinflussen. Die Ergebnisse der vorliegenden Studie könnten genutzt werden, um das Genbefundgespräch und die ärztliche Betreuung betroffener Frauen noch bedürfnis- und patientenorientierter zu gestalten und die Frauen bei der Bewältigung dieser neuen Situation weiter zu unterstützen. Um nach dem Genbefundgespräch möglicherweise noch bestehenden Unsicherheiten und Informationsbedürfnissen zu begegnen, könnten für diese Frauen schriftliche, strukturierte, evidenzbasierte und laiengerechte Informationen in deutscher Sprache entwickelt werden.

2. Einleitung

2.1. Familiärer Brustkrebs

In Deutschland erkrankt etwa eine von acht Frauen im Laufe ihres Lebens an Brustkrebs. Die bösartige Neubildung der Brustdrüse ist mit 69.000 neu diagnostizierten Erkrankungsfällen pro Jahr die häufigste Krebserkrankung der Frau in Deutschland [1]. Bei 30 % der erkrankten Frauen lässt die Familienanamnese und/oder das Erkrankungsalter auf eine familiäre Form (auch: genetische Form) des Brustkrebses schließen [2]. Diesen familiären Krebserkrankungen liegen pathogene Varianten (auch: Mutationen) in verschiedenen Genen zugrunde. Da diese in den Samen- oder Eizellen vorhanden sind, werden sie als Keimbahnmutationen bezeichnet, die von Generation zu Generation weitervererbt werden können. Die am längsten bekannten und am besten erforschten Risikogene für familiären Brustkrebs sind die Hochrisikogene *BRCA1* und *BRCA2,* auf die ca. 24 % der familiären Brustkrebserkrankungen zurückzuführen sind. Der technische Fortschritt in der Molekulargenetik und immer breitere und kostengünstigere Einsatz von Next-Generation-Sequencing führte in den letzten Jahren zur Identifizierung einer Reihe weiterer Risikogene für familiären Brustkrebs, die zunächst als moderate Risikogene eingestuft wurden. Liegt eine pathogene Variante in einem Hochrisikogen oder moderaten Risikogen vor, so ist das Risiko, an Brustkrebs zu erkranken, gegenüber dem Risiko der Allgemeinbevölkerung lebenslang erhöht. Die Nachkommen von Eltern, bei denen ein Elternteil eine pathogene Variante in einem Risikogen trägt, haben unabhängig vom Geschlecht eine 50%ige Wahrscheinlichkeit, die pathogene Variante von diesem Elternteil zu erben. Sollte aufgrund der eigenen Anamnese und/oder einer familiären Häufung von Krebserkrankungen der Verdacht bestehen, dass in einer Familie ein erhöhtes Risiko für familiären Brustkrebs vorliegt, kann in einem der 23 universitären Zentren des Deutschen Konsortiums Familiärer Brust- und Eierstockkrebs eine genetische Untersuchung und Beratung in Anspruch genommen werden. Mithilfe der genetischen Untersuchung ist es möglich, eine eventuell vorliegende pathogene Variante zu identifizieren und ein individuelles Risikoprofil zu erstellen. Anhand identifizierter Index-Personen können auch weitere Anlagenträgerinnen in der blutsverwandten Familie durch eine genetische Untersuchung identifiziert und risikoadaptiert in Bezug auf ihre individuellen präventiven Möglichkeiten beraten werden.

2.1.1. Genetische Beratung und Untersuchung

Die 1996 vom Deutschen Konsortium Familiärer Brust- und Eierstockkrebs etablierten und validierten Kriterien, nach denen eine genetische Untersuchung und Beratung angeboten werden sollte, finden nach wie vor ihre Anwendung [2]. Diese Einschlusskriterien beziehen sich auf familiäre Belastungen, die mit einer mindestens 10%igen Wahrscheinlichkeit für das

Vorliegen einer pathogenen Variante in einem Risikogen einhergehen[3]. Liegt eines dieser Kriterien vor, sollte betroffenen Frauen eine genetische Beratung und Untersuchung angeboten werden (Tabelle 1).

Aktuell werden im Deutschen Konsortium Familiärer Brust- und Eierstockkrebs zwei weitere Kriterien evaluiert, bei denen – trotz unauffälliger Familienanamnese – die Wahrscheinlichkeit für das Vorliegen pathogener Varianten möglicherweise erhöht ist[4-6]. Diese zusätzlichen Kriterien sind 1.) mindestens eine Frau mit triple-negativem Brustkrebs vor dem 51. Lebensjahr und 2.) mindestens eine Frau mit Eierstockkrebs vor dem 81. Lebensjahr.

Tabelle 1) Einschlusskriterien für eine genetische Untersuchung[2]

In einer Linie der Familie sind…
… mindestens 3 an Brustkrebs erkrankte Frauen.
… mindestens 2 an Brustkrebs erkrankte Frauen, davon 1 vor dem 51. Lebensjahr.
… mindestens 1 an Brustkrebs und 1 an Eierstockkrebs erkrankte Frau.
… mindestens 2 an Eierstockkrebs erkrankte Frauen.
… mindestens 1 an Brust- und Eierstockkrebs erkrankte Frau.
… mindestens 1 an Brustkrebs erkrankte Frau mit einem Erkrankungsalter von ≤ 35 Jahren
… mindestens 1 an bilateralem Brustkrebs erkrankte Frau mit einem Erkrankungsalter von ≤ 50 Jahren.
… mindestens 1 an Brustkrebs erkrankter Mann und 1 an Brust- oder Eierstockkrebs erkrankte Frau.

Um ein strukturiertes Screening-Instrument für den breiten Einsatz in der genetischen Beratung zu etablieren, wurden diese Kriterien von Rhiem et al.[7] in eine Checkliste integriert, anhand derer ein Risikoscore ermittelt werden kann (Abbildung 1). Frauen mit einem Risiko-Score ≥ 3 haben ein mindestens 10%iges Risiko, Trägerin einer pathogenen Variante in einem Risikogen zu sein und eine genetische Beratung und Untersuchung wird empfohlen[3].

Frauen, die sich für eine genetische Untersuchung entscheiden und ein positives genetisches Testergebnis für eine pathogene Variante in einem Risikogen für familiären Brustkrebs haben, werden zu einem persönlichen ärztlichen Gespräch zur Genbefundmitteilung und Risikoberatung (im Folgenden: Genbefundgespräch) in ein spezialisiertes Zentrum für familiären Brust- und Eierstockkrebs eingeladen. Am Zentrum Familiärer Brust- und Eierstockkrebs der Uniklinik Köln wird diese individuelle genetische Beratung von einer Fachärztin oder einem Facharzt für Gynäkologie und Geburtshilfe mit einer speziellen Ausbildung für erblichen Brust- und Eierstockkrebs oder für Humangenetik durchgeführt. Alle Beratenden absolvieren viermal im Jahr ein spezielles Kommunikationscurriculum, das vom

Fachbereich Psychosomatische Medizin und Psychotherapie der Uniklinik Köln durchgeführt wird.

Abbildung 1) Checkliste zur Erfassung einer familiären Belastung für Brust- und Eierstockkrebs[8]

Checkliste zur Erfassung einer möglichen erblichen Belastung für Brust- und/oder Eierstockkrebs

incl. DCIS und Borderline

Name Patientin/Patient: **Geburtsdatum:**

DKG KREBSGESELLSCHAFT Zertifizierung

A. Patient/in und deren Geschwister / Kinder

Auftreten bei Patientin/Patient	Anzahl	Gewichtung	Ergebnis
eines Mammakarzinoms bei der Patientin **vor** dem 36. Geburtstag		3	0
eines triple-negativen Mammakarzinoms bei der Patientin vor dem 60. Geburtstag*		3	0
eines unilateralen Mammakarzinoms bei der Patientin **vor** dem 50./51.* Geburtstag		2	0
eines bilateralen Mammakarzinoms bei der Patientin, das erste **vor** dem 50./51.* Geburtstag		3	0
eines uni- oder bilateralen Mammakarzinoms bei der Patientin **nach** dem 51. Geburtstag		1	0
eines uni- oder bilateralen Mammakarzinoms bei dem Patienten (männlich)		2	0
eines Ovarialkarzinoms bei der Patientin vor dem 80. Geburtstag*		3	0
eines Ovarial-/Tuben-/primären Peritonealkarzinoms bei der Patientin		2	0
Auftreten bei Kindern, Geschwistern und deren Kindern			
eines Mammakarzinoms bei Schwestern/Töchtern/Nichten **vor** dem 36. Geburtstag		3	0
eines unilateralen Mammakarzinoms bei Schwestern/Töchtern/Nichten **vor** dem 50./51.* Geburtstag		2	0
eines bilateralen Mammakarzinoms bei Schwestern/Töchtern/Nichten, das erste **vor** dem 50./51.* Geburtstag		3	0
eines uni- oder bilateralen Mammakarzinoms bei Schwestern/Töchtern/Nichten **nach** dem 51. Geburtstag		1	0
eines uni- oder bilateralen Mammakarzinoms bei Brüdern/Söhnen/Neffen		2	0
eeines Ovarial-/Tuben-/primären Peritonealkarzinoms bei Schwestern/Töchtern/Nichten		2	0
		A	0

B. Mütterliche Linie (incl. Mutter)

Auftreten	Anzahl	Gewichtung	Ergebnis
eines Mammakarzinoms bei einer Angehörigen **vor** dem 36. Geburtstag		3	0
eines unilateralen Mammakarzinoms bei einer Angehörigen **vor** dem 50./51.* Geburtstag		2	0
eines bilateralen Mammakarzinoms bei einer Angehörigen, das erste **vor** dem 50./51.* Geburtstag		3	0
eines uni- oder bilateralen Mammakarzinoms bei einer Angehörigen **nach** dem 51. Geburtstag		1	0
eines Mammakarzinoms bei einem angehörigen Mann		2	0
eines Ovarial-/Tuben-/primären Peritonealkarzinoms bei einer Angehörigen		2	0
Summe weitere mütterliche Linie		B	0

C. Väterliche Linie (incl. Vater)

Auftreten	Anzahl	Gewichtung	Ergebnis
eines Mammakarzinoms bei einer Angehörigen **vor** dem 36. Geburtstag		3	0
eines unilateralen Mammakarzinoms bei einer Angehörigen **vor** dem 50./51.* Geburtstag		2	0
eines bilateralen Mammakarzinoms bei einer Angehörigen, das erste **vor** dem 50./51.* Geburtstag		3	0
eines uni- oder bilateralen Mammakarzinoms bei einer Angehörigen **nach** dem 51. Geburtstag		1	0
eines Mammakarzinoms bei einem angehörigen Mann		2	0
eines Ovarial-/Tuben-/primären Peritonealkarzinoms bei einer Angehörigen		2	0
Summe väterliche Linie		C	0

D. Der höhere Wert aus B und C	D	0
E. Summe aus A und D = Risiko-Score	A+D	0

Ausfüllhinweis

Zunächst wird die Anzahl bekannter Erkrankungsfälle bei den Geschwistern und Kindern, einschließlich der aktuellen Erkrankung der Patientin sowie in der mütterlichen und väterlichen Linie erfragt.

Diese Zahlen werden mit den jeweiligen Gewichtungen multipliziert. Dann wird die Summe aus diesen Ergebnissen errechnet und in die Felder A und B und C eingetragen.

Der höhere der beiden Werte aus den Feldern B und C wird in Feld D eingetragen.

Der Gesamtscore errechnet sich dann aus der Summe der Felder A und D.
Eine Risikoberatung in den ausgewiesenen Zentren ist bei Scores ≥ 3 Punkten zu empfehlen
*Diese Einschlusskriterien gelten nur in Kooperation mit den zertifizierten FBREK-Zentren , die diese im Rahmen der Wissen generierenden Versorgung validieren. Die anderen Einschlusskriterien entsprechen den Vorgabe des EBM.

Version: 11. Januar 2022 (C)
Ärztekammer Westfalen-Lippe,
Deutsche Krebsgesellschaft,
Deutsche Gesellschaft für Senologie,
Deutsches Konsortium für Erblichen Brust- und Eierstockkrebs

Während des Genbefundgesprächs erhalten Frauen mit dem Befund einer pathogenen Variante in einem Risikogen für familiären Brustkrebs ausführliche, individuelle Informationen über das Testergebnis, die Vererbungswahrscheinlichkeit an die Kinder, die mit der pathogenen Variante verbundenen Krebsrisiken sowie die Präventionsmaßnahmen, die den Frauen gemäß ihres Risikoprofils angeboten werden können. Besteht, wie etwa bei einer pathogenen Variante im *BRCA1*- oder *BRCA2*-Gen, neben einem erhöhten Brustkrebsrisiko auch ein erhöhtes Eierstockkrebsrisiko, erfolgt eine ausführliche risikoadaptierte Beratung bezüglich Brust- und Eierstockkrebs. Im Hinblick auf andere potenziell assoziierte Krebsrisiken (z.B. Pankreaskarzinom) wird den Frauen eine weitere Beratung in einem auf diese Krebsform

spezialisierten Zentrum empfohlen. Ergänzend zu diesen mündlichen Informationen können die Frauen verschiedene schriftliche Informationen erhalten: Dazu gehören allgemeine Informationen über familiären Brust- und Eierstockkrebs, Informationen über die Selbsthilfe-Institution BRCA-Netzwerk e.V., Möglichkeiten der psychoonkologischen Unterstützung, eine Broschüre mit Informationen über das Programm der multimodalen intensivierten Früherkennungsuntersuchung der Brust (im Folgenden: iFE) und - falls zutreffend - Informationen über risikoreduzierende Operationen. Darüber hinaus erhält jede Frau im Anschluss an das Gespräch per Post einen persönlichen Arztbrief und einen Informationsbrief für die Angehörigen. Der Arztbrief ist eine kurze, schriftliche Zusammenfassung des Genbefundgesprächs und enthält Informationen über: 1. den Namen der pathogenen Variante, 2. das Eierstockkrebsrisiko, das mit dieser pathogenen Variante verbunden sein könnte, 3. das Brustkrebsrisiko, das mit dieser pathogenen Variante verbunden sein könnte, 4. die risikoreduzierende Entfernung von Eierstöcken und Eileitern und/oder die risikoreduzierende Mastektomie, falls empfohlen, 5. die Möglichkeit der Teilnahme am iFE, 6. weitere Krebsrisiken, die mit der pathogenen Variante verbunden sein könnten, 7. die Vererbungswahrscheinlichkeit, 8. die Möglichkeit einer psychoonkologischen Betreuung.

2.1.2. Risikogene für familiären Brustkrebs

Bereits in den späten 1980er und frühen 1990er Jahren waren Forscher auf der Suche nach einem Gen, das für die Prädisposition für die Entstehung von Brustkrebs verantwortlich ist. Nach der Identifikation von Chromosom 17 als möglichem Sitz dieses Gens im Jahr 1990 konnten wenige Jahre später die Gene *BRCA1* und *BRCA2* als Hochrisikogene für familiären Brustkrebs auf Chromosom 17 und 13 identifiziert und analysiert werden[9-11]. Seit Beginn der 2000er Jahre wurden weitere Risikogene identifiziert, die bei der Entwicklung von Brustkrebs eine Rolle spielen. Diese neueren Gene wurden zunächst als moderate Risikogene eingestuft. Die TruRisk® Genpanel-Analyse des Deutschen Konsortiums Familiärer Brust- und Eierstockkrebs berücksichtigt bei vorliegendem Verdacht auf eine pathogene Variante in einem Risikogen alle aktuell bekannten Risikogene für familiären Brust- und Eierstockkrebs, darunter die sogenannten 11 Core Gene (*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, PALB2, RAD51C, RAD51D, TP53*) und 7 weitere Syndrom-assoziierte Gene, bei denen ein erhöhtes Brust- und/oder Eierstockkrebsrisiko vermutet wird (*EPCAM, MLH1, MSH2, MSH6, PMS2, PTEN, STK11*)[12]. Zusätzlich werden weitere 16 Gene untersucht (z. B. *NBN, FANCM, XRCC2, RECQL*), die aktuell vom Deutschen Konsortium Familiärer Brust- und Eierstockkrebs im Rahmen von Studien weiter erforscht und validiert werden.

Um Hochrisikogene und moderate Risikogene voneinander abzugrenzen, definierten Couch et al.[13] 2017 ein 2- bis 5-fach erhöhtes Erkrankungsrisiko als moderat und ein >5-fach erhöhtes Erkrankungsrisiko als hoch. Das National Institute for Health and Care Excellence (NICE)

definierte 2019 ein Risiko von 30 % als den Schwellenwert für ein hohes Risiko (Tabelle 2)[14]. Auch weitere internationale Studien sowie die Leitlinie der AGO Kommission Mamma berufen sich inzwischen auf die Einteilung des NICE.[12,15].

In den letzten Jahren hat sich die Forschung zunehmend mit der Bedeutung und Untersuchung sogenannter single nucleotide polymorphism (SNP) beschäftigt. Darunter versteht man Niedrigrisikovarianten, die jede einzeln für sich genommen das Brustkrebsrisiko nur unwesentlich erhöhen, jedoch zusammen multiplikativ wirken und deren Gesamtheit im sogenannten polygenen Risikoscore (PRS) abgebildet wird. Dieser polygene Risikoscore kann das Brustkrebsrisiko, das mit einer pathogenen Variante in einem Hochrisikogen oder einem moderaten bis hoch-moderaten Risikogen assoziiert ist, weiter modifizieren[16,17]. Die Bestimmung des PRS für Brustkrebs wird im Zentrum Familiärer Brust- und Eierstockkrebs der Uniklinik Köln bereits in der regulären Versorgung von Frauen mit einer pathogenen Variante in einem Hochrisikogen oder einem moderat bis hoch-moderaten Risikogen angewendet und in die Berechnung des individuellen Risikoprofils einbezogen[18,19].

Tabelle 2) Brustkrebs Risikokategorien nach den Richtlinien des National Institute for Health and Care Excellence (NICE)[14]

	Hohes Brustkrebsrisiko	Moderates Brustkrebsrisiko
Lebenszeitrisiko ab dem 20. Lebensjahr	≥30 %	>17 % und <30 %
Risiko zwischen dem 40. und 50. Lebensjahr	>8 %	3 bis 8 %

2.1.2.1 Hochrisikogene für familiären Brustkrebs: *BRCA1* und *BRCA2*

Die Assoziation der Gene *BRCA1* und *BRCA2* mit dem gehäuften Auftreten von Brustkrebs wurde Anfang der 1990er Jahre von Miki et al.[10] und Wooster et al.[11] entdeckt und beschrieben. Diese Assoziation war auch namensgebend für die beiden Gene, denn *BRCA* steht für Breast Cancer. Aktuell werden ca. 24 % der familiären Brustkrebserkrankungen auf eine pathogene Variante in einem dieser beiden Hochrisikogene zurückgeführt[3,7]. Die eigene Familienanamnese im Hinblick auf Brustkrebserkrankungen sowie das Alter zum Zeitpunkt der Brustkrebsdiagnose sind die stärksten Prädiktoren für das Tragen einer pathogenen Variante im *BRCA1*- oder *BRCA2*-Gen[7]. Neuesten Studien zufolge[20] beträgt das kumulative Brustkrebsrisiko bis zum 80. Lebensjahr (Lebenszeitrisiko) bei Vorliegen einer pathogenen Variante im *BRCA1*-Gen 72 % und bei Vorliegen einer pathogenen Variante im *BRCA2*-Gen 69 %. Im Vergleich dazu liegt das kumulative Lebenszeitrisiko für Brustkrebs in der weiblichen Allgemeinbevölkerung bei 12,4 %[1]. Das kumulative Lebenszeitrisiko, bis zum 80. Lebensjahr

an Eierstockkrebs zu erkranken, ist mit 44 % (bei einer pathogenen Variante im *BRCA1*-Gen) und 17 % (bei einer pathogenen Variante im *BRCA2*-Gen) etwas geringer, im Vergleich zum Lebenszeitrisiko für sporadischen Eierstockkrebs in der Allgemeinbevölkerung von 1,3 % jedoch deutlich erhöht[1].

2.1.2.2 Moderate bis hoch-moderate Risikogene für familiären Brustkrebs: *ATM, CHEK2* und *PALB2*

Eine signifikante Assoziation der Risikogene *ATM*, *CHEK2* und *PALB2* mit der Entstehung von Brustkrebs konnte in zwei 2021 publizierten Fall-Kontroll-Studien mit sehr großen Kohorten von insgesamt über 150.000 Frauen erneut bestätigt werden[15,21]. Für die meisten der zunächst als moderat bezeichneten Risikogene sind jedoch die Prävalenz, die altersspezifischen Krankheitsrisiken, die Tumorsubtypen und die Wirksamkeit von Präventionsmaßnahmen noch nicht ausreichend bekannt und bestehen weiterhin Unsicherheiten und eine nicht überzeugende oder unzureichende Datengrundlage[22,23]. Narod[23] stellt fest, dass es weiterer Forschung bedarf, um das Ausmaß des Krebsrisikos und das Krebsspektrum für jedes dieser moderaten Risikogene zu bestimmen.

Für *ATM* wird aktuell ein Lebenszeitrisiko für Brustkrebs von ca. 20 % bis 33 % angenommen, wobei das Risiko altersabhängig ist und unter 50 Jahren 5 % bis 8 % beträgt[15,24,25]. *ATM* wird derzeit weiterhin als moderates Risikogen für familiären Brustkrebs eingestuft[12]. Zusätzlich wird ein erhöhtes Risiko für das Auftreten von Pankreaskarzinomen angenommen[26-28]. Bezüglich eines erhöhten Risikos für das Auftreten von Eierstockkrebs gibt es widersprüchliche Ergebnisse: Laut Reyes et al.[29] gibt es ein möglicherweise erhöhtes Eierstockkrebsrisiko für Trägerinnen von pathogenen *ATM*-Varianten. Das Deutsche Konsortium Familiärer Brust- und Eierstockkrebs bewertete das Eierstockkrebsrisiko zuletzt jedoch als nicht erhöht[25]. Aussagen bezüglich einer möglichen Assoziation von *ATM* mit dem Auftreten von Prostatakarzinomen beim Mann können vom Deutschen Konsortium Familiärer Brust- und Eierstockkrebs aufgrund einer derzeit als unzureichend bewerteten Datenlage nicht getroffen werden[25].

Auch *CHEK2* wird aktuell weiterhin den moderaten Risikogenen für familiären Brustkrebs zugeordnet[12]. Bei einer pathogenen Variante im *CHEK2*-Gen wird in aktuellen Studien von einem Lebenszeitrisiko für Brustkrebs von circa ≥25 % bis ≥30 % ausgegangen[15,21,30]. Von Cybulski et al.[30] wurde ein Einfluss der Familienanamnese auf das individuelle mit der pathogenen Variante assoziierte Brustkrebsrisiko beschrieben: während das Brustkrebsrisiko einer Frau mit einem an Brustkrebs erkrankten Verwandten 2. Grades 28 % beträgt, beträgt dieses bei einer Frau mit einem an Brustkrebs erkrankten Verwandten 1. Grades 34 %. Bei der *CHEK2* Variante c.1100delC konnte außerdem ein Einfluss des Alters auf das

Brustkrebsrisiko festgestellt werden: demnach ist das Brustkrebsrisiko für Frauen unter 35 Jahren am größten und es sinkt mit steigendem Alter[22,31]. Zusätzlich ist beim Auftreten der Variante c.1100delC auch das kontralaterale Brustkrebsrisiko leicht erhöht[22,25]. Weitere, mit dieser Variante assoziierte Krebserkrankungen sind das Prostatakarzinom, das kolorektale Karzinom, das papilläre Schilddrüsenkarzinom, das Magenkarzinom und das Nierenzellkarzinom[21,22]. Außerdem wird auch für Männer ein erhöhtes Brustkrebsrisiko bei Vorliegen einer pathogenen Variante im *CHEK2*-Gen angenommen. Das Risiko für das Auftreten von Eierstockkrebs ist bei *CHEK2* nicht erhöht[21].

Bei Vorliegen einer pathogenen Variante im *PALB2*-Gen wurde 2007 zunächst von einem im Vergleich zur Allgemeinbevölkerung etwa zweifach höherem Risiko für weiblichen Brustkrebs ausgegangen und daher eine im Vergleich zu *BRCA1* und *BRCA2* (damals eine etwa zehnfache Erhöhung des Risikos) moderate Risikoerhöhung angenommen[32]. In den neuesten Studien werden pathogene Varianten im *PALB2*-Gen jedoch mit einem Lebenszeitrisiko für Brustkrebs von inzwischen etwa 50 % assoziiert[15,21,33]. Laut Tischkowitz et al.[17] kann *PALB2* inzwischen als das drittwichtigste Brustkrebsgen nach *BRCA1* und *BRCA2* bezeichnet werden. Das mit *PALB2* assoziierte Brustkrebsrisiko wird durch die Familienanamnese und das Alter beeinflusst. Zusätzlich wird ein moderat erhöhtes Risiko für Eierstockkrebs beschrieben mit einem Erkrankungsrisiko von 5 % bis zum 80. Lebensjahr sowie ein erhöhtes Risiko für das Auftreten von Pankreaskarzinomen[25,33]. Für Männer mit einer pathogenen Variante im *PALB 2*-Gen ist das Brustkrebsrisiko ebenfalls erhöht.

In Anlehnung an die unter 2.1.2 vorgestellte Einteilung des NICE wird *PALB2* in den aktuellen Empfehlungen der Kommission Mamma der Arbeitsgemeinschaft Gynäkologische Onkologie e.V. (AGO) von 2022 nicht mehr als moderates Risikogen eingestuft, sondern bereits als Hochrisikogen bewertet[2,12,17,21]. Auch die interdisziplinäre S3-Leitlinie der Deutschen Krebsgesellschaft, Deutschen Krebshilfe und AWMF von 2021 stellte fest, dass *PALB2* mit einem ähnlich hohen Risiko einherzugehen scheint wie *BRCA1* und *BRCA2*[2]. In einem aktuellen Leitfaden für die klinische Praxis des American College of Medical Genetics and Genomics, erarbeitet von einer internationalen Arbeitsgruppe um Tischkowitz[17], stellen die Autor:innen fest, dass *PALB2* die Unterscheidung zwischen „moderatem Risiko“ und „hohem Risiko“ verwischt, da sich die Bandbreite der mit *PALB2* assoziierten Brustkrebsrisiken mit den Risiken der Hochrisikogene und der moderaten Risikogene überschneidet. Sie plädieren dafür, die dichothome Einteilung in „moderates Risiko“ und „hohen Risiko“ zu verlassen und das Risiko nicht als kategorische/diskrete Variable sondern vielmehr als kontinuierliche Variable zu betrachten, die sich von hoch bis moderat bewegt und von der Familienanamnese, dem PRS und anderen Faktoren (z. B. Lebensstil) beeinflusst wird[17].

2.2. Möglichkeiten der Prävention und Früherkennung von Brustkrebs im deutschen Versorgungskontext

Frauen mit einer pathogenen Variante in einem Risikogen für familiären Brustkrebs werden in Deutschland gemäß der aktuell gültigen Konsensusempfehlungen des Deutschen Konsortiums Familiärer Brust- und Eierstockkrebs[25], der aktuellen interdisziplinären S3-Leitlinie für die Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms der AWMF[2] sowie der aktuellen Empfehlungen der Kommission Mamma der Arbeitsgemeinschaft Gynäkologische Onkologie e.V. (AGO)[12] verschiedene präventive Optionen angeboten.

Die Teilnahme am iFE wird sowohl Frauen mit einer pathogenen Variante in einem Hochrisikogen als auch Frauen mit einer pathogenen Variante in einem moderaten bis hoch-moderaten Risikogen empfohlen. Zu den Maßnahmen des iFE gehören neben einer ärztlichen Tastuntersuchung der Brust eine Kernspintomographie der Brust, der Ultraschall der Brust sowie die Mammographie (Tabelle 3).

Tabelle 3) Aufbau des Programms der multimodalen intensivierten Früherkennungsuntersuchung der Brust (iFE) [12,34]

Verfahren	*BRCA1/2*	Moderate Risikogene
Kernspintomographie (MRT)	1 x jährlich ab dem 25. Lebensjahr*	1 x jährlich ab dem 30. Lebensjahr
Ultraschall der Brust (Sonographie)	2 x jährlich ab dem 25. Lebensjahr	1 x jährlich ab dem 30. Lebensjahr (2 x jährlich bei PALB2)
Mammographie (Röntgenuntersuchung)	Alle 1-2 Jahre ab dem 40. Lebensjahre	Alle 1-2 Jahre ab dem 40. Lebensjahr
Tastuntersuchung durch den Arzt oder die Ärztin	2 x jährlich ab dem 25. Lebensjahr	1 x jährlich ab dem 30. Lebensjahr (2 x jährlich bei PALB2)

*oder 5 Jahre vor dem jüngsten Erkrankungsalter in der Familie

Eine Evaluation des iFE über den Zeitraum von 10 Jahren konnte zeigen, dass Brustkrebserkrankungen bei Frauen mit einer pathogenen Variante in *BRCA1* oder *BRCA2* durch das iFE in rund 80 % der Fälle in frühen, potentiell heilbaren Stadien entdeckt werden[34]. Im Hinblick auf den Endpunkt Mortalität sind endgültige Daten zum Stellenwert des iFE bei Frauen mit einer pathogenen Variante im *BRCA1*- oder BRCA*2*-Gen jedoch noch ausstehend. Bezüglich des iFE bei Frauen mit pathogenen Varianten in

den moderaten bis hoch-moderaten Risikogenen liegen weder für den Endpunkt Gesamtmortalität noch für die Morbidität oder Lebensqualität Daten vor[2,22]. Eine abschließende Bewertung des Nutzens des iFE für Frauen mit hohem oder moderat-erhöhtem Risiko für familiären Brustkrebs im Hinblick auf diese patientenrelevanten Endpunkte ist daher noch ausstehend.

Bisher nicht an Brustkrebs erkrankten Frauen mit einer pathogenen Variante in den Genen *BRCA1* und *BRCA2* werden zusätzlich zur Teilnahme am iFE risikoreduzierende Operationen angeboten: die risikoreduzierende bilaterale Mastektomie (RRBM) und die risikoreduzierende Salpingo-Oophorektomie (RRSO). Die RRBM reduziert beim Vorliegen pathogener Varianten in den beiden Hochrisikogenen die Brustkrebsinzidenz[12,22]. Darüber hinaus weisen erste Daten darauf hin, dass die RRBM bei Frauen mit einer pathogenen Variante im *BRCA1*-Gen zusätzlich zu einer Reduktion der Mortalität führen könnte[22,35] Die RRSO reduziert die Eierstockkrebsinzidenz und -mortalität sowie Gesamtmortalität und wird bei einer pathogenen Variante im *BRCA1*-Gen ab ca. 35 Jahren und bei einer pathogenen Variante im *BRCA2*-Gen ab ca. 40 Jahren empfohlen, jeweils unter Berücksichtigung des Erkrankungsalters in der Familie und des individuellen Status der Familienplanung[12]. Frauen mit einer pathogenen *BRCA1-* oder *BRCA2*-Variante, die bereits einseitig an Brustkrebs erkrankt sind, wird alternativ zur Teilnahme am iFE die risikoreduzierende kontralaterale Mastektomie (RRKM) angeboten.

Eine weitere präventive Option für nicht an Brustkrebs erkrankte Frauen mit einer pathogenen Variante in den Hochrisikogenen *BRCA1* und *BRCA2*, die aktuell in Deutschland noch diskutiert wird, ist die medikamentöse Prävention mit Tamoxifen für Frauen >35 Jahren und mit Raloxifen oder Aromatasehemmern für postmenopausale Frauen[12,36]. Diese endokrinen chemopräventiven Therapien werden jedoch in der aktuellen S3-Leitlinie noch nicht empfohlen und sollten nur nach individueller und umfassender Beratung angeboten werden, da der Nutzen von verschiedenen individuellen Risikofaktoren abhängt[2]. Die chemopräventive medikamentöse Therapie mit dem humanen monoklonalen RANKL-Antikörper Denosumab wird derzeit diskutiert und ist zum jetzigen Zeitpunkt noch Gegenstand aktueller Forschung[36,37].

Bei Frauen mit erhöhtem Risiko für familiären Brustkrebs ohne pathogene Variante in den Genen *BRCA1* oder *BRCA2* ist der Nutzen einer RRBM oder RRKM nicht nachgewiesen und wird daher in den aktuellen deutschen Leitlinien nicht als präventive Option empfohlen[2]. Dies gilt prinzipiell auch für Frauen mit einer pathogenen Variante in einem moderaten bis hoch-moderaten Risikogen für familiären Brustkrebs. Tung et al.[38] stellen in dem Zusammenhang fest, dass ein Schwellen-Erkrankungsrisiko, das eine risikoreduzierende Operation rechtfertigt, noch nicht festgelegt wurde. Narod[23] merkt ebenfalls an, dass die RRBM ein fraglicher Ansatz für Frauen mit einem Lebenszeitrisiko für Brustkrebs von 20 bis 25 % ist und weist darauf hin,

dass für die Mehrheit der Frauen mit einer pathogenen Variante im *ATM*- oder *CHEK2*-Gen die Teilnahme am iFE die einzige präventive Option ist. Frauen mit einer pathogenen Variante in einem moderaten bis hoch-moderaten Risikogen für familiären Brustkrebs wird in Deutschland aktuell nur die Teilnahme am iFE empfohlen und angeboten. Für Frauen mit einer pathogenen Variante in den Genen *CHEK2* Variante c.1100delC oder *PALB2* können jedoch nach den Empfehlungen des Deutschen Konsortiums Familiärer Brust- und Eierstockkrebs eine RRBM oder RRKM unter Berücksichtigung der eigenen sowie familiären Vorgeschichte, der verbundenen Risiken und des persönlichen Risikoprofils auf individueller Einzelfallbasis diskutiert werden[22].

2.3. Situation von Frauen mit einer pathogenen Variante in den moderaten bis hoch-moderaten Risikogenen *ATM*, *CHEK2* und *PALB2*

Die Situation von Frauen mit einer pathogenen Variante in einem moderaten bis hoch-moderaten Risikogen für familiären Brustkrebs unterscheidet sich zusammenfassend auf mehreren Ebenen von der Situation von Frauen mit pathogenen *BRCA1*- und *BRCA2*-Varianten: die Erkrankungsrisiken sind niedriger, die betroffenen Organe vielfältiger, die präventiven Optionen limitierter und die wissenschaftliche Studienlage teilweise noch eingeschränkt und in steter Entwicklung und Veränderung. Betroffene Frauen sind daher mit einer anderen und sehr speziellen Situation konfrontiert. Die mit der pathogenen Variante assoziierten Risiken sind geringer, doch die mit der pathogenen Variante verbundene Unsicherheit ist durch die limitierten präventiven Optionen und fehlende Evidenz größer.

2.3.1. Dimension medizinisches Wissen und Informationsbedarf

Während für die Hochrisikogene *BRCA1* und *BRCA2* bereits schriftliche, strukturierte, evidenzbasierte, laiengerechte, deutschsprachige Informationsmaterialien entwickelt und evaluiert wurden[39-42], ist für Frauen mit einer pathogenen Variante in moderaten bis hoch-moderaten Risikogenen für familiären Brustkrebs keine solche schriftliche Information dieser Art verfügbar. Angesichts der mit einer pathogenen Variante in moderaten bis hoch-moderaten Risikogenen verbundenen Unsicherheit, mit der die Frauen konfrontiert sind, ist davon auszugehen, dass betroffene Frauen weiterführende Fragen und einen Bedarf an Information und Unterstützung haben, dem aktuell noch nicht ausreichend begegnet wird. Studien zu den Informationsbedürfnissen in Bezug auf familiären Brustkrebs wurden bereits mit unterschiedlichen Zielgruppen – an Brustkrebs erkrankte Frauen, noch nicht genetisch getestete Frauen, Frauen mit einer pathogenen *BRCA1*- oder *BRCA2*-Variante – und zu unterschiedlichen Zeitpunkten – vor der genetischen Untersuchung und Beratung und nach der genetischen Untersuchung und Beratung – durchgeführt. Studien, die sich mit den Informationsbedürfnissen nach der genetischen Beratung beschäftigen, zeigten vor allem

einen Informationsbedarf bezüglich der risikoreduzierenden Operationen und einen Unterstützungsbedarf im Zusammenhang mit dem Entscheidungsprozess für oder gegen eine präventive Maßnahme[43-45]. Diese Studien beziehen sich jedoch auf die Situation von Frauen mit einer pathogenen *BRCA1*- oder *BRCA*2-Variante und sind aufgrund der unterschiedlichen Erkrankungsrisiken und angebotenen präventiven Optionen nicht auf Frauen mit einer pathogenen Variante in einem moderaten bis hoch-moderaten Risikogen übertragbar. Die (medizinischen) Informations- und Unterstützungsbedürfnisse dieser speziellen Zielgruppe wurden bisher nicht wissenschaftlich untersucht.

2.3.2. Dimension Emotionen und Bewältigung

Eine qualitative Studie von Reyes et al.[29] aus dem Jahr 2021 untersuchte die sehr spezielle Erfahrung der Unsicherheit, die mit einer pathogenen Variante in einem moderaten Risikogen für familiären Brustkrebs verbunden ist und mit der betroffene Frauen konfrontiert sind. Die Studie fokussierte sich auf Frauen, bei denen eine pathogene Variante in den Risikogenen *CHEK2* oder *ATM* nachgewiesen wurde und die noch nicht an Krebs erkrankt waren. Die Teilnehmerinnen der Studie nahmen die genetische Beratung und Untersuchung in Anspruch mit der Erwartung, dass die Ergebnisse Klarheit über das Krebsrisiko und klare Empfehlungen für den Umgang mit diesem Risiko liefern würden. Doch obwohl sie klar als Trägerinnen einer pathogenen Variante in einem moderaten Risikogen für Brustkrebs identifiziert wurden, erlebten sie nach dem Erhalt des genetischen Testergebnisses weiterhin Unsicherheiten in Bezug auf das Krebsrisiko und den Umgang damit. Reyes et al. stellten die Vermutung auf, dass die Teilnehmerinnen nicht erwartet hatten, dass ein pathogener Befund immer noch mit Unsicherheiten einhergehen würde. Dean[46] explorierte in einer qualitativen Studie die Unsicherheit von nicht an Krebs erkrankten Frauen mit einer pathogenen *BRCA1*- oder *BRCA2*-Variante und wies ebenfalls darauf hin, dass es zwar das Ziel der genetischen Untersuchung ist, die Unsicherheit zu reduzieren, durch das Testergebnis jedoch weitere Unsicherheiten hinsichtlich präventiver Optionen und Erkrankungsrisiken entstehen. Esteban et al.[47] untersuchten in einer quantitativen Studie die psychologischen Auswirkungen von genetischen Untersuchungen bei Patient:innen mit einem klinischen Verdacht auf familiären Krebs (erblicher Brust- und Eierstockkrebs oder Lynch-Syndrom) in Spanien. Zwölf Monate nach dem Erhalt der Ergebnisse der genetischen Untersuchung wiesen Träger:innen einer Variante mit einem moderaten Risiko im Vergleich zu Träger:innen von Varianten mit einem hohen Risiko höhere Werte für Stress und Unsicherheit auf.

Neben dem Thema der Unsicherheit sind jedoch auch weitere Aspekte und Themen der emotionalen Dimension von Bedeutung. Unklar ist aktuell, welche weiteren Gefühle, Überzeugungen und Erfahrungen mit dieser Unsicherheit und der sehr speziellen Situation von Frauen mit einer pathogenen Variante in einem moderaten bis hoch-moderaten Risikogen

verbunden sind und welche Bewältigungsmechanismen gewählt werden, um mit dieser Situation zurechtzukommen und umzugehen.

2.4. Herausforderungen für die genetische Beratung

Mit dem technischen Fortschritt in der Molekulargenetik und dem immer breiteren und kostengünstigeren Einsatz von Next-Generation-Sequencing gewinnt die genetische Beratung von Frauen mit pathogenen Varianten in moderaten bis hoch-moderaten Risikogenen für familiären Brustkrebs zunehmend an Bedeutung für die klinische Versorgung. Narod[23] wirft in diesem Zusammenhang die Frage auf, wie gut wir dafür ausgerüstet und darauf vorbereitet sind. Denn die genetischen Berater:innen stehen vor der Aufgabe, Frauen mit pathogenen Varianten in moderaten bis hoch-moderaten Risikogenen über weniger sicher belegte und sich derzeit noch häufig ändernde Risikoeinschätzungen sowie weniger evidenzbasierte präventive Optionen zu informieren[48]. Ein positives Testergebnis in einem Risikogen für familiären Brustkrebs markiert darüber hinaus den Beginn einer lebenslangen Unsicherheit auf den unterschiedlichsten Ebenen[46,49], die es nicht nur medizinisch zu verstehen, sondern auch emotional zu bewältigen und zu verarbeiten gilt. Möglicherweise bestehende (medizinische) Informations- und Unterstützungsbedürfnisse und auch emotionale Bedürfnisse, die mit der Situation und dem genetischen Testergebnis verbunden sind, sollten daher während der genetischen Beratung gleichermaßen erkannt und adressiert werden. Dafür ist eine umfangreiche und bedürfnisorientierte verbale Informationsvermittlung während des persönlichen Genbefundgesprächs besonders wichtig. Studien zufolge ist zudem davon auszugehen, dass bis zu 80 % der medizinischen Informationen, die von Gesundheitspersonal mündlich mitgeteilt werden, vergessen werden und insbesondere genetische Information, die mündlich mitgeteilt wird, nicht korrekt erinnert wird [50-52]. Vor diesem Hintergrund erscheint die Entwicklung einer schriftlichen, strukturierten, evidenzbasierten, laiengerechten, deutschsprachigen Information für diese Zielgruppe als eine wichtige zusätzliche Maßnahme, um Missverständnissen vorzubeugen und Informationslücken zu schließen.

2.5. Fragestellungen und Ziel der Arbeit

Ziel der vorliegenden Studie ist es, die spezielle Situation von Frauen mit einer pathogenen Variante in einem moderaten bis hoch-moderaten Risikogen für familiären Brustkrebs im Hinblick auf den medizinischen Wissensstand und mögliche Informationslücken und -bedürfnisse, mit der Situation verbundene Gefühle, individuelle Erfahrungen und Bewältigungsstrategien sowie bestehende Unterstützungsbedürfnisse zu untersuchen. Von Interesse sind in diesem Zusammenhang insbesondere die Risikogene, bei denen das Brustkrebsrisiko das Haupterkrankungsrisiko ausmacht, so dass der Fokus auf die Risikogene *ATM, CHEK2* und *PALB2* gelegt wurde und Syndrom-assoziierte Risikogene, die mit einem

hohen Risiko für weitere schwere Krebserkrankungen einhergehen (z.B. *CDH1, PTEN, TP53*), nicht berücksichtigt wurden.

Eine zu Beginn durchgeführte systematische Literaturrecherche in fünf verschiedenen Datenbanken (Pubmed, CINAHL, EMBASE, PsychINFO, Cochrane) identifizierte im Hinblick auf die genannten Bedürfnisse und Aspekte in erster Linie Studien, die sich auf die Situation von Frauen mit einem erhöhten Risiko für familiären Brustkrebs ohne nachgewiesene pathogene Variante in einem Risikogen oder mit einer pathogenen Variante in den Genen *BRCA1* oder *BRCA2* fokussieren. Da die Situation von Frauen mit einer pathogenen Variante in einem moderaten bis hoch-moderaten Risikogen eine andere ist als die von Frauen mit einer pathogenen Variante in den Hochrisikogenen *BRCA1* und *BRCA2,* können Ergebnisse von Studien, die sich mit pathogenen Hochrisikovarianten befassen, nicht einfach auf pathogene Varianten mit moderatem bis hoch-moderatem Risiko übertragen werden[29,38]. Es wurde daher ein qualitativer Ansatz gewählt, um erste Einblicke in die Situation, Gedanken, Meinungen und individuellen Erfahrungen von Frauen mit einer pathogenen Variante in einem moderaten bis hoch-moderaten Risikogen für familiären Brustkrebs zu gewinnen.

Bei der genetischen Beratung betroffener Frauen spielen sowohl die zu Grunde liegenden medizinischen Fakten als auch die aufkommenden Emotionen und das individuelle Bewältigungsverhalten eine wichtige Rolle. Kenntnisse und Einblicke in beide Dimensionen können helfen, die genetische Beratung noch bedürfnis- und patientenorientierter zu gestalten. Waltz et al.[48] zufolge ist die Forschung darüber, wie Erkrankungsrisiken und präventive Entscheidungen oder Empfehlungen in Bezug auf Risikogene für familiären Brustkrebs jenseits von *BRCA1* und *BRCA2* kommuniziert werden können, von zentraler Bedeutung. Die Ergebnisse der vorliegenden Untersuchung können sowohl zur Optimierung der genetischen Beratung und direkten Kommunikation beitragen als auch zur Entwicklung schriftlicher, strukturierter, evidenzbasierter, laiengerechter, deutschsprachiger Informationen für Frauen mit einer pathogenen Variante in einem moderaten Risikogen genutzt werden mit dem Ziel, die Versorgungssituation der betroffenen Frauen weiter zu verbessern.

Zu Beginn der vorliegenden Studie wurde *PALB2* als moderates Risikogen eingestuft, aktuell wird dieses Gen jedoch wie unter 2.1.2.2. beschrieben als Hochrisikogen bewertet[2,12,17]. In der vorliegenden Dissertationsschrift wurde für die Risikogene *ATM*, *CHEK2* und *PALB2* daher die Bezeichnung moderate bis hoch-moderate Risikogene gewählt. In den zwischen 2019 und 2022 erschienenen Veröffentlichungen der Ergebnisse dieser Arbeit wurden die Risikogene *ATM*, *CHEK2* und *PALB2* entsprechend des damaligen Kenntnisstandes alle als moderate Risikogene bezeichnet.

3. Publikationen

Stracke C, Kautz-Freimuth S, Lemmen C, Rhiem K, Schmutzler R, Stock S. Medizinische Informationsbedarfe von Frauen mit einer Mutation in einem sogenannten „moderaten Risikogen“ für familiären Brust- und Eierstockkrebs. *Das Gesundheitswesen* 2019, **81**(08/09): 698 - 698. https://doi.org/10.1055/s-0039-1694462

Stracke C, Lemmen C, Rhiem K, Schmutzler R, Kautz-Freimuth S, Stock S. Medical knowledge and information needs among women with pathogenic variants in moderate-risk genes for hereditary breast cancer attending genetic counseling at an academic hospital in Germany – A qualitative approach. *Journal of Genetic Counseling* 2022, **31**: 698-712. https://doi.org/10.1002/jgc4.1536

Stracke C, Lemmen C, Rhiem K, Schmutzler R, Kautz-Freimuth S, Stock S. “You Always Have It in the Back of Your Mind” – Feelings, Coping, and Support Needs of Women with Pathogenic Variants in Moderate-Risk Genes for Hereditary Breast Cancer Attending Genetic Counseling in Germany: A Qualitative Interview Study. *International Journal of Environmental Research and Public Health* 2022, **19**(6): 3525. https://doi.org/10.3390/ijerph19063525

Kongresstag 2: 17.09.2019

Stracke, C[1]; Kautz-Freimuth, S[1]; Lemmen, C[1]; Rhiem, K[2]; Schmutzler, R[2]; Stock, S[1]

Medizinische Informationsbedarfe von Frauen mit einer Mutation in einem sogenannten „moderaten Risikogen“ für familiären Brust- und Eierstockkrebs

„Neue Ideen für mehr Gesundheit“

Gemeinsame Jahrestagung der Deutschen Gesellschaft für Medizinische Soziologie (DGMS) und der Deutschen Gesellschaft für Sozialmedizin und Prävention (DGSMP) – Die gemeinsame Jahrestagung in Düsseldorf findet statt unter Beteiligung des MDK Nordrhein und des MDS

16.–18. September 2019, Düsseldorf

Tagungspräsident: Prof. Dr. Nico Dragano, Direktor des Instituts für Medizinische Soziologie, Centre for Health and Society, Medizinische Fakultät der Heinrich-Heine-Universität Düsseldorf; Programmkomitee: Dr. Hanno Hoven, Prof. Dr. Julika Loss, Prof. Dr. Susanne Moebus, Prof. Dr. Claudia Pischke, Prof. Dr. Olaf von dem Knesebeck, Dr. Gert von Mittelstaedt, Dr. Morten Wahrendorf, Prof. Dr. Ulla Walter, Dr. Simone Weyers

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Einleitung:

Brustkrebs ist mit jährlich 72.000 neudiagnostizierten Fällen die häufigste Krebserkrankung von Frauen in Deutschland. Circa 30% sind durch eine familiäre Keimbahnmutation bedingt, wobei außer den Hochrisikogenen BRCA1/2 verstärkt Mutationen in sogenannten „moderaten Risikogenen“ im Fokus stehen. In einem Genbefundgespräch erhalten Mutationsträgerinnen gezielte Informationen zu ihrem Genbefund und ihren Risiken. Ziel dieser Studie war es, durch leitfadengestützte Einzelinterviews den medizinischen Wissensstand von Frauen mit einer ihnen bereits bekannten Mutation in einem „moderaten Risikogen“ sowie fortbestehende Informationsbedürfnisse herauszuarbeiten.

Methoden:

Es wurden halbstrukturierte, leitfadengestützte Einzelinterviews mit Frauen geführt, die eine Mutation in einem „moderaten Risikogen“ aufweisen. Die Rekrutierung erfolgte zielgerichtet über das Zentrum Familiärer Brust- und Eierstockkrebs der Uniklinik Köln. Die Erstellung des Leitfadens richtete sich nach den Methoden des Problemzentrierten Interviews nach Witzel. Die Analyse der Interviews orientierte sich an der qualitativen Inhaltanalyse nach Mayring und erfolgte computergestützt (MAXQDA).

Ergebnisse:

Insgesamt wurden 12 Frauen (29 – 59 Jahre) mit Mutation in den Risikogenen CHEK2 (n = 8), ATM (n = 3) oder PALB2 (n = 1) rekrutiert, darunter 3 gesunde und 9 bereits an Brustkrebs erkrankte Frauen. Es ergab sich ein hoher medizinischer Informationsbedarf. Insbesondere bezüglich Vererbung und Erkrankungsrisiken entsprach der Wissenstand nicht den im Genbefundgespräch vermittelten Informationen. Unverständnis bestand außerdem bezüglich der Zusammenhänge zwischen Brustkrebstherapie und Mutationsstatus. Diese Unklarheiten können mit Angst, Beunruhigung und Schuldgefühlen verbunden sein sowie eigene Konzepte bezüglich der Krankheitsentstehung begünstigen.

Diskussion:

Frauen mit Mutation in einem „moderaten Risikogen“ für Brustkrebs entwickeln trotz Genbefundberatung im Lauf der Zeit weiteren Informationsbedarf. Um negativen Gefühlen entgegenzuwirken, sollten evidenzbasierte, laienverständliche und bedürfnisorientierte schriftliche Informationen entwickelt werden.

Quelle: Stracke C,Kautz-Freimuth S,Lemmen C,Rhiem K,Schmutzler R,Stock S. Medizinische Informationsbedarfe von Frauen mit einer Mutation in einem sogenannten „moderaten Risikogen“ für familiären Brust- und Eierstockkrebs. Das Gesundheitswesen. 2019; 81(08/09): 698 - 698. doi:10.1055/s-0039-169446

UNIKLINIK KÖLN | Institut für Gesundheitsökonomie und Klinische Epidemiologie | Zentrum Familiärer Brust- und Eierstockkrebs

Medizinische Informationsbedürfnisse von Frauen mit Mutationen in moderaten Risikogenen für familiären Brust- und Eierstockkrebs

- Ergebnisse einer qualitativen Untersuchung -

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Hintergrund

Brustkrebs ist mit jährlich 72.000 neu diagnostizierten Fällen die häufigste Krebserkrankung von Frauen in Deutschland. Circa 30 % sind durch eine familiäre Keimbahnmutation bedingt, wobei außer den Hochrisikogenen *BRCA1/2* auch Mutationen in moderaten Risikogenen im Fokus stehen[1]. In einem Genbefundgespräch erhalten Mutationsträgerinnen gezielte Informationen zu ihrem Gentestergebnis, den individuellen Risiken und präventiven sowie therapeutischen Optionen. Ziel dieser Studie war es, durch leitfadengestützte Einzelinterviews den medizinischen Wissensstand von Frauen mit einer ihnen bereits bekannten Mutation in einem moderaten Risikogen sowie fortbestehende Informationsbedürfnisse herauszuarbeiten.

Material und Methodik

Zielgruppe: Frauen mit einem positiven Mutationsbefund in einem der folgenden Gene: *CHEK2, RAD51C, RAD51D, PALB2, ATM* oder *PTEN*

Rekrutierung: Zielgerichtete Rekrutierung im Zentrum Familiärer Brust- und Eierstockkrebs, Universitätsklinikum Köln

Datenerhebung: Halbstrukturierte, leitfadengestützte Einzelinterviews, orientiert an Problemzentriertem Interview (PZI) nach Witzel[2]

Transkription: Verbatim Transkription nach Dresing[3]

Datenanalyse: Qualitative Inhaltsanalyse nach Mayring[4], computergestützte Auswertung mit MAXQDA

Ergebnisse

Charakteristika der Studienteilnehmerinnen:

Teilnehmerinnen: n=12 (29-58 Jahre)
Mutationen: *CHEK2* (n=8), *ATM* (n=3), *PALB2* (n=1)
Eigenanamnese: an BK erkrankt (n=9), nicht erkrankt (n=3)
Familienanamnese: positiv (n=11), negativ (n=1)
Familienplanung abgeschlossen: ja (n=11), nein (n=1)

Zusätzliche Informationsbedürfnisse zu:

- Lebensstiländerungen
- Risikofaktoren
- Familienplanung

"Weil es geht einem natürlich besser, wenn man selbst auch das Gefühl hat, man tut was dagegen."

Medizinischer Wissensstand:

Es bestehen Unklarheiten bzgl. Informationen, die bereits beim Genbefundgespräch vermittelt wurden:

1) Unverständnis der Fachtermini

- „Moderates Risikogen" – N=4 Bedeutung unklar
- „Tumor-suppressorgen" – N=5 unbekannt

„Also mit dem Begriff "moderat" kann ich schon was anfangen, aber inwieweit mich das dann betrifft oder inwieweit das für mich ein Risiko ist, das ist halt nie klargeworden."

2) Verwechslung von Vererbungs- und Erkrankungswahrscheinlichkeit der Kinder

3) Unklarheit bzgl. Zusammenhang von Mutation, Brustkrebserkrankung & -therapie

„Aber das muss doch auch irgendwas mit den Hormonen zu tun haben, sonst würde ich ja nicht Tamoxifen nehmen, ne? (…) Also das dieses Zusammenspiel ist mir irgendwie überhaupt nicht so richtig klar"

Bedeutung von Wissenslücken, Unklarheiten und Informationsbedürfnissen für den Umgang mit der Mutation:

1) Eigenrecherche im Internet → Gefahr der Fehlinterpretation der gefundenen, nicht laiengerecht aufgearbeiteten Fachinformationen

2) Entwicklung von Schuldgefühlen → Bedarf an verständlichen Informationen über die nicht beeinflussbare Vererbungswahrscheinlichkeit, um Schuldzuweisungen und negativen Gefühlen vorzubeugen

3) Entwicklung eigener Konzepte bzgl. der Krankheitsentstehung →

Ich werde (wieder) krank, wenn…

- ….ich zu viel Stress habe (n=2)
- …ich mein Leben nicht ändere (n=2)
- …ich mich der Krankheit ergebe und negativ denke (n=1)
- …ich mich zu sehr um andere und zu wenig um mich selber kümmere (n=2)

„Diese Last halt, ne, dieses Gen da jetzt, ne, vererbt zu haben und die Angst, gerade wenn das Mädchen vielleicht dann auch, ne, jetzt schwanger werden möchte und Kinder haben möchte (…)"

Fazit

Frauen mit Mutationen in einem moderaten Risikogen für Brustkrebs entwickeln trotz Genbefundberatung im Lauf der Zeit weiteren Informationsbedarf. Um negativen Gefühlen, Unsicherheiten und Verständnisproblemen entgegenzuwirken, sollten für ratsuchende Frauen evidenzbasierte, laienverständliche und bedürfnisorientierte Informationen in schriftlicher, audiovisueller oder webbasierter Form entwickelt werden. Spezifische Kommunikationsschulungen für beratende ÄrztInnen können zudem ein besseres Verständnis für die im Genbefundgespräch vermittelten Informationen fördern.

Quellen: 1. Rhiem K et al, Benchmarking of a checklist for the identification of familial risk for breast and ovarian cancers in a prospective cohort. Breast J 2019 May, 25(3): 455-460; 2. Witzel A, The problem-centered interview. Forum Qualitative Sozialforschung, 2000, 1(1); 3. Dresing T et al, Manual (on) Transcription. Transcription conventions, software guides and practical hints for qualitative researchers. 2015, Marburg; 4. Mayring P, Qualitative content analysis. 2000, 1(2).

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ORIGINAL ARTICLE

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Medical knowledge and information needs among women with pathogenic variants in moderate-risk genes for hereditary breast cancer attending genetic counseling at an academic hospital in Germany—A qualitative approach

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Abstract

With 69,000 newly diagnosed cases every year, breast cancer (BC) is the most frequent cancer disease among women in Germany. Familial clustering is seen in about 30% of newly diagnosed cases. Besides the high-risk genes *BRCA1*/2, there are also moderate-risk BC genes (MBCG) that are associated with a 20%–50% risk of BC, such as *CHEK2*, *ATM*, and *PALB2*. In Germany, carriers of pathogenic variants in MBCG receive specific information on their test results, individual risks, and preventive options during genetic counseling for the disclosure of the results in a specialized center. Little is known about the medical knowledge that women have after attending counseling. This study aims to identify the medical knowledge, further information needs, and the possible impact of a lack of information on dealing with everyday life for women with pathogenic variants in MBCG who have attended genetic counseling at an academic hospital in Germany.

Problem-centered, guided, individual interviews were conducted with twelve women carrying pathogenic variants in MBCG. The interview guide was developed based on the methods of the problem-centered interview according to Witzel. The interview analysis was based on Mayring's qualitative content analysis. The women were between 29 and 59 years old and carried pathogenic variants in the risk genes *CHEK2* ($n = 8$), *ATM* ($n = 1$), or *PALB2* ($n = 3$). Several medical uncertainties and information needs emerged from the data, concerning (a) medical terms, (b) risk perception, (c) BC therapy for hereditary BC, (d) lifestyle advice and risk factors, and (e) family planning and risk-reducing mastectomy. Women with pathogenic variants in MBCG might develop their own conceptions regarding the onset of disease and inheritance. In order to meet the need for information and address the uncertainties that may still

Sibylle Kautz-Freimuth and Stephanie Stock should be considered joint senior author.

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exist after genetic counseling, structured, evidence-based and comprehensible written information in German should be developed for this group.

KEYWORDS
education, genetic counseling, hereditary breast cancer, information needs, moderate-risk breast cancer genes, risk perception

1 | INTRODUCTION

Breast cancer (BC) is the most common cancer in women in Germany, with up to 69,000 newly diagnosed cases every year (Institut & Gesellschaft der epidemiologischen Krebsregister in Deutschland e. V., 2019). Familial clustering is seen in about 30% of cases (Deutsche Krebsgesellschaft and Deutsche Krebshilfe & AWMF, 2020; Rhiem et al., 2019). Pathogenic variants (also known as mutations) in the high-risk genes *BRCA1/2*, which are associated with a lifelong risk of ~70% for BC and 17%–44% for ovarian cancer (OC), can be found in about 25% of these cases (Deutsche Krebsgesellschaft and Deutsche Krebshilfe & AWMF, 2020; Kast et al., 2016; Kuchenbaecker et al., 2017; Miki et al., 1994; Wooster et al., 1994).

Since 2002, further BC risk genes have been identified, such as *CHEK2*, *ATM*, *RAD51C/D*, and *PALB2*. While *CHEK2*, *RAD51C/D*, and *ATM* pathogenic variants are associated with a moderately increased risk of BC (20%–25%), *PALB2* is considered to be a moderate to high-risk gene with about 50% lifelong risk of BC (Breast Cancer Association Consortium, 2021; Hu et al., 2021; Yang et al., 2020). The risk is modified by genotype, family history, and age. Male *PALB2* pathogenic variant carriers also have an increased risk of BC. Furthermore, *PALB2*, *CHEK2*, and *ATM* pathogenic variants are associated with an increased risk of pancreatic cancer (Ohmoto et al., 2019; Zhan et al., 2018). In addition to this, *CHEK2* pathogenic variants are associated with an increased risk of colon and prostate cancer (Cybulski et al., 2007; Southey et al., 2016). While there is no significant evidence that *ATM* or *CHEK2* pathogenic variants increase the risk of OC, *RAD51C/D* pathogenic variant carriers face an increased lifetime risk of OC. Recent data also indicate a slightly increased risk of OC for *PALB2* pathogenic variant carriers (Loveday et al., 2011; Meindl et al., 2010; Southey et al., 2016; Yang et al., 2020). These data underline the fact that moderate-risk BC genes (MBCG) can confer different risks, which may manifest differently in different organs.

Since the type of cancer and the cancer risks associated with pathogenic variants in MBCG are different from those associated with pathogenic variants in *BRCA1/2* genes, carriers of MBCG pathogenic variants are offered different preventive strategies: Women carrying MBCG pathogenic variants are generally offered the option of following the multimodal intensified surveillance program for the breast from the age of 30. In contrast, according to German guidelines (AGO Breast Committee, 2021; Deutsches Konsortium Familiärer Brust-und Eierstockkrebs, 2020; Deutsche Krebsgesellschaft and Deutsche Krebshilfe & AWMF, 2020), women carrying *BRCA1/2* pathogenic variants can additionally opt for risk-reducing mastectomy (RRM) and/or risk-reducing removal of ovaries and fallopian tubes. In Germany, women who test positive for MBCG pathogenic variants are informed in detail about their individual cancer risks and their preventive options during the disclosure of the test result in a personal post-test genetic counseling session (PTGC). This takes place in a specialized center for familial breast and ovarian

What is known about this topic

Women at increased risk of hereditary breast cancer (BC) who have not yet been tested for pathogenic variants report information needs concerning associated cancer risks, risk-reducing surgeries, and supportive interventions, as well as the need to improve access to information (Grant et al., 2006; Iredale et al., 2003; Thewes et al., 2003), while the post-test information needs of women with *BRCA1/2* pathogenic variants mostly concern the decision-making process regarding BC surveillance or risk-reducing surgery (Dean et al., 2017; Metcalfe et al., 2000; Yuen et al., 2020). The post-test information needs of women with pathogenic variants in moderate-risk BC genes (MBCG) have not been assessed thus far. However, since the type of cancer, the associated cancer risks, and the preventive options that are currently available for women with pathogenic variants in MBCG differ from those for women with *BRCA1/2* pathogenic variants, it can be assumed that the information needs of the two groups also differ.

What this paper adds to the topic

Women with pathogenic variants in MBCG may continue to have medical uncertainties and unmet information needs several months after post-test genetic counseling. These information needs and misunderstandings concern medical terms, cancer risk perception, BC therapy for hereditary BC, lifestyle advice and risk factors, modes of inheritance, and family planning and risk-reducing mastectomy. Since structured, evidence-based, comprehensible, written information in German does not yet exist for these women, the results of this study might contribute to the development of needs-oriented written patient information for this target group.

cancer and is carried out by a specialist in gynecology and obstetrics or a specialist in human genetics. However, studies suggest that verbal medical information given by healthcare practitioners, especially genetic information, often cannot be recalled correctly (Brown et al., 2016; Kessels, 2003; Thewes et al., 2003). To date, information recall following genetic counseling has only been studied for *BRCA1/2* pathogenic variant carriers (Brédart et al., 2017; Jacobs et al., 2015; Scherr et al., 2016; Vos et al., 2012). The accuracy of post-test information recall was low in *BRCA1/2* pathogenic variant carriers affected by BC or OC, especially concerning information on associated risks and the likelihood of inheritance (Jacobs et al., 2015; Vos et al., 2012). In addition to this, genetic literacy among the general population is low (Chapman et al., 2019). Knowledge and satisfaction can be improved by replacing or supplementing the verbal information communicated during genetic counseling with written information (Jacobs et al., 2019). For *BRCA1/2* pathogenic variant carriers, evidence-based, lay-oriented, written information media in German has already been developed (Krebshilfe, 2018; Verlag für Gesundheitskommunikation, 2013), whereas there are still no structured, evidence-based, and comprehensible written information media in German for women with pathogenic variants in an MBCG. Identifying the information needs of the target group is an essential step in the development of evidence-based health information (Ärztliches Zentrum für Qualität in der Medizin, 2006; Lühnen et al., 2017; Salm et al., 2021). As such, in order to provide women with pathogenic variants in MBCG with structured, evidence-based, and needs-oriented written health information, it is important to assess their information needs first.

Studies on unmet information needs regarding hereditary BC have been conducted with different target groups—affected, unaffected, tested, not tested—and at different points in the counseling process—pre-test situation or post-test situation. Most of these studies focus on the pre-test situation and study women with *BRCA1/2* pathogenic variants or women at risk of hereditary BC who have not been tested for pathogenic variants. Common findings across different studies included occasionally poor information recall, a need for information on RRM, and a desire for Internet-based sources of information.

Many studies focus on the pre-test genetic counselling situation, or on women who are at high risk of hereditary BC but have not been tested. Thewes et al. (2003) conducted a quantitative study on the information needs of women who were unaffected by BC and had mostly not been tested, yet had a moderately to highly increased risk of BC due to their BC family history. The participants had a poor recall of the information provided during their genetic counseling, and expressed interest in Internet-based information and supportive interventions, including information on diet and lifestyle. Grant et al. (2006) investigated the perceptions after genetic counseling of women at low/moderate risk of BC who had not been tested for a pathogenic variant. They observed that the genetic information that had been communicated, particularly the perceived risks, was not always well understood by the participants. Lobb et al. (2004) studied the process of genetic counseling for women from high-risk BC families who attended pre-test genetic counseling. They found that significantly more of the women's expectations were met when discussing risk-reducing surgeries.

Only few studies on information needs focus on the post-test counseling situation for *BRCA1/2* pathogenic variant carriers, and all of them identified an information need concerning risk-reducing surgeries. Yuen et al. (2020) conducted in-depth interviews with *BRCA1* and *BRCA2* pathogenic variant carriers both affected and unaffected by a *BRCA1/2*-related cancer (OC, BC or prostate cancer) in Asia, and identified post-test information and support needs related to the decision-making process for choosing between breast surveillance and risk-reducing surgery. They observed proactive online information-seeking behavior among many participants due to a lack of sufficient information. Dean et al. (2017) examined the post-test information concerns and needs of unaffected women with a *BRCA1/2* pathogenic variant. They also identified a need for information regarding risk-reducing surgeries versus increased surveillance, and a need for support in decision-making. Metcalfe et al. (2000) conducted a quantitative study and investigated the information needs of women who had tested positive for *BRCA1/2* pathogenic variants, both those affected and those unaffected by BC or OC, and who had attended pre- and post-test genetic counseling. The unmet information needs of both survivors and previvors concerned information on risk-reducing surgery, chemoprevention, and new screening modalities. A difference was identified between the information needs of previvors and those of survivors, indicating that survivors needed more information relating to BC treatment than to previvors.

Two studies compared the perspective of women at increased risk of hereditary BC with that of (genetics-related) health professionals. Young et al. (2019) identified the following information needs reported by the at-risk young adults but not by the health professionals: information on male cancer risk, finding reputable information, and understanding test results and risk terminology. Jacobs et al. (2017) were able to identify key messages agreed upon by both *BRCA1/2* pathogenic variant carriers affected by OC or BC and expert health professionals in order to provide a guide for communicating about *BRCA1/2* with affected women. These key messages were dominant inheritance, the availability of predictive testing, the importance of pre-test discussion, the risks of BC and OC, and the options for risk-reducing surgeries.

While there is already plenty of evidence on the information needs of women at high risk of BC, the situation for women with pathogenic variants in MBCG has not yet been explored. However, since the associated cancer types, the associated cancer risks, and the currently recommended preventive options available to women with pathogenic variants in MBCG differ from those for women with *BRCA1/2* pathogenic variants, it can be assumed that the information needs of the two groups also differ. There has thus far been no assessment of the medical knowledge and information needs of women with pathogenic variants in MBCG, both those affected by BC and those unaffected by BC, after their PTGC. The aim of this study was to gain a first insight into the medical knowledge of

women with pathogenic variants in MBCG, their information needs, and the potential impact of a lack of information on dealing with everyday life. The results of this study could form the basis for offering more needs-oriented counseling and developing structured, evidence-based, needs-oriented, and lay-friendly written information in German for this special group of women with pathogenic variants in MBCG.

2 | METHODS

An initial systematic literature search on the post-test information and support needs of women with pathogenic variants in MBCG was conducted using five databases (Pubmed, CINAHL, EMBASE, PsychINFO, Cochrane). Since most of the studies identified concerned the needs of *BRCA1/2* pathogenic variant carriers or of women at increased risk who had not been tested, a qualitative approach using in-depth, semi-structured, individual, face-to-face interviews was applied in order to gain a deeper insight into the needs and experiences of the target group. The conduct and analysis of the study are based on the COREQ Checklist (Tong et al., 2007). The quotes used in this manuscript have been translated from German into English according to the TRAPD-EES translation guidelines (European Social Survey, 2018).

2.1 | Post-test genetic counseling

In Germany, women who are tested positive for pathogenic variants in MBCG are invited to personal PTGC in a specialized center for familial breast and ovarian cancer for the disclosure of the genetic test result. All the participants in this study attended counseling at the Center for Familial Breast and Ovarian Cancer at the University Hospital of Cologne. This individual genetic counseling is performed in person by a doctor who is a specialist in gynecology and obstetrics with specialized training in hereditary breast and ovarian cancer or a specialist in human genetics. All the counselors complete special communication curricula conducted four times a year by a specialist in psychosomatic medicine and psychotherapy. During the counseling sessions, women with pathogenic variants in MBCG receive detailed, individual, oral information regarding their test results, the probability of them inheriting the pathogenic variant, and associated cancer risks, with a focus on BC, OC, and contralateral BC. With regard to other potentially associated cancer risks, such as pancreatic cancer, further consultation in a specialized center is recommended to the women. The counseling doctor explains the preventive measures that can be offered to the women and discusses any further questions that the women might have. The consultation takes ~30 min. The women receive the following written information: a brochure containing general information on hereditary breast and ovarian cancer, a brochure containing information on the multimodal intensified breast surveillance program, and—if applicable—information on risk-reducing operations. In addition to this, each of the woman receives a doctor's letter and an information letter addressed to their relatives. The doctor's letter is a short, written summary of the PTGC and contains information on: (a) the name of the pathogenic variant, (b) the ovarian cancer risk that might (or might not) be associated with this pathogenic variant, (c) the breast cancer risk that might be associated with this pathogenic variant, (d) the risk-reducing removal of ovaries and fallopian tubes and/or the RRM, if recommended, (e) the option of participating in the multimodal intensified breast surveillance program, (f) further cancer risks that might be associated with the pathogenic variant, (g) the probability of the women's offspring inheriting the pathogenic variant, and 8. the option for psycho-oncological support. The information letter addressed to the relatives contains information on: (a) the reasons for the genetic test, (b) the name of the pathogenic variant, (c) the basics of how the pathogenic variant is inherited, (d) the possibility of early detection and participation in the multimodal intensified breast surveillance program, and 5. a telephone number for tumor-risk consultation at the Center for Familial Breast and Ovarian Cancer. The information letter also emphasizes that it is the relatives' own decision as to whether or not they want to get tested, which is important in order to protect the 'right not to know' genetic information.

2.2 | Participants and recruitment

The participants were recruited using purposive sampling (Patton, 2015) in order to achieve maximum variation regarding different pathogenic variants. Eligible women were identified by the Center for Familial Breast and Ovarian Cancer at the University Hospital of Cologne and invited to participate in the study. Women with pathogenic variants in one of the genes *CHEK2*, *RAD51C*, *RAD51D*, *PALB2* or *ATM*, either with or without a personal history of BC and/or OC, and who were at least 18 years old and in a medically and psychologically stable condition, were eligible for participation. Further inclusion criteria for the study participants were an adequate understanding of the German language and a temporal and emotional distance from the disclosure of the genetic test result. In order to ensure the temporal distance from the disclosure, the interview needed to be conducted at least six months after the PTGC. In order to ensure that the participants both possessed the required emotional distance and were in a medically and psychologically stable condition, recruitment was carried out by experienced gynecologists during a medical consultation, as this situation allowed them to assess the women's medical, emotional, and psychological states. The personal genetic counseling for the genetic result disclosure was provided by doctors of the Center for Familial Breast and Ovarian Cancer at the University Hospital of Cologne. Women interested in the program were contacted to obtain consent, and a face-to-face interview was arranged. Since no *RAD51C/D* pathogenic variant carriers met the inclusion criteria during the recruitment period, it was not possible to include women with this pathogenic variant in the study. The data collection depended on the criterion of

theoretical saturation. The recruitment process for eligible women was closed when no additional data or themes appeared (Döring & Bortz, 2016; Flick, 2014). After the 12th interview, it was possible to assign more than 80% of the 85 codings derived from this interview to pre-existing codes.

2.3 | Data collection and setting

The interviews were conducted at the Center for Familial Breast and Ovarian Cancer, the Institute of Health Economics and Clinical Epidemiology, the BRCA-Network in Bonn, or the participant's hometown between February 2017 and October 2017. They lasted 75 to 180 min.

The instruments of the problem-centered interview (PCI) were applied (Witzel, 2000). This method was chosen because the PCI focuses on the interviewees' experiences and perceptions of a very specific problem/topic, in this case being a pathogenic variant carrier. The essential element of the PCI is the interview guide, which consists of a pre-formulated, open introductory question and further questions to generate storytelling and comprehension. These further questions provide a communicative atmosphere and help to define the conversation, which is very important when dealing with such a complex topic. The interview guide and the questions were developed based on theoretical assumptions regarding the perceptions, experiences, and needs of women with a risk of hereditary BC derived from the findings of the initial systematic literature search. As additional topics emerged during the course of the interviews, the interview guide was revised. The interview guide was piloted by one woman carrying a *CHEK2* pathogenic variant, who was not included in the study. Other instruments of the PCI include the short questionnaire for collecting data on social and medical characteristics, and the postscript for documenting situational and nonverbal aspects. The interviews were conducted by the first and fifth authors. Both interviewers were female and had a medical background. In order to avoid social desirability bias, neither was involved in the PTGC; instead, they observed several PTGCs at the Center for Familial Breast and Ovarian Cancer in order to ensure familiarity with the counseling situation.

2.4 | Data analysis

All the interviews were audiotaped and transcribed verbatim (Dresing et al., 2015). The analysis is based on Mayring's qualitative content analysis, which aims to systematically analyze the text using a category system (Mayring, 2000). This category system or coding frame consists of main categories and subcategories, to which relevant data are assigned. MAXQDA software was used to assist in coding and extracting the data. All the transcripts were deductively organized by the interview guide and then inductively categorized in order to further identify relevant themes and categories emerging from the data. After the fourth interview, the codes and categories defined by the first author were validated internally with the second and the fifth authors. After the last interview, the final codebook was discussed and reviewed again with the second and the fifth authors until consensus was reached.

3 | RESULTS

3.1 | Participants

Twelve women aged between 29 and 58 years were interviewed. Eight of the women (67%) had a positive pathogenic variant status for the *CHEK2* gene, three (25%) for the *PALB2* gene, and one (8%) for the *ATM* gene. Nine of the women were affected by BC (75%), and three (25%) were not affected by BC. None of the women had ovarian cancer or any other type of cancer apart from BC. Eleven out of the twelve women (92%) had completed their family planning, and eleven of them (92%) had a positive family history for BC. Their educational levels were classified into three categories: 'No formal education', 'Vocational training' (requirement: either Secondary Education or Higher Education Entrance Qualification), and 'Bachelor's degree or above'. To enable an international comparison, corresponding ISCED 2011 (International Standard Classification of Education) levels have been added (OECD, European Union, & UNESCO Institute for Statistics, 2015). The characteristics of the participants are shown in Table 1.

3.2 | Results of qualitative analysis

The qualitative data coding and thematic analysis of the interview data produced 815 codings, which were categorized into 81 codes. The codes were organized into main categories and subcategories and then analyzed further to identify key areas and major themes. Based on this analysis, three major themes were identified, providing results regarding: (a) medical knowledge, (b) information needs, and (c) impact of a lack of information on dealing with everyday life. Table 2 gives an overview of these three major themes that emerged from the data and the representative quotes. Each of the major themes is discussed in detail below.

3.2.1 | Medical knowledge

Several uncertainties were identified regarding medical information that had been communicated during the PTGC.

The participants were asked if they knew the meaning of certain medical terms that had been mentioned in the PTGC (e.g., 'moderate-risk gene', 'tumor suppressor gene', 'computer-based breast cancer risk assessment'). The meanings of these terms were not clear to all participants: Nine participants (75%) stated that they had not heard the term 'tumor suppressor gene' before and/or did not fully understand the meaning of the term 'moderate-risk gene'. One participant

TABLE 1 Characteristics of the participants

	Pathogenic variant (year of disclosure)	Time between PTGC and interview (months)	BC status	Age (years)	Marital status	Children (number)	Family history of BC	Educational level/ISCED level
001	*CHEK2* (2015)	23	Survivor	47	Married	3	No (participant =index patient)	Vocational training/ISCED 3
002	*CHEK2* (2012)	55	Previvor	38	Married	2	Yes (mother, grandmother, great-aunt)	Vocational training/ISCED 3
003	*CHEK2* (2015)	25	Survivor	47	Divorced	2	Yes (aunt, cousin)	Vocational training (health sector)/ISCED 4
004	*ATM* (2016)	10	Survivor	38	Married	1	Yes (mother, half-sister, grandmother)	Vocational training/ISCED 3
005	*CHEK2* (2014)	40	Previvor	34	Divorced	3	Yes (aunt)	No formal graduation
006	*PALB2* (2016)	15	Survivor	49	Married	1	Yes (mother, grandmother)	Vocational training/ISCED 3
007	*PALB2* (2016)	14	Previvor	29	In a relationship	-	Yes (mother, grandmother, great-grandmother)	Vocational training/ISCED 3
008	*CHEK2* (2013)	54	Survivor	55	Married	1	Yes (mother)	Vocational training/ISCED 3
009	*CHEK2* (2016)	12	Survivor	50	Married	2	Yes (mother, both grandmothers, both great-aunts)	Vocational training (health sector)/ISCED 4
010	*PALB2* (2011)	72	Survivor	58	Married	1	Yes (mother)	Bachelor's degree or above/ ISCED 6 or 7
011	*CHEK2* (2011)	71	Survivor	44	Married	2	Yes (grandmother)	Bachelor's degree or above/ ISCED 6 or 7
012	*CHEK2* (2015)	29	Survivor	57	Married	1	Yes (sister, aunt)	Bachelor's degree or above/ ISCED 6 or 7

Abbreviations: BC, breast cancer; ISCED, International Standard Classification of Education 2011 (OECD, European Union, & UNESCO Institute for Statistics, 2015); PTGC, post-test genetic counseling;
Note: vocational training, dual training system in Germany, requirement: either secondary education or higher education entrance qualification.

TABLE 2 Themes that emerged from the data and representative quotes

Major theme	Subtheme	Representative quote
1. Medical knowledge	1.1 Several medical terms were not understood or remembered	*"Well, I can make something out of the term 'moderate', but to what extent this affects me or to what extent it is a risk for me that has never become clear." [49 years old, survivor, PALB2]*
	1.2 The probability of the participants' children of inheriting the pathogenic variant was confused with their children's probability of developing cancer	*"At first, I thought they had nothing to do with it, until I was told, no, no, your brother can also be a carrier." [55 years old, survivor, CHEK2]*
	1.3 The connection between the pathogenic variant status and BC therapy was not clear	*"And then months later this information came through, that it is the CHEK2 gene. Then of course I thought again, hm, hopefully this was the right therapy." [50 years old, survivor, CHEK2]*
	1.4 Special communication challenges were posed by the long-term consequences of chemotherapy and radiation	*"You are simply no longer at that, yes, memory level after such an illness." [50 years old, survivor, CHEK2]*
2. Information needs	2.1 Information on lifestyle changes as a health-promoting intervention	*"Stress, life habits, I think this is quite a decisive factor." [50 years old, survivor, CHEK2]*
	2.2 Information on risk factors that may trigger the onset or recurrence of the disease	*"Then, after the illness, I was even more afraid that sugar could now trigger the cancer again." [57 years old, survivor, CHEK2]*
	2.3 Information on family planning and risk-reducing mastectomy	*"You have to live with the thought, okay, I'm healthy for the next two years, get pregnant and then you worry for ten months about whether something might be happening in the breast." [29 years old, previvor, PALB2]*
3. Impact of a lack of information on dealing with everyday life	3.1 Specialized medical information found online was misunderstood and misinterpreted	*"This is all very medical. (…) You probably only understand half of it." [38 years old, survivor, ATM]*
	3.2 Own conceptions regarding the onset and progression of disease were developed: You get sick (again) if you 1.) do not change your life 2.) have too much stress 3.) care too little of yourself	*"I don't want to obsess about it, because I always think: If you obsess about it, it will happen even faster." [38 years old, survivor, ATM]*
	3.3 Own conceptions regarding the inheritance of the pathogenic variant were developed: The more you have inherited in appearance or character from one parent, the more likely you are to have also inherited the pathogenic variant	*"We assume that she has it [the pathogenic variant] too, because we have a hell of a lot from dad's side." [34 years old, previvor, CHEK2]*

said: *"Well, I can make something out of the term 'moderate,' but to what extent this affects me or to what extent it is a risk for me has never become clear." [49 years old, survivor, PALB2].*

Another uncertainty concerns different risk probabilities linked with the pathogenic variant. The probability of the participants' children of inheriting the pathogenic variant was confused with their children's probability of developing cancer. Talking about the risk of passing the pathogenic variant on to her son, which is 50%, one participant said: *"That's what I was told, 30%, I think. Is that true from your information?" [57 years old, survivor, CHECK2]* Given that nine participants (75%) mentioned that one of their key concerns regarding the pathogenic variant or overall situation was their children's risk of inheriting the pathogenic variant or developing BC, it is essential to understand the underlying difference. *"The most important question is to what extent this gene is inherited? That is actually still my most important question today." [47 years old, survivor, CHECK2].*

Furthermore, the survivors expressed misunderstandings concerning the connection between the pathogenic variant, BC disease, and BC therapy. Some survivors were taking tamoxifen, an estrogen receptor modulator that is part of the long-term therapy for hormone receptor positive BC. Three women (25%) did not understand why one might take tamoxifen. One participant was taking the drug, but it was unclear to her which processes it actually affects. *"But that [the pathogenic variant] must also have something to do with the hormones, otherwise I wouldn't take Tamoxifen, would I? (…) Well, this interaction is somehow not really clear to me at all." [44 years old,*

TABLE 3 Special concerns of a young childless previvor *[29 years old, previvor, PALB2]*

Special concern	Quote
When is the right timing to get pregnant?	*"I drove my partner crazy with it, really, so I thought, actually you should have children now because who knows what happens. You don't want to paint too gloomy a picture but if, if you take your time and it goes wrong, then you don't know whether you could forgive yourself."*
Should I get an RRM?	*"So just when they said, yes, tissue removal [risk-reducing mastectomy] would not be NECESSARY, (…) but for yourself you just think, you just think about it differently."*
Would a pregnancy influence my risk to get BC?	*"You have to live with the thought, okay, I'm healthy for the next two years, get pregnant and then you worry for ten months about whether something might be happening in the breast."*

Abbreviations: BC, breast cancer; RRM, risk-reducing mastectomy.

survivor, CHEK2] Similarly, another woman assumed a connection between her pathogenic variant status and the BC therapy: *"And then months later, this information came through, that it is the CHEK2 gene. Then of course I thought again, hm, hopefully this was the right therapy." [50 years old, survivor, CHEK2]* One survivor pointed out her difficulty in distinguishing clearly between information about the pathogenic variant and information about the disease: *"Because there is simply too much information coming from everywhere. There's the gene mutation, then there was the chemo, then there was the radiation. You get told things everywhere." [47 years old, survivor, CHEK2].*

There was a wide range of education levels among the interviewees: from no formal graduation and unemployed (8%) to university degree (25%). The educational levels and corresponding ISCED levels of the participants are shown in Table 1. Misunderstandings of certain medical terms or general information needs were mentioned by participants with all educational levels. Two women with ISCED level 6 or 7 indicated a great need for information in general, as did the participant with no formal graduation. The woman with no formal education noted: *"Well, I think you can't get too much information about that." [34 years old, previvor, CHEK2]* One of the women with high education level explained her interest in the medical background of the pathogenic variant: *"Trying to explain it biologically, not just with numbers. That would really interest me." [58 years old, survivor, PALB2].*

An additional communication challenge was posed by the long-term side effects of chemotherapy and/or radiation on mental performance. One participant (8%) described her situation following surgery, chemotherapy, and radiation: *"You are simply no longer at that, yes, memory level after such an illness." [50 years old, survivor, CHEK2]* She also pointed out the need for written patient information: *"I understood everything, but you really need something in writing, because at that moment you're so agitated and if you're not feeling well anyway, then you can't take it all in."*

Further medical information received during the PTGC that the participants perceived as important/helpful or less important was also identified. Facts about their sons' risk of being a carrier of the pathogenic variant and of developing cancer were considered very important information. The same applied to more detailed information regarding the risk of BC, including information on other organs that might be affected, the exact risk numbers for BC, information on other prevention programs that might exist, and information on life expectancy as a pathogenic variant carrier. The women considered precise information regarding the mechanisms of genetic inheritance and how the genetic test works to be of lesser importance.

One of the participants (8%) pointed out that it is important to communicate that the risk numbers are correct at the time of the PTGC but might change in the future, as there is still much research to be done on the risks associated with different pathogenic variants. She suggested it should be communicated that *"we only work with numbers that we add up, that some machines calculate for us, but which might not be correct in 5 years." [58 years old, survivor, PALB2]* Another woman also added that it is important *"that it's recorded somewhere where it's pointed out that this is variable." [38 years old, previvor, CHEK2].*

In addition, two participants (17%) stated that it is important to consider whether the information provided has a consequence for the decisions and actions of the women. *"If this has no consequence at that point, I don't think it would help. It only drives people crazy," [57 years old, survivor, CHEK2]* one participant said. Another woman shared this point of view: *"What do you do with the information? (…) What consequences should I draw from it? (…) So everything that is relevant, where I can have an influence on it in prevention or something like that, I think that is important." [58 years old, survivor, PALB2].*

3.2.2 | Information needs

Further information needs on topics that were not addressed in the PTGC were identified.

Six participants (50%) wished to receive information on lifestyle changes as a health-promoting measure, especially nutrition and physical activity. One participant said: *"Of course, you feel better if you also have the feeling that you are doing something about it." [38 years old, previvor, CHEK2]* This also includes the knowledge regarding risk factors that might trigger the outbreak of the disease. One participant explained: *"What I can minimize as a risk, I would wish to know that in order to then also adapt my behavior accordingly." [49 years old, survivor, CHEK2]* Another woman stated: *"Then, after the illness, I was even more afraid that sugar could now trigger the cancer again." [57 years old, survivor, CHEK2].*

One participant (8%) described family planning and RRM as her key worries concerning the pathogenic variant and overall situation, and did not feel sufficiently informed about this issue. However, this was an individual case: She was the only childless previvor below the age of 30. Her special concerns are summarized in Table 3.

Having experienced her mother's BC disease and mastectomy, she thinks a lot about getting an RRM herself. Another previvor, who also experienced her mother's BC disease and therapy, had a similar opinion on RRM: *"If you haven't experienced this, you can't understand the step [risk-reducing mastectomy] I would have taken if it had been meant to be. But then I said for myself: I don't care what the others then think." [38 years old, previvor, CHEK2].*

3.2.3 | Impact of a lack of information on dealing with everyday life

The women's uncertainties concerning medical knowledge and their further information needs seem to have an impact on how they deal with the pathogenic variant in everyday life.

Five participants (42%) reported on researching their MBCG online, but they only found specialized expert information that was unsuitable for laypersons and difficult to understand. They noticed: *"You don't really find any information where it's all written down together," [49 years old, survivor, PALB2]* and *"This is all very medical. (…) You probably only understand half of it." [38 years old, survivor, ATM]* One risk of online research is the misinterpretation of the information, which can lead to further fear and worry. One participant reported: *"So now I know that it lies on the 22nd chromosome and that there are several other diseases on the 22nd chromosome (…) hm, if the 22nd chromosome is somehow damaged, do you have something else as well? And then I Googled of course. I can't hear very well, I don't know if that may also be connected somehow." [50 years old, survivor, CHEK2].*

Another consequence of a lack of medical information seems to be the women developing their own conceptions regarding the outbreak and progression of BC. We identified different conceptions among the women regarding situations or behavior that might lead to the development or a recurrence of cancer. Two participants (17%) thought that excessive stress levels promote the onset of cancer. One of them had a high stress level just before she was diagnosed with BC, and reflected on that very situation: *"Just before this diagnosis was made, I said to my husband at home: 'you're all getting on my nerves here, you're making me really sick.' (…) And lately I have been feeling this again. Maybe within the last year and a half. And that's why I tell you quite honestly, if I came here and they diagnosed it again, I'd say it must be connected with it." [55 years old, survivor, CHEK2]* Another participant shared this view: *"Stress, life habits, I think this is quite a decisive factor." [50 years old, survivor, CHEK2]* A further conception was that taking too much care of other people and too little of oneself leads to getting cancer (again) or being affected by a pathogenic gene variant. This assumption was made by two participants (17%), one of whom said: *"You look after your kids first before you look after yourself. But that [the disclosure of the pathogenic variant] has now taught me a lesson." [34 years old, previvor, CHEK2]* The second one said: *"You didn't have any time to yourself sometimes. And then suddenly the body says: Well, that's it. Now it's enough and now we'll put you on the back burner for a while." [47 years old, survivor, CHECK2]* A third assumption that was identified was the belief that one could to get cancer (again) if one does not change one's lifestyle. This assumption was made by two participants (17%), one of whom pointed out: *"I have to create a new normality for myself that prevents whatever was, whatever the trigger was." [49 years old, survivor, PALB2].*

The lack of certain information can also lead to women developing their own concepts regarding the inheritance of the cancer. Three women (25%) believed that the more they have inherited in appearance/character from one parent, the more likely they were to have also inherited the pathogenic variant. One participant said of her younger sister: *"We assume that she has it [the pathogenic variant] too, because we have a hell of a lot from our dad's side." [34 years old, previvor, CHEK2]* Another woman had a very similar assumption: *"My mother had to deal with varicose veins, that's what I'm now dealing with. My sisters have no problems with that. (…) I have the same hair as my mother (…). So, from that point of view it was no surprise to me at all." [55 years old, survivor, CHEK2]* Another participant stated: *"That's why I was so gob smacked. I took after my father. Not that I never thought I'd get cancer, but breast cancer, like Mum, wasn't on my agenda." [58 years, survivor, PALB2].*

4 | DISCUSSION AND CONCLUSION

4.1 | Discussion

The aim of this study was to explore the medical knowledge of women with pathogenic variants in MBCG, their information needs, and the impact of a lack of information on dealing with the pathogenic variant in everyday life. Since an initial systematic literature search conducted in five individual databases (Pubmed, CINAHL, EMBASE, PsychINFO, Cochrane) only identified studies on the needs of women with *BRCA1/2* pathogenic variants or women at increased risk of hereditary BC who had not been tested, a qualitative approach was chosen in order to gain first insights into the perspectives and ideas of these women. This is the first study investigating the information needs of this specific target group.

The study results indicate that women with pathogenic variants in MBCG might not recall all the medical information they received during their PTGC. This is in line with results on risk perception and information recall of women with *BRCA1/2* pathogenic variants or women at increased risk of hereditary BC who had not been tested (Grant et al., 2006; Jacobs et al., 2015; Thewes et al., 2003; Vos et al., 2012). In a qualitative study of women at low/moderate risk of BC without a proven pathogenic variant conducted by Grant et al. (2006), the participants did not recall all the risk probabilities they were given during counseling. Studies on information recall suggest that up to 80% of medical information provided by healthcare practitioners is forgotten and the more information patients

are told, the more they forget (Brown et al., 2016; Kessels, 2003). Furthermore, half of the information is remembered incorrectly (Kessels, 2003). This is consistent with the results of the present study in terms of the participants' recall of medical facts: The children's risk of inheriting the pathogenic variant, which is 50%, was confused with the children's risk of getting cancer once they inherited the pathogenic variant, which varies between 20% and 50% depending on the affected gene. Understanding these differences is important in order to facilitate proper risk assessment. Surprisingly, this misunderstanding occurred even though the risk of inheriting the pathogenic variant was mentioned in the doctor's letter that the participants received after the PTGC. However, since genomic literacy among the general population is very low (Brown et al., 2016; Chapman et al., 2019; Lanie et al., 2004), and confusion of genetic terms ('gene', 'chromosome', 'DNA') is particularly common (Mesters et al., 2005), there remains a sense of misunderstanding and unanswered questions in spite of the detailed counseling and the provision of the doctor's letter. Structured, comprehensible, written health information media for women with pathogenic variants in MBCG could help avoid the anxiety and confusion caused by these information gaps and misunderstandings.

Another misunderstanding concerned the connection between pathogenic variant status and BC therapy, especially tamoxifen intake. Tamoxifen might be considered for primary chemoprevention in unaffected women with *BRCA1/2* pathogenic variants after thorough consideration, as recommended in the Guidelines Breast by the AGO Breast Committee (AGO Breast Committee, 2021). For unaffected women with a moderate risk of BC, primary chemoprevention is recommended as a consideration, although data are lacking on its effect on women with pathogenic variants in MBCG (AGO Breast Committee, 2021; Owens et al., 2019). The participants in this study who did not understand the reason for their medication had already had BC. In these cases, tamoxifen was part of the long-term medical therapy for their hormone receptor positive BC. However, this was not clear to them. This issue shows that survivors might feel overwhelmed by the amount and complexity of information they receive, as they are confronted with information not only on the pathogenic variant, but also on their BC disease and the treatment options available to them. It seems to be very important to distinguish clearly between these two topics when communicating with survivors. A study on the needs of *BRCA1/2* pathogenic variant carriers by Metcalfe et al. (2000) also identified a difference between the information needs of previvors and survivors, indicating that survivors needed more information relating to BC treatment than previvors.

Another finding of this study that only concerns survivors is the communication challenge posed by the long-term effects of chemotherapy. Cancer-related cognitive impairments (CRCI)—defined as perceived or objective impairments in memory, attention, clarity of thought, speed of information processing and concentration—are often a result of chemotherapy, especially in BC patients (Henneghan, 2016; Hodgson et al., 2013). This should be considered when communicating complex issues during or shortly after chemotherapy. Due to these communication challenges and the aforementioned problem of distinguishing between information on the pathogenic variant and that on BC disease, consideration should be given to the idea of producing two separate sets of structured, written information for survivors and previvors.

In the sample for this study, misunderstandings of certain medical terms or general information needs were mentioned by both participants with no formal graduation and those with graduate education. In a study by Matsuyama et al. (2011), lower education was significantly associated with higher information needs. This is consistent with the study findings of Mistry et al. (2010), who also identified a higher need for information regarding psychological, social, and medical topics among cancer patients with lower educational status. Mistry et al. explained this association with the ability of higher-educated patients to satisfy their own information needs by using active information seeking strategies, such as the use of written materials and the Internet. Applying this context to the participants of this study may explain why participants with graduate education also indicated information needs: Since there is no lay-friendly information on MBCG available in German online, and no written material other than the doctor's letter is available for these pathogenic variants, the women with higher education levels are unable to satisfy their need for information on their own. Jacobs-Lawson et al. (2009) studied the educational level and information needs of lung cancer patients and found out that 'regardless of their educational level, all participants wanted to know the details of the treatment, prognosis, having all their questions answered in a way that they could understand'. However, the authors identified that the need to cater to less disease-specific and more psychosocial and personal needs, such as available resources, issues of hope, and people who can help, was greater among groups with high school diplomas or a lower level of education than among the group with the highest level of education. Further research is required in order to examine whether this association can also be applied to the target group of this study. In addition to this and considering the heterogeneity of the study sample in terms of age, personal medical history, family medical history, and family situation, investigation is required into whether any of these factors are more likely than the educational level to correlate with the extent of the need for information.

According to the findings of this study, women with pathogenic variants in MBCG have information needs even several months or years after their PTGC. One key issue is the provision of more information on health-promoting lifestyle and avoidable risk factors. Lifestyle advice is also a major concern among sporadic BC survivors (Cheng et al., 2018). Moreover, in a study by Thewes et al. (2003) on the information needs of women at increased risk of BC due to their BC family history, the participants also expressed interest in supportive interventions, including information on diet and lifestyle. Guidelines for sporadic BC already consider the influence of exercise, nutrition and body weight on the incidence, recurrence, and mortality of sporadic BC (AGO Breast Committee, 2021; Deutsche Krebsgesellschaft and Deutsche Krebshilfe & AWMF, 2020). Furthermore, recent studies on the influence of lifestyle factors on BC prevalence among women with *BRCA1/2* pathogenic variants

suggest that physical activity is associated with a reduced risk of BC, while smoking is a risk factor for the development of BC in *BRCA1/2* pathogenic variant carriers (Grill et al., 2017; Kehm et al., 2020; Kiechle et al., 2016). Although there are no data as yet on the association between lifestyle changes and BC caused by pathogenic variants in MBCG, the results implicate a need for this information, and we suggest addressing topics such as advice on lifestyle and avoidable risk factors during PTGC.

Another of the information needs concerns RRM and family planning. To date, there is no recommendation for RRM for carriers of pathogenic variants in MBCG (AGO Breast Committee, 2021; Deutsche Krebsgesellschaft and Deutsche Krebshilfe & AWMF, 2020). Women carrying MBCG pathogenic variants are generally given the option of following the multimodal intensified surveillance program for the breast from the age of 30 (Deutsches Konsortium Familiärer Brust-und Eierstockkrebs, 2020). However, the findings may indicate that, in particular, young previvors who are struggling to find the right timing to get pregnant might also consider having an RRM, and do not feel sufficiently informed on the process. A need for information on risk-reducing surgeries was also identified by studies of women with *BRCA1/2* pathogenic variants (Dean et al., 2017; Lobb et al., 2004; Metcalfe et al., 2000; Yuen et al., 2020). Werner-Lin conducted qualitative studies with young previvors carrying *BRCA1/2* pathogenic variants (Werner-Lin, 2008; Werner-Lin et al., 2012). The authors identified distress caused by the urgency of having children and finding a partner on the one hand and effectively minimizing cancer risks via risk-reducing surgeries on the other hand. A systematic review by Young et al. (2017) investigating risk perception and cancer knowledge among young adults from *BRCA1/2* families also identified distress and decision-making conflicts surrounding the timing of risk-reducing surgeries and family planning. Since the risk-reducing removal of ovaries and fallopian tubes represents addition preventive options for carriers of these high-risk BC pathogenic variants alongside RRM, the decision for or against risk-reducing surgeries has even greater consequences in terms of childbearing for carriers of *BRCA1/2* pathogenic variants than for carriers of MBCG pathogenic variants. Furthermore, a woman's feelings and positive attitudes toward RRM might be influenced by their mother's experience with BC and surgical breast therapy. These findings are consistent with previous studies (Fisher et al., 2014; Mahon, 2014; Singh et al., 2013), indicating that decisions about RRM are affected by family experiences with cancer and that 'perceptions of cancer risk are heavily influenced by the family history and are motivators in preventive surgery more than the actual risk estimations themselves' (Singh et al., 2013). The previvors' concerns regarding childbearing plans, their family history, and experiences with RRM should be addressed during PTGC. In Germany, the option of RRM for women who carry an MBCG pathogenic variant is now discussed on a case-by-case basis in specialized centers. This might prove a welcome approach and meets the needs and wishes of individual women.

The findings indicate that the knowledge regarding the pathogenic variant and the need for further information might have an impact on the way the women deal with the pathogenic variant in everyday life. Some of the women had developed conceptions concerning the outbreak and progression of the disease. One conception was that stress might lead to the occurrence or recurrence of cancer. The evidence for stress being one of the drivers of the development of BC is not conclusive. A review from 2006 found no association between BC incidence and stressful life events, work-related stress or perceived global stress (Nielsen & Grønbæk, 2006). Other, more recent, reviews made the cautious conclusion that stress, and stressful life events in particular, may potentially contribute to cancer (Batty et al., 2017; Chiriac et al., 2018). As such, it is not yet possible to make a definite statement regarding any potential association. Furthermore, these results refer to sporadic BC and cannot simply be transposed onto hereditary BC.

There was also another conception developed concerning inheritance of the pathogenic variant: some women assumed that the more a person inherits from a parent in terms of looks or character, the more likely they are to have also inherited the pathogenic variant. This is in line with other studies that investigate perceptions of inheritance (Rees et al., 2001). There is a strong need for understandable, clear, and basic information regarding the modes of inheritance and the inheritance patterns of pathogenic variants that explain that these cannot be influenced and that they are not linked to looks or character traits inherited from one parent.

4.2 | Study limitations

Our study has several limitations. We interviewed only one woman who had no children, and only one woman without a family history of BC. We recommend further studies in order to gain deeper and more extensive insights into the needs and perceptions of these women. Furthermore, quantitative studies are needed in order to explore the potential differences between these subgroups. This also applies to the potential differences between the carriers of pathogenic variants of different MBCG. A further limitation is the selection bias of our study. As purposive sampling was employed, the participants might have already been interested in sharing their experiences. Another potential limitation is the small sample size, which included just twelve participants. However, since it was possible to assign more than 80% of the codings from the 12th interview to pre-existing codes, a theoretical saturation was postulated. Furthermore, the results of this study may not be transferable across different settings or to institutions with other counseling standards and norms.

One of the strengths of our study is the qualitative approach, which enabled us to explore different topics, living contexts and circumstances on a one-to-one basis. As individual interviews offer a protected setting, the participants were not influenced by other opinions and the interviewer was able to react spontaneously to statements and emotions. Another of the strengths of our study is the heterogeneity of the study sample, which represents a target group whose information needs have not yet been investigated: the

women interviewed had pathogenic variants in different MBCG, represented both survivors and previvors, and some had completed their family planning while others had not. This provided a first in-depth insight into a broad spectrum of different perspectives, life situations, feelings, and opinions from this specific target group and thus made it possible to identify numerous unclear topics and questions that may be relevant for this specific target group. In contrast with other studies on the needs of women with a risk of hereditary BC, which focus on either previvors or survivors (Dean, 2016; Dean et al., 2017; Jeffers et al., 2014), this study included both groups and identified needs that were unique to survivors based on medical history.

4.3 | Conclusion and practice implications

Women with pathogenic variants in an MBCG continue to have information needs several months or years after they have received specialized PTGC at a German center for familial breast and ovarian cancer. It emerged that, despite the detailed counseling situation in the specialized center, much of the information provided was not understood, was forgotten, or was not addressed. Based on the findings of this study, PTGC could be modified to make it more patient-centered. Specific communication training for counseling physicians might also improve the patients' understanding of the information provided. Moreover, written information is remembered more effectively by patients than oral information and might prove necessary in order to improve the knowledge of women with pathogenic variants in MBCG and to counteract negative feelings and uncertainties. According to current German guidelines for evidence-based health information, identifying the information needs of the target group is essential for the development of evidence-based health information. As such, these results may serve as an initial basis for developing written, structured and comprehensible information in German for women with pathogenic variants in MBCG. Whether these findings can be transferred to other settings and other counseling centers with different counseling standards remains the subject of future research.

AUTHORS CONTRIBUTIONS

Author Claudia Stracke confirms that she had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. All the authors gave their final approval for this version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Claudia Stracke: contributed to the study concept/design and methods, performed data collection, performed data analysis, interpreted data, wrote the original draft of the manuscript, revised the manuscript, acted as corresponding author. Clarissa Lemmen contributed to the methods, performed internal validation of the codebook/data analysis, reviewed and edited the manuscript. Kerstin Rhiem contributed to the funding acquisition, provided resources, reviewed and edited the manuscript. Rita Schmutzler contributed to the funding acquisition, provided resources, reviewed and edited the manuscript. Sibylle Kautz-Freimuth contributed to the study concept/design and methods, performed data collection, performed internal validation of the codebook/data analysis, administered and supervised the project, reviewed and edited the manuscript. Stephanie Stock contributed to the study concept/design, provided resources, administered and supervised the project, reviewed and edited the manuscript.

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COMPLIANCE WITH ETHICAL STANDARDS

CONFLICT OF INTERESTS

Claudia Stracke, Clarissa Lemmen, Kerstin Rhiem, Rita Schmutzler, Sibylle Kautz-Freimuth, and Stephanie Stock declare that they have no conflict of interest.

HUMAN STUDIES AND INFORMED CONSENT

This study was approved by the Ethics Commission of the Medical Faculty of the University of Cologne (ethics votes of 22 November 2016, reference number 16-098). All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all participants for being included in the study.

ANIMAL STUDIES

No non-human animal studies were carried out by the authors for this article.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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Article

"You Always Have It in the Back of Your Mind"—Feelings, Coping, and Support Needs of Women with Pathogenic Variants in Moderate-Risk Genes for Hereditary Breast Cancer Attending Genetic Counseling in Germany: A Qualitative Interview Study

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Abstract: Hereditary breast cancer accounts for approximately 30% of newly diagnosed breast cancer (BC) cases. Pathogenic variants in moderate-risk BC genes (MBCG) differ from those in high-risk genes in terms of associated cancer risks, affected organs, and available preventive options. Little is known about how MBCG pathogenic variant carriers who have attended post-test genetic counseling perceive their situation, how they cope with their situation, and which support needs they might have. Problem-centered, guided, individual interviews were conducted with twelve women carrying pathogenic variants in MBCG. The interview analysis was based on Mayring's qualitative content analysis. The women were between 29 and 59 years old and carried pathogenic variants in the risk genes *CHEK2* (n = 8), *ATM* (n = 1), or *PALB2* (n = 3). Women reported a wide range of feelings, both positive (relief, calmness) and negative (overwhelm, fear, grief, guilt). All women applied strategies of emotion-focused coping to deal with this lifelong situation. Appraisal and evaluation of the affected mother's coping might influence the patient's own behavior and coping style. These results could be used during and after post-test genetic counseling to provide more needs-oriented counseling, and to help women in adjusting to and coping with being a pathogenic variant carrier.

Keywords: genetic counseling; hereditary breast cancer; moderate-risk breast cancer genes; coping; qualitative research; support needs

1. Introduction

Hereditary breast cancer accounts for 30% of newly diagnosed breast cancer (BC) cases and is linked with germline pathogenic variants in the high-risk genes *BRCA1* or *BRCA2* in approximately 24% of cases [1,2]. These pathogenic variants are associated with a lifelong risk of approximately 70% for BC and approximately 17% (*BRCA1*) to 44% (*BRCA2*) for ovarian cancer (OC) [3]. Advances in next-generation sequencing and multigene panels have enabled the identification of additional moderate-risk BC genes (MBCG) that also play a role in the development of hereditary BC, such as *CHEK2*, *ATM*, *RAD51C/D*, and *PALB2*. Two recent case–control studies confirmed with very large cohorts that there is a significant association between pathogenic variants in these genes and the development of BC [4,5]. Current research indicates that *CHEK2*, *RAD51C/D*, and *ATM* pathogenic

variants are associated with a lifetime risk of BC of approximately 20% to 35% and are accordingly regarded as moderate-risk genes [4–8]. *PALB2* is associated with a lifetime risk of BC of approximately 50% and rather considered to be a moderate-to high-risk gene [9]. In addition, male *PALB2* pathogenic variant carriers also have an increased risk of BC [9]. Further cancer risks that are associated with these MBCG are pancreatic cancer for *ATM*, *CHECK2*, and *PALB2*, and colon and prostate cancer for *CHEK2* [10–13]. *RAD51C/D* pathogenic variants are associated with an increased risk for OC, and recent data on *PALB2* indicate an increase in the risk of OC as well [9,12,14,15].

With the expanding use of gene-panel testing, counseling women with pathogenic variants in MBCG will become increasingly important for the clinical setting [16]. Given this scenario, the question arises of how well medical providers are equipped to advise these patients [16]—not only regarding the above-mentioned cancer spectrum and risk estimates, but also regarding preventive options that can be offered to the carriers of these pathogenic variants. In Germany, women carrying MBCG pathogenic variants are generally recommended to follow the multimodal intensified breast surveillance program for the breast (physical examination, sonogram, MRI) from the age of 30 [17]. These preventive options are explained to the women in person by a specialized doctor at the post-test genetic counseling (PTGC). They also receive a brochure containing information on the multimodal intensified breast surveillance program. For women with pathogenic variants in the high-risk genes *BRCA1/2,* additional preventive options are offered: besides this multimodal intensified breast surveillance program, they can opt for a risk-reducing surgery of the healthy breast tissue and/or the adnexa. According to current recommendations in Germany, these risk-reducing surgeries are usually not recommended for women with pathogenic variants in MBCG and they usually only have the choice to participate in the multimodal intensified breast surveillance program [18,19]. Tung et al. [20] emphasize that a threshold risk that justifies risk-reducing mastectomy (RRM) has not been established, yet. Narod [16] also points out that "preventive salpingo-oophorectomy is not justified, and preventive mastectomy is a questionable approach for women with a lifetime breast cancer risk of 20 to 25%. For the majority of women with a mutation in *ATM* or *CHEK2*, management consists of screening alone". Since the associated cancer risks are smaller but the uncertainty is higher, women with pathogenic variants in MBCG face a different and especially challenging situation compared to carriers of pathogenic variants in the high-risk genes. Genetic counselors must therefore be prepared to communicate less certain risks and less evidenced management options to women carrying pathogenic variants in MBCG [21]. In order to address this particular situation in the counseling session, not only in terms of medical information needs but also on an emotional level, it is important and helpful to have information about women's feelings, coping mechanisms, and support needs. According to Waltz et al. [21], research on how to communicate risk and treatment decisions concerning BC genes beyond *BRCA1/2* is crucial. Furthermore, studies focusing on high-risk pathogenic variants should not be extrapolated to those who carry moderate-risk pathogenic variants [20,22]. Reyes et al. conducted a qualitative study with women carrying a *CHEK2* or *ATM* pathogenic variant and focused on this very special experience of uncertainty regarding specific cancer risk estimates and regarding the effectiveness of certain risk management strategies [22]. Beyond this, to the authors' knowledge, emerging feelings, coping styles, and support needs of women confronted with a pathogenic variant in a MBCG have not been assessed so far. The aim of this study was to obtain a closer insight into (1) how the women perceive the situation following the disclosure of the genetic test result, (2) the personal coping strategies of women carrying pathogenic variants in MBCG, (3) the influence of the familial medical history on the coping style, and (4) what kind of additional support the women need to cope with their life-long increased cancer risk.

2. Materials and Methods

To obtain a first overview, an initial systematic literature search on the situation of women with pathogenic variants in MBCG was performed in five databases (Pubmed,

CINAHL, EMBASE, PsychINFO, Cochrane). Most of the studies that were identified focused on the situation of *BRCA1*/2 pathogenic variant carriers or of women who were at high risk of hereditary BC but had not been tested. Hence, a qualitative approach was chosen to gain a deeper insight into the situation of women with pathogenic variants in MBCG, using in-depth, semi-structured, individual, face-to-face interviews. This research was supported by the European Commission for the HORIZON 2020 project BRIDGES (Breast Cancer Risk after Diagnostic Gene Sequencing), grant number 634935. The conduct and analysis of the study were based on the COREQ (Consolidated Criteria for Reporting Qualitative Studies) Checklist, a checklist of 32 items that should be included in reports of qualitative research [23]. The TRAPD (Translation, Review, Adjudication, Pretesting, and Documentation) EES translation guidelines [24] were applied to translate the quotes used in this manuscript from German into English. This method included two translators, who produced parallel independent translations of the German quotes, and one further person to review and compare the different versions and discuss them with the translators. The preferred translations were selected through consensus.

2.1. Post-Test Genetic Counseling

In Germany, genetic counseling is mandatory before genetic testing, as declared by the German Genetic Diagnostics Act [25]. Women who test positive for a pathogenic variant that is associated with an increased risk of BC are then invited to a personal PTGC, where they are informed in detail about their test result, associated cancer risks, and their preventive options. The PTGC takes place in a specialized center for familial breast and ovarian cancer and is carried out by a doctor who is a specialist in gynecology and obstetrics with specialized training in hereditary breast and ovarian cancer or a specialist in human genetics. All the participants in this study attended a personal PTGC at the Center for Familial Breast and Ovarian Cancer at the University Hospital of Cologne. During this counseling session, the women received detailed, individual, oral information regarding their test results, the probability of them inheriting the pathogenic variant, associated cancer risks, and preventive measures that could be offered to the women. With regard to potentially associated cancer risks other than BC and OC (e.g., pancreatic cancer), further consultation in a specialized center is recommended to the women. Additionally, women receive the following written information: a brochure on hereditary breast and ovarian cancer in general, a brochure on the multimodal intensified breast surveillance program, a doctor's letter that summarizes the PTGC and offers information on psycho-oncological support, and an information letter addressed to their relatives. Further information about the PTGC can be found in Stracke et al. [26].

2.2. Participants and Recruitment

The participants were recruited using purposive sampling [27]. Inclusion criteria covered women with pathogenic variants in one of the risk genes *CHEK2*, *RAD51C*, *RAD51D*, *PALB2*, or *ATM*, either with or without a personal history of BC and/or OC, and who were at least 18 years old and in a medically and psychologically stable condition. To ensure this stable condition, recruitment was carried out by experienced gynecologists during a medical consultation, as this situation allowed them to assess the women's medical and psychological states. Further inclusion criteria were an adequate understanding of the German language and a time interval to the PTGC of at least 6 months to ensure a temporal and emotional distance from the disclosure of the genetic test result. Eligible women were identified by the Center for Familial Breast and Ovarian Cancer at the University Hospital of Cologne and invited to participate in the study. Women interested in participating in the study were contacted to obtain consent, and a face-to-face interview was arranged. Since no *RAD51C*/*D* pathogenic variant carrier met the inclusion criteria during the recruitment period, it was not possible to include women with this pathogenic variant in the study. Data collection depended on the criterion of theoretical saturation and the recruitment process was closed after the 12th interview, since it was possible to assign more than 80% of

the 85 codings derived from this interview to pre-existing codes and no additional data or themes appeared [28,29].

2.3. Data Collection

In-depth, semi-structured, individual, face-to-face interviews were carried out between February 2017 and October 2017. Interviews were conducted by the first and fifth authors; both were female and had a medical background. To avoid social desirability bias, none of the interviewers were involved in the PTGC. To ensure familiarity with the counseling situation, both interviewers observed several PTGCs at the Center for Familial Breast and Ovarian Cancer prior to the start of the interviews.

The interview guide was based on the problem-centered interview (PCI) [30]. This method was chosen because the PCI focuses on the interviewees' experiences and perceptions of a very specific topic, in this case being a carrier of a pathogenic variant in an MBCG. The interview guide was developed based on theoretical assumptions about the perceptions, problems, and experiences of women with a risk of hereditary BC derived from the findings of the initial systematic literature search. The interview guide began by asking about the reasons and circumstances that motivated or influenced the woman to undergo genetic testing. This pre-formulated, open introductory question was supposed to center the conversation on the problem under study. Further questions to generate storytelling and comprehension were applied during the course of the interview and provided a communicative atmosphere. Categories and topics to be addressed during the interview and explored through various guiding questions were, for example, the perception and atmosphere of the PTGC, information that was unclear/not understood, feelings during the PTGC, communication with the family after the PTGC. One pretest interview was conducted with one woman with a *CHEK2* pathogenic variant to pilot the interview guide. This pretest interview was not included in the analysis. The interview guide was further revised as new topics emerged during the course of the interviews. Additional instruments of the PCI included the short questionnaire to collect data on social and medical characteristics, and the postscript to document situational and nonverbal aspects. The interviews were conducted at the Center for Familial Breast and Ovarian Cancer, the Institute of Health Economics and Clinical Epidemiology, the BRCA-Network in Bonn, or the participant's hometown and lasted 75 to 180 min. All the interviews were audiotaped and transcribed verbatim [31]. Approval was obtained from the Ethic Commission of the Medical Faculty of the University of Cologne (ethic votes of 22 November 2016, reference number 16-098).

2.4. Data Analysis

Mayring's qualitative content analysis was applied to systematically analyze the interview transcripts, using a category system [32]. The category system consists of main categories and subcategories. The initial main categories (= codes) were developed based on the interview guide and the theoretical assumptions derived from the findings of the initial systematic literature search. Initial main codes included, for example, "Opinion about personal psycho-oncological counseling" and "Opinion about self-help groups". During the coding process, further relevant themes and categories emerging from the data were identified and categorized by the first author into main categories and subcategories. These categories, which emerged from the data, included, for example, the categories "Feelings associated with being a carrier of a pathogenic variant" and "Impact of family medical history." Codes and categories were validated internally with the second and the fifth authors after the fourth interview. After the last interview, the first, second, and fifth authors discussed and reviewed the final codebook until a consensus was reached. The MAXQDA software program was used to assist in coding and extracting the data. Additionally, the qualitative results were quantified, and percentages provided to give an impression of the frequency of the studied topics.

3. Results

3.1. Study Participants

Twelve women participated in this study. The percentages mentioned below always refer to the total number of 12 women. Table 1 gives an overview of the characteristics of the study participants. Participants were between 29 and 58 years old and the majority had children (92%). Eight women (67%) had a positive pathogenic variant status for the *CHEK2* gene, three (25%) for the *PALB2* gene, and one (8%) for the *ATM* gene. Nine women (75%) were affected by BC in the past (referred to as survivors in the following) and three women (25%) had no history of BC (referred to as previvors in the following). The majority (92%) had a positive family history for BC in the nuclear family (mother or sister) or extended family (aunt, cousin, grandmother). Educational level was classified into "No formal education" (8%), "Vocational training" (67%), and "Bachelor's degree or above" (25%). To enable an international comparison, corresponding ISCED 2011 (International Standard Classification of Education) levels have been added [33].

Table 1. Participant characteristics (n = 12).

Characteristic of the Participants	n (%)
Age	
<30 years	1 (8%)
30–40 years	3 (25%)
41–50 years	4 (33%)
>50 years	4 (33%)
Pathogenic variant	
ATM	1 (8%)
CHEK2	8 (67%)
PALB2	3 (25%)
Time between PTGC and interview	
6–12 months	2 (17%)
12–36 months	5 (42%)
>36 months	5 (42%)
BC Status	
Survivor	9 (75%)
Previvor	3 (25%)
Marital status	
Married	9 (75%)
Divorced	2 (17%)
In a relationship	1 (8%)
Family history of BC	
No family history of BC (participant is index patient)	1 (8%)
BC in nuclear family	8 (67%)
BC in extended family	3 (25%)
Children	
No children	1 (8%)
One or more children	11 (92%)
Educational level/ISDEC level	
No formal education	1 (8%)
Vocational training/ISCED 3	6 (50%)
Vocational training (health sector)/ISCED 4	2 (17%)
Bachelor's degree or above/ISCED 6 or 7	3 (25%)

PTGC = post-test genetic counseling; BC = breast cancer; survivor = pathogenic variant carrier affected by BC; previvor = pathogenic variant carrier unaffected by BC; nuclear family = parents and siblings; extended family = grandparents, cousins, aunt/uncle; vocational training = dual training system in Germany, requirement: either Secondary Education or Higher Education Entrance Qualification; ISCED = International Standard Classification of Education 2011 [33]. Percentages shown in the table have been rounded to the nearest whole percent.

3.2. Results of Qualitative Analysis

The thematic analysis of the interview data produced 815 codings that were categorized into 81 codes. The codes were organized into main categories and subcategories

and further systematized to identify key areas and major themes. Six major themes were identified, showing results on (1) feelings associated with the disclosure of the genetic test result, (2) feelings associated with the overall situation, (3) feelings associated with being a carrier of a pathogenic variant, (4) coping styles, (5) impact of familial medical history, and (6) support needs.

Table 2 gives an overview of these major themes and subthemes that emerged from the data and the representative quotes. The order of the subthemes is according to the number of women. Each of the major themes is discussed in detail below.

Table 2. Major themes that emerged from the data and representative quotes.

Major Theme and Subthemes	Number of Women n (%)	Representative Quote
1. Feelings associated with the disclosure of the genetic test result		
1.1. Overwhelm	8 (67%)	*"I think I just switched off after that [the disclosure of the genetic test result] because I didn't want to hear any more. (…) I just wanted to go home." [34 years old, previvor, CHEK2]*
1.2. Relief	6 (50%)	*"Because then I finally had something to hold on to. So for me, there were so many people among us who died of it, and no one can tell you why. (…) Yes, it is something. You can explain it now why it was like this for my mother." [38 years old, previvor, CHEK2]*
1.3. Certainty and indifference	3 (25%)	*"But you think to yourself, 'Yes … well … okay … you were expecting it. Just go home. Have a cup of coffee (laughing).'" [29 years old, previvor, PALB2]*
1.4. Grief through the memory of deceased loved ones	3 (25%)	*"So, at the first moment, I immediately had to think of my sister because she had that, too." [34 years old, previvor, CHEK2]*
1.5. BC diagnosis was perceived as worse than disclosure of pathogenic variant	2 (17%)	*"So therefore, this genetic test result was actually, I think, not that important for us anymore, I would say. (…) That [the BC diagnosis 1 year before] was rather the shock in the family." [55 years old, survivor, CHEK2]*
1.6. Loneliness	1 (8%)	*"But it wasn't until the doctor told me that straight to the point, I had tears running down my face. That was somehow quite strange, but yes, I would not do it again today, drive there on my own. But I didn't really know what was going to happen because I'm not actually afraid. But this confrontation has triggered everything in me." [47 years old, survivor, CHEK2]*
2. Feelings associated with the overall situation		
2.1. Fear and concern	7 (58%)	*"My mother became ill for the first time at the age of 40. I'm now approaching 40, and of course with every examination more and more panic comes along." [38 years old, previvor, CHEK2]*
2.2. Calmness and acceptance	5 (42%)	*"But because I have already completed my [breast cancer] therapy, and I assume that I have lowered my risk so far. I was not worried or anxious now." [38 years old, survivor, ATM]*
2.3. Feeling of a lack of understanding by the relatives	4 (33%)	*"And the fact that this is something that I'm concerned about. He [the husband] just can't understand." [49 years old, survivor, PALB2]*
2.4. Need for safety	4 (33%)	*"For me, personally, I would like to minimize all risk factors as soon as I personally can to prevent a new outbreak." [49 years old, survivor, PALB2]*

Table 2. *Cont.*

Major Theme and Subthemes	Number of Women n (%)	Representative Quote
2.5. Differentiation from the needs of other women	3 (25%)	*"Then I'll just say what I consider important, so that maybe afterwards you can understand why I might have very different needs than any of the other women you're interviewing." [58 years old, survivor, PALB2]*
3. Feelings associated with being a carrier of a pathogenic variant		
3.1. Resentment	1 (8%)	*"It's also about not having any resentment towards your parents, and I think that's very, very important, especially with such a disease that is inherited." [50 years old, survivor, CHEK2]*
3.2. Burden	1 (8%)	*"This burden, you can't help it, but still this burden of passing the gene on to the children and the fear, especially if the girl maybe wants to get pregnant now and have children and, and, and, and, the hormone balance shifts. I think I would have been a bit afraid." [50 years old, survivor, CHEK2]*
3.3. Guilt	1 (8%)	*"Well, he [the participant's father] doesn't say it like that, he always says he didn't have that much time. But I do think so. Yes, I think he also has a bit of a guilty conscience." [44 years old, survivor, CHEK2]*
3.4. Facing negative reactions from family members	1 (8%)	*"Well, for example, my niece/I have a problem there now. We got along great with each other (…). Therefore, I was so disappointed and hurt. That was really hard." [50 years old, survivor, CHEK2]*
4. Coping		
4.1. Emotion-focused coping	12 (100%)	*"That you have this awareness of oneself that many things that you don't want to do, you don't have to do. Well, this awareness, this mindfulness towards oneself." [47 years old, survivor, CHEK2]*
4.2. Problem-focused coping	10 (83%)	*"I have this confidence that they'll find it, and when they do, it's up to me to also act immediately or to say, okay, right now." [55 years old, survivor, CHEK2]*
4.3. Meaning-focused coping	5 (42%)	*"And that's why the breast cancer was a stroke of luck. She [the psycho-oncologist] cleared that up [her anxiety and panic disorder]. I recognized it." [58 years old, survivor, PALB2]*
5. Impact of familial medical history		
5.1. Intensive experience with death and/or disease in the past	2 (17%)	*"Well, I'm someone, I say of myself, I can handle it pretty well because I've seen it all the way to the end happening with my mother." [38 years old, previvor, CHEK2]*
5.2. Appraisal and evaluation of the way the mother dealt with the disease	5 (42%)	*"My parents have both surrendered to their disease at some point. And I have noticed that, of course. And from my observation, at the moment they surrendered to the disease, it got worse. And I decided for myself right from the start. I won't do that. I am going to fight that enemy. And I won't surrender to that enemy." [49 years old, survivor, PALB2]*
6. Support needs		
6.1. Personal psycho-oncological counseling	3 (25%)	*"Although, I think, I would prefer a one-on-one conversation because sometimes the individual aspects get lost in the group." [29 years old, previvor, PALB2]*
6.2. Self-help groups	4 (33%)	*"Yes, it would actually be interesting to see how they deal with it. Also, those affected because I just don't have access to my aunt now who also has it [the pathogenic variant]." [34 years old, previvor, CHEK2]*

BC = breast cancer; total number of women n = 12; percentages shown in the table have been rounded to the nearest whole percent.

3.2.1. Feelings Associated with the Disclosure of the Genetic Test Result

At the time of the disclosure of the genetic test result during the PTGC, eight women (67%), both survivors and previvors, reported that they had felt overwhelmed by the situation. One of them remembered:

"I have not been receptive at this point of time" [47 years old, survivor, CHEK2].

Another woman stated:

"Yes, although I had expected the genetic test result to be positive, I have to say I was a bit shocked when I received this information. And then you are, I guess, not that receptive" [38 years old, survivor, ATM].

At the same time, six out of the twelve participants (50%), both survivors and previvors, also experienced feelings of relief at the time of the disclosure of the genetic test result. Four of them (33%) experienced both relief and overwhelm. One of them describes this confluence:

"On the one hand, the relief. Yes, it is something. You can explain now why it was like that with my mother. But of course, there is also this shock. Oh my God, now you have it too. What will happen, if?" [38 years old, previvor, CHEK2].

The different reasons for the participants feeling relief are described in Table 3.

Table 3. Feelings associated with the disclosure of the genetic test result: Relief.

Relief Because …	**Number of Women n (%)**	**Representative Quote**
… I don't have a *BRCA*1/2 pathogenic variant	3 (35%), survivors	*"So for me it was a relief that I don't have this big gene variation, and in my mind I already saw myself under the knife because of the ovaries." [57 years old, survivor, CHEK2]*
… I have an explanation and confirmation	1 (8%), survivor	*"The goal was actually, maybe I actually wanted to have a confirmation because my aunt got sick." [47 years old, survivor, CHEK2]*
… I finally have something to hold on to and luckily it is not *BRCA1/2*	1 (8%), previvor	*"Because then I finally had something to hold on to. So for me, there were so many people among us who died of it, and no one can tell you why. (…) Yes, it is something. You can explain it now why it was like this for my mother." [38 years old, previvor, CHEK2]*
… .my family members will be included in the multimodal intensified breast surveillance program	1 (8%), survivor	*"But the bottom line is I was glad I had that gene because it got my daughter and sister into the trial or into preventive care." [49 years old, survivor, PALB2]*

Survivor = affected pathogenic variant carrier; previvor = unaffected pathogenic variant carrier; total number of women n = 12; percentages shown in the table have been rounded to the nearest whole percent.

Three women felt relief because—against their expectation—their test result was negative for *BRCA*1/2 pathogenic variants. One participant felt relief because she finally had an explanation and confirmation of her increased risk. One previvor was very relieved not to have *BRCA1/2* and because she finally had something concrete to hold onto. One woman was relieved because, with her having a pathogenic variant, her daughter and sister were included into the multimodal intensified breast surveillance program of the university hospital.

The three participants (25%) who did not feel overwhelmed reported feelings of certainty and indifference regarding the moment of the genetic test disclosure. They all had experienced women suffering from BC in their nuclear family. One participant said:

"But you think to yourself, 'Yes . . . well . . . okay . . . you were expecting it. Just go home. Have a cup of coffee (laughing)'" [29 years old, previvor, PALB2].

Further feelings arose during the PTGC. Three previvors experienced grief through the memory of deceased loved ones at the moment of genetic test disclosure:

"So, at the first moment, I immediately had to think of my sister because she had that, too" [34 years old, previvor, CHEK2].

Two women, both survivors, explained that the genetic test disclosure was not as stressful and upsetting as the previous BC diagnosis had been:

"That means this whole thing, the breast cancer diagnosis the year before, that was a lot more upsetting and awful" [50 years old, survivor, CHEK2].

One participant was not accompanied by friends or family and felt lonely during disclosure.

3.2.2. Feelings Associated with the Overall Situation

Concerning the overall situation, seven women (58%) experienced feelings of fear or concern (Table 4). These feelings have been described in the context of (1) the health of children or blood relatives, (2) developing BC, (3) the BC therapy and its sequelae, (4) abnormal findings in the intensified breast surveillance program or a recurrence, and (5) unclear statements and information concerning the risks associated with the pathogenic variant.

Table 4. Feelings associated with the overall situation: Fear and concern.

Fear and Concern . . .	Number of Women n (%)	Representative Quote
. . . for the health of children/relatives	2 (17%), survivors	*"What worried me a bit was that this was also found in leukemia patients. Then it was like that, my aunt, who is my father's sister, is now suffering from senile leukemia, and I started to think about whether . . . [started to cry]." [38 years old, survivor, ATM]*
. . . about getting BC	2 (17%), previvors	*"My mother became ill for the first time at the age of 40. I'm now approaching 40, and of course with every examination more and more panic comes along." [38 years old, previvor, CHEK2]*
. . . regarding the BC therapy and its sequelae	1 (8%), survivor	*"NO, I say, you're not going to puncture my port with 500 leukocytes [defined as critical leukopenia]. I found that really/Well, things happen that are really, really bad and then you get scared." [50 years old, survivor, CHEK2]*
. . . regarding abnormal findings in the intensified breast surveillance program or a recurrence	1 (8%), survivor	*"Yes, of course it is every year, when I drive to Cologne, you are of course super nervous a week before and think, 'Oh, hopefully it's not something again.'" [44 years old, survivor, CHEK2]*
. . . regarding unclear statements and information about the risks associated with the pathogenic variant	2 (17%), (previvor, survivor)	*"How high the risk is, because, as I said, of course I was a bit confused now by this statement of my gynecologist. That I was told this 15 percent in Cologne and because of the frequency in the family he said 45 percent now." [38 years old, previvor, CHEK2]*

BC = breast cancer; survivor = affected pathogenic variant carrier; previvor = unaffected pathogenic variant carrier; total number of women n = 12; percentages shown in the table have been rounded to the nearest whole percent.

On the other hand, five participants (42%), all survivors, expressed rather feelings of calmness and acceptance towards the overall situation. One participant stated:

"I'll now tell you quite honestly. In my case, there is nothing I can do about it now" [47 years old, survivor, CHEK2].

Another woman shared this view:

"I do everything that can be done. I regularly go for checkups" [55 years old, survivor, CHEK2].

Furthermore, four women (33%), two survivors and two previvors, experienced a feeling of a lack of understanding by their relatives regarding their way of coping with the pathogenic variant. *"They [the children] have blocked this" [47 years old, survivor, CHEK2],* one participant said. Another woman stated: *"They [the relatives] could not understand this"*

[38 years, previvor, CHEK2]. Four women (33%) expressed a high need for safety, which was expressed in the fact that they would be willing to do anything (including risk-reducing surgery) to minimize their cancer risk in the future. One woman explained:

> *"And I say very clearly, if there is something, operate straight away, full stop" [55 years old, survivor, CHEK2].*

For three women (25%), all survivors with a family history of BC, it was important to distance themselves from the feelings and needs of other women who were in similar situations. One explained right at the beginning of the interview that she might not be the right person to talk to because she was different from others due to her individual medical family history. Another woman shared this view:

> *"Then I'll just say what I consider important, so that maybe afterwards you can understand why I might have very different needs than any of the other women you're interviewing" [58 years old, survivor, PALB2].*

3.2.3. Feelings Associated with Being a Carrier of a Pathogenic Variant

Concerning the feelings associated with being a carrier of a pathogenic variant, one participant spoke about *"the burden of passing the gene on to the children" [50 years old, survivor, CHEK2]* and the fear associated with it. She also pointed out:

> *"It's also about not having any resentment towards your parents, and I think that's very, very important, especially with such a disease that is inherited" [50 years old, survivor, CHEK2].*

Another participant talked about her father's feelings about being a carrier of a pathogenic variant:

> *"Well, he [the participant's father] doesn't say it like that, he always says he didn't have that much time. But I do think so. Yes, I think he also has a bit of a guilty conscience" [44 years old, survivor, CHEK2].*

Furthermore, the women's feelings might also be influenced by the behavior or statements of (female) relatives. One woman describes the repelling behavior of her niece after the genetic test disclosure:

> *"Well, for example, my niece/I have a problem there now. We got along great with each other (…). Therefore, I was so disappointed and hurt. That was really hard" [50 years old, survivor, CHEK2].*

3.2.4. Coping

Women with pathogenic variants for hereditary BC must cope with this situation their whole life. One aim of this study was to find out how these women manage to cope with their pathogenic variant and the lifelong uncertainty and to identify resources that they draw on. Coping was defined and classified according to the Transactional Model of Stress and Coping by Lazarus and Folkmann [34] into emotion-focused coping, problem-focused coping, and meaning-focused coping. While emotion-focused coping refers to the thoughts and actions people use to regulate or reduce distress, problem-focused coaching refers to strategies people use to manage or solve the problem that is causing the distress. Meaning-focused coping helps the person to make sense of what is happening and appraise benefit where possible. Table 5 gives an overview of the different types of coping and strategies that were identified and are presented in the following.

All twelve women mentioned resources or coping strategies assigned to emotion-focused coping. A very important aspect was the support from their partner, family, and friends, which was mentioned by eight participants (67%). Another very important aspect mentioned by six women (50%) was strategies that can be summarized as self-care strategies. This includes meditation, mindfulness, and consideration of one's own needs and desires and not only those of others. Further emotion-focused coping strategies were

psychotherapy and self-help groups, sports and nature-related activities, religion, and acceptance and repression.

Ten women (83%) described strategies classified as problem-focused coping. Taking part in the multimodal intensified breast surveillance program of the university hospital was mentioned by nine out of twelve women (75%). Another important aspect was health-promoting behavior such as healthy eating or exercise. Health-promoting strategies were mentioned by four (33%) participants. In addition, for two women (17%), the direct confrontation with the pathogenic variant and the disease was important to cope with their situation. Further problem-focused coping strategies included willingness to undergo (risk-reducing) surgery and becoming more aware of their own health and more sensitive towards body changes.

Table 5. Overview of the different types of coping.

Type of Coping and Number of Women n (%)	Strategies	Number of Women n (%)	Representative Quote
Emotion-focused coping, n = 12 (100%)	Family, partner, and friends	8 (67%)	*"Family, friends, that was the most important thing at that time. Well, there is nothing more important." [50 years old, survivor, CHEK2]*
	Self-care	6 (50%)	*"To do things that are good for me, that makes me feel good and not others, yes. Sometimes you do things when you say, 'Oh well, yes, come on, I'll do that now—even though you don't want to. And you just shouldn't do that all the time, should you.'" [47 years old, survivor, CHEK2]*
	Psychotherapy and self-help groups	2 (17%)	*"I am so grateful to fate, that she [the psycho-oncologist] built me up." [58 years old, survivor, PALB2]*
	Sports, nature, and activity	2 (17%)	*"Yes, I always have to deal with it intensely in order to understand everything. When in doubt, go outside. I am a nature person, garden, outside, bike." [58 years old, survivor, PALB2]*
	Religion	1 (8%)	*"But that [her religious belief] has already given me, has already given me such a foothold again." [50 years old, survivor, CHEK2]*
	Acceptance and repression	1 (8%)	*"Well, there is not much I can do about my situation anyway." [47 years old, survivor, CHEK2]*
Problem-focused coping, n = 10 (83%)	Participation in the multimodal intensified breast surveillance program	9 (75%)	*"That [the intensified breast surveillance] is the, I think, the be-all and end-all for me. I say that in all honesty." [55 years old, survivor, CHEK2]*
	Lifestyle changes	4 (33%)	*"Because of course you are feeling better when you have the feeling that you are doing something about it." [38 years old, previvor, CHEK2]*
	Willingness to undergo (risk-reducing) surgeries	3 (25%)	*"And I say very clearly, if there is something, operate straight away, full stop." [55 years old, survivor, CHEK2]*
	Awareness of the body, health, and physical changes	3 (25%)	*"Well, I became more sensitive, I already became so because of the disease. So, I watch out more, when does something hurt or I don't know, and I go see the doctor sooner than I used to." [44 years old, survivor, CHEK2]*
	Confrontation with the gene and the disease	2 (17%)	*"Look at the enemy, then you'll know if you can handle it." [58 years old, survivor, PALB2]*
Meaning-based coping, n = 5 (42%)	Opportunity for sharing the BC experience with children, relatives, or other women	3 (25%)	*"But it would also, if she had it, calm me down, because one could hand over one's own experiences. So, you could also tell them, 'Listen, even if you do it and you have it, you don't have to be afraid.'" [47 years old, survivor, CHEK2]*

Table 5. *Cont.*

Type of Coping and Number of Women n (%)	Strategies	Number of Women n (%)	Representative Quote
	Awareness of what is good for oneself and how to enjoy life	2 (25%)	*"You notice that throughout the chemo treatment. You realize what is good for you and what is not good for you. And you become very sensitive thereby." [47 years old, survivor, CHEK2]*
	Identification and appreciation of personal strengths	2 (17%)	*"The others also said, 'Man, you got through it really well, you did great. (. . .) And I was happy and blessed and also proud that I managed it differently. (. . .) Maybe I even got aware of some personal strengths that I would not have appreciated otherwise.'" [57 years old, survivor, CHEK2]*
	Chance to address pre-existing mental health issues through psycho-oncology	1 (8%)	*"And that's why the breast cancer was a stroke of luck. She [the psycho-oncologist] cleared that up [her anxiety and panic disorder]. I recognized it." [58 years old, survivor, PALB2]*

Total number of women n = 12; percentages shown in the table have been rounded to the nearest whole percent.

Five women (42%), all survivors, mentioned aspects that reframe or reappraise the situation in positive ways and that can be classified as meaning-based coping. Three (25%) were happy to be able to share the knowledge and experience that they gained due to their BC disease with their children and other women; one of them even considered writing a book about her experiences. Two women stated that, because of their own BC disease, they became aware of what is good for themselves, and that one should enjoy life to the fullest and be grateful. Two became aware of their own personal strengths in the way they handled the overall situation. Another woman explained that it was only through psycho-oncology counseling during her BC disease that she was able to address pre-existing underlying psychological conditions that she did not deal with before.

3.2.5. Impact of Familial Medical History

Except for one woman, all participants had a family history of BC, either in their nuclear (67%) or extended (25%) family. This experience might have influenced the women's feeling, views, and coping style. Three women (25%) whose mothers died of cancer mentioned that they had already dealt with the topics of disease and death very intensively:

> *"For me, it [death] is just part of it because my parents passed away very early. For me, it's just an ordinary topic" [49 years old, survivor, PALB2].*

Another aspect of the family medical history was the evaluation and appraisal of the patient's mother's way of dealing with her own diagnosis of BC. Three women expressed a negative opinion about their mothers' way of dealing with their cancer disease. One woman explained:

> *"This generation doesn't go to see a doctor. This is a generation that closes its eyes and sticks its head in the sand. (. . .) That's why I deal with those things completely differently than my mother. And I am simply a completely different person in such matters" [55 years old, survivor, CHEK2].*

On the other hand, one woman expressed a positive opinion about how her mother dealt with the BC disease:

> *"Well, I am not afraid at all of actually getting sick. Not at all. My mom did a good job" [29 years old, previvor, PALB2].*

3.2.6. Support Needs

Five women (42%) indicated that they did not need either personal psycho-oncological counseling or support through self-help groups. For two of them, one survivor and one

previvor, and both with a medical family history of BC, talking to family members was more important than talking to counselors or therapists. One of them said:

> *"It was offered to me, to seek psychological help. But I did not want that for myself. Well, I am someone, I say of myself, I can handle that quite well because I have seen it until the end with my mother. (…) Family is more important to me, before I talk to someone else about it" [38 years old, previvor, CHEK2].*

The other one had a very close relationship with her sister, who also carried a MBCG pathogenic variant and had been affected by BC, and with whom she talked a lot about the pathogenic variant and how to deal with the BC disease. The other three women did not mention an intensive exchange with their family but had no need for psycho-oncological counseling or support that was offered through a self-help group, either.

Five out of twelve women (42%) mentioned that they had already seen a therapist or counselor. Two of them, both survivors, shared very positive experiences about it:

> *"Also with the cancer, we also talked about that. So, there were many things, that had to be sorted out. And that helped me quite well" [47 years old, survivor, CHEK2].*

This participant even stated that she would still be interested in further specialized counseling as offered by the university hospital, but that it was too far away from her hometown to make use of this offer. The other woman revealed:

> *"And I perceived that [the personal psycho-oncological counseling] really helpful during that time, again and again and again" [58 years old, survivor, PALB2].*

Both were not interested in self-help groups. The other three women attended counseling once in the past but reported that they had no need for personal psycho-oncological support regarding the pathogenic variant. Two of them, one survivor and one previvor, were interested in self-help groups instead. One of them was a previvor without any contact with other pathogenic variant carriers in the family and the other woman was a survivor, who described very positive experiences regarding self-help groups during her BC disease:

> *"Well, after my experience with psychologists, that's quite nice, but I believe that if you talk to other affected people, you can, yes, much more relate to that. You have much more empathy and you get told much more what you can do, right?" [50 years old, survivor, CHEK2].*

Two interviewees indicated that they would be interested in both psycho-oncological support and self-help groups. One was a survivor and the other one was a previvor, and both experienced the disease through their mothers and had close relationships with their families.

Eventually, some interviewees added general comments regarding the topic of psycho-oncological counseling. Three of them considered it important to have local services and that there was no need to travel to the university hospital. One woman emphasized that it was important for the psycho-oncology counselor to have medical professional knowledge.

4. Discussion

The aim of this study was to explore the feelings, coping styles, and support needs of women confronted with a pathogenic variant in a MBCG. After conducting an initial systematic literature search in five databases (Pubmed, CINAHL, EMBASE, PsychINFO, Cochrane), a qualitative approach was chosen to gain first insights into the feelings and coping situations of these women.

The results of the study revealed a wide range of feelings, both positive and negative. Overwhelm and being emotionally and/or mentally overloaded at the moment of the disclosure of the genetic test result were mentioned by almost all participants, regardless of whether they were survivors or previvors. Studies have shown that feelings of overwhelm and emotional overload may arise when severe diseases are diagnosed. Samson et al. [35] indicate that the disclosure of the genetic test result to unaffected *BRCA1/2*

pathogenic variant carriers can be perceived to be as threatening as being diagnosed with BC. Augestadt et al. [36] conducted a qualitative study with women newly diagnosed with BC or OC who were consecutively offered testing for *BRCA1* and *BRCA2* pathogenic variants at the time of cancer diagnosis without receiving genetic counselling prior to genetic testing. Many of these women already felt overwhelmed and mentally overloaded when being offered genetic testing because of the amount of information that they received. The results of our study indicate that not only the diagnosis of a severe disease and the offer of genetic testing can be overwhelming and stressful, but also the disclosure of the genetic test result. This is in line with Leonarczyk and Mawn [37], who conducted a qualitative study with *BRCA1/2* previvors. The participants also experienced the diagnosis of the *BRCA1/2* pathogenic variant as profoundly traumatic and overwhelming. The participants of our study also described that—due to this overwhelm—they were not able to fully assimilate the genetic and medical information provided orally during the PTGC. According to Kessels [38] and Brown et al. [39], recall of medical information is low in general, suggesting that 80% of medical information provided by healthcare professionals is forgotten. In addition, genomic literacy in the general population is very low [39,40] and confusion of genetic terms is particularly common [41]. There is a clear need to provide women with additional written information media, either as a written information booklet or web-based in the form of a website or app, to make sure that they comprehend what the pathogenic variant implies for their health and that of their families.

A further feeling associated with the disclosure of the genetic test result that was identified was relief that—other than expected—the genetic test result was negative for *BRCA1/2* pathogenic variants. Since *BRCA1/2* pathogenic variants are associated with a higher cancer risk, it may comfort some women that the test result is negative. This finding is in line with Reyes et al. [22], who recently studied the uncertainty experienced by carriers of *ATM* and/or *CHEK2* pathogenic variants. Participants of this study also reported relief due to the relatively lower risk of developing BC compared to individuals with pathogenic variants in high-risk genes, such as *BRCA1/2*. This information might be comforting and helpful for MBCG pathogenic variant carriers and may be communicated during the PTGC. However, Waltz et al. [21] examined the use of *BRCA1/2* as a reference or gold standard in communicating other BC-related genes and its possible implications for patients. They found out that the use of *BRCA1/2* as "anchors" may confuse patients and impact their understanding of the uncertainty. Hence, this should be paid attention to when using *BRCA1/2* as a reference at the PTGC. Both feelings, overwhelm and relief, can occur at the same time and demonstrate the complexity of feelings that can occur and with which the genetic counselor may be confronted during the PTGC.

Some feelings arose only or mainly in different subgroups. Some survivors expressed feelings of calmness or acceptance while previvors expressed fear and concern, especially when they had already experienced the BC disease through their mother. Grief and sadness were experienced during disclosure by those who had already lost close family members because of BC. This variety of feelings indicates that the feelings of affected women may differ from those of unaffected women and that the family medical history might have an influence on their needs and feelings as well. As a consequence, information and counseling might need to be adapted to these specific situations to make sure that all feelings and needs are appropriately addressed.

Concerning the feelings associated with being a carrier of a pathogenic variant, several feelings came up during the interviews: feelings of guilt, the burden of inheriting a pathogenic variant, the parents' bad conscience, and the blaming of the female relatives were described by the participants. This is in line with other studies focusing on *BRCA1/2* pathogenic variant carriers. In a study by Lynch et al. [42], participants revealed feelings of guilt about passing the pathogenic variant on to their children and worry about their children developing cancer. The authors identified these concerns as two of the four major burdens of carriers of pathogenic variants. Hallowell [43] and Grant et al. [44] use the term "genetic responsibility" to describe this special situation and the feeling of being responsi-

ble for the health of others. Fisher et al. [45] focused on the offspring's perspectives and described how the daughter expressed blame towards her mother for having passed along her increased risk. These findings indicate that in order to prevent blame and negative feelings, there is a strong need for understandable, clear, and basic information regarding the modes of inheritance and the inheritance patterns of pathogenic variants. It might be important to explain that these inheritance patterns cannot be influenced and that there is no one to blame for anything.

All participants of this study used coping strategies that can be classified as emotion-focused coping according to the definition of Lazarus and Folkman [34], e.g., seeking support from family and friends or self-care strategies. According to Folkman, emotion-focused coping strategies refer to the thoughts and actions people use to regulate or reduce distress and are used more in situations that have to be accepted and cannot be controlled, such as chronic illness [46]. Since carrying a pathogenic variant is also something that one must accept and cannot change, the result of our study is in line with this assumption. Having an increased risk for hereditary BC implies being confronted with and challenged by uncertainty for a lifetime [22,47,48]. Studies even suggest that women who carry a pathogenic variant in an MBCG experience higher levels of uncertainty compared to carriers of a pathogenic variant in the high-risk genes *BRCA1/2* [20,22,49]. This difference might be caused by the limited empirical data about cancer risk estimates and about the effectiveness of risk management strategies for MBCG. According to Uncertainty Management Theory [50], uncertainty may not only be anxiety-inducing but also enhance coping and the aim should therefore be to manage uncertainty, not to reduce it. The coping styles of women at increased risk for hereditary BC have also been assessed by Pieterse et al. [51] in a quantitative study applying the coping styles of the Utrecht Coping List [52]. They found out that "Seeking social support" was a favorable coping style since it was associated with lower levels of psychological distress. Holland and Holahan [53] determined that a high level of social support led to higher levels of emotional well-being in BC patients, and in a study by Ozdemit and Arslan [54], social support predicted effective stress management in women with BC.

In addition to emotion-focused coping, Lazarus and Folkman define problem-focused coping as the strategies that people use to manage or solve the problem that is causing the distress [34]. The most important strategy that can be assigned to this coping style and that was mentioned by 75% of the study participants was participation in the multimodal intensified breast surveillance program of the university hospital. However, there are also qualitative studies with *BRCA1/2* pathogenic variant carriers indicating that participation in a multimodal intensified breast surveillance program might lead to fear and worry caused by (false positive) abnormal findings, follow-up tests, and biopsies. Werner-Lin [55] and Hoskins and Greene [56] use the terms "surveillance fatigue" and "screening fatigue" to describe this very special situation of young women at high risk for hereditary BC who regularly participate in intensified breast surveillance and experience the ongoing screening as stressful, uncomfortable, and scary. In these studies, surveillance fatigue was one of the reasons for young previvors choosing an RRM at an early age. According to Metcalfe et al. [57], in unaffected women who carry a *BRCA1/2* pathogenic variant, cancer-related distress decreased significantly after having both RRM and risk-reducing salpingo-oophorectomy. The participants of our study mostly experienced the multimodal intensified breast surveillance program as helpful and positive. One reason for this difference might be the age of our participants, with only one woman under the age of 30. This young previvor's concerns were further elaborated in Stracke et al. [26] and were similar to those of the young previvors described by Werner-Lin and Hoskins and Greene [55,56]. Another reason might be the absence of an alternative prevention option other than the multimodal intensified breast surveillance program, since RRM is not generally recommended for carriers of pathogenic variants in MBCG in Germany [18,58].

A further coping style that was mentioned by 42% of the participants—all survivors—was meaning-focused coping. As with emotion-focused coping, meaning-

focused coping appears to be used more in situations that are chronic and cannot be changed, such as chronic illness, and it might be used when initial coping efforts fail [46]. Studies with cancer patients found that meaning-based coping led to a restoration of well-being and was associated with a higher quality of life [59,60]. Furthermore, Vehling et al. [61] found that a global sense of meaning is an important protective factor concerning the development of distress in cancer patients.

The results of our study indicate that a family history of BC—especially in the nuclear family—might also have an impact on the coping style and the attitudes and views of the participants. Some women expressed a positive or negative opinion about how their mother dealt with the BC disease. This appraisal and evaluation of the mother's coping might influence the patient's own behavior and coping style. Studies have found that a family history of BC influences BC prevention decisions among healthy women at elevated risk of BC [62,63]. Furthermore, women who have a first-degree relative who is a BC survivor might be more optimistic in their beliefs about the benefits of early detection [62]. Mæland et al. [64] found that the loss of a mother due to OC affects women living with a hereditary cancer risk and influences how they deal with their genetic cancer risk.

The participants had very diverse and heterogeneous views on the topics of psycho-oncological support and self-help. While some were interested in both and expressed a relevant need, others were rather reserved, preferring their family as a primary contact. This diversity was also found in a qualitative study on the support needs of affected and unaffected *BRCA1/2* pathogenic variant carriers by Hughes and Phelps [65], indicating that "different people want different things at different stages in their life and throughout their genetic journey". They proposed a Model of Support that consists of multiple elements, such as social events, a 24 h phone line, a chat forum, and a central organizing body, which is professional and peer-led [65]. Farrely et al. [66] suggested the implementation of a telephone-based peer support intervention for women who carry a *BRCA1/2* pathogenic variant. In addition to the calls, they encouraged the use of text messaging and/or email and concluded that a mixed-medium intervention might be preferable and the most effective. Segal et al. [67] investigated the interest in interventions to support the disclosure process of *BRCA1/2* pathogenic variant carriers to their offspring and also suggested that one type of support may not be suitable for all women. Eventually, a quantitative study on the support needs of unaffected women with a family history of BC found that demographic variables did not predict the interest in attending a support group [68].

There are a few limitations of our study. We interviewed only one woman without children, and only one woman without a family history of BC. We recommend further studies to gain deeper insights into the feelings, coping styles, and support needs of these women. Furthermore, quantitative studies are needed to explore potential differences between the different subgroups and between the different MBCG pathogenic variants. A further limitation is the selection bias. As purposive sampling was employed, the participants might have already been interested in sharing their personal experiences. Another potential limitation is the sample size, which included just twelve participants. However, a theoretical saturation was postulated since it was possible to assign more than 80% of the codings from the 12th interview to pre-existing codes. Furthermore, the results of this study may not be transferable across different settings or to institutions with other counseling standards and processes.

One of the strengths of our study is the qualitative approach, which enabled us to explore a wide range of feelings, living contexts, and circumstances on a one-to-one basis. Thanks to the protected settings of the individual interviews, the participants were able to open up and share very private thoughts and experiences and the interviewer was able to react spontaneously to statements and emotions. Another strength is the heterogeneity of the study sample: the women interviewed had pathogenic variants in different MBCG, represented both survivors and previvors, and some had completed their family planning while others had not. This provided a first in-depth insight into a broad spectrum of different perspectives, life situations, feelings, and opinions from this specific target group.

5. Conclusions

The aim of this study was to obtain a closer insight into the situation of women carrying pathogenic variants in MBCG. We were able to explore feelings during and following the disclosure of the genetic test result, women's personal coping strategies, possible influences of familial medical history, and the women's attitudes towards psycho-oncological support and self-help. This study demonstrates that women with pathogenic variants in MBCG experience a wide range of feelings at the time of the disclosure of the genetic test result during the PTGC and continue to have a wide range of feelings several months or years after the disclosure. Negative feelings such as overwhelm, fear and concern, grief, and guilt, as well as positive feelings such as relief, calmness, and acceptance, might occur, even at the same time. This should be taken into account and might be addressed by counselors and physicians at the PTGC or at the annual multimodal intensified breast surveillance appointments, if necessary. To deal with this lifelong situation and the lifelong uncertainty posed by the pathogenic variant, all participants mentioned resources or coping strategies that can be assigned to emotion-focused coping, and most participants also described strategies that are classified as problem-focused coping. Some affected women mentioned aspects that can be classified as meaning-based coping. Women with a family history of BC—especially in the nuclear family—might express a positive or negative opinion about how their mothers dealt with the BC disease. This appraisal and evaluation of their mother's coping might influence their own behavior and coping style. These valuable insights into the women's feelings and coping mechanisms might help to improve the PTGC sessions, to make counselling more patient-centered, and to provide more needs-oriented information for carriers of pathogenic variants in MBCG. Concerning the topics of psycho-oncological support and self-help, the participants had a very diverse and heterogeneous view. Hence, psychological support and the possibility to join self-help groups should be offered to women carrying pathogenic variants in MBCG at the PTGC as well as at follow-up appointments.

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4. Diskussion

Ziel dieser Arbeit war es, die spezielle Situation von Frauen mit einer pathogenen Variante in einem moderaten bis hoch-moderaten Risikogen für Brustkrebs im Hinblick auf ihren medizinischen Wissensstand und mögliche Informationslücken und -bedürfnisse, mit der Situation verbundene Gefühle, individuelle Erfahrungen und Bewältigungsstrategien sowie bestehende Unterstützungsbedürfnisse zu untersuchen.

Mit Hilfe von qualitativen, leitfadengestützten Einzelinterviews mit Frauen mit einer pathogenen Variante in den Risikogenen *ATM, CHEK2* und *PALB2* konnten erstmals Einblicke in die spezielle Situation und Erfahrungswelt der Zielgruppe gewonnen werden. Es zeigte sich, dass auch nach dem persönlichen ärztlichen Genbefundgespräch ein Informationsbedarf zu verschiedenen medizinischen Themen besteht und während des Genbefundgesprächs mündlich kommunizierte Inhalte teilweise falsch oder gar nicht erinnert werden. Die mit dem Genbefundgespräch, der pathogenen Variante oder dem Status als Anlageträgerin verbundenen Gefühle sind sehr vielfältig und können sowohl positiv (Erleichterung, Gelassenheit) als auch negativ (Überwältigung, Angst, Trauer, Schuldgefühle) sein. Alle Frauen wandten Strategien des emotionsorientierten Copings an, um mit dieser lebenslangen Situation umzugehen. Die Einschätzung und Bewertung der Bewältigungsstrategien erkrankter Mütter oder erkrankter Familienmitglieder kann das eigene Verhalten und die eigenen Bewältigungsmechanismen der Frauen beeinflussen.

4.1. Dimension medizinisches Wissen und Informationsbedarf

4.1.1. Medizinischer Wissensstand

Die vorliegenden Studienergebnisse deuten darauf hin, dass Frauen mit pathogenen Varianten in moderaten bis hoch-moderaten Risikogenen für Brustkrebs sich nicht an alle medizinischen Informationen erinnern können, die sie während ihres Genbefundgesprächs erhalten haben. Insbesondere im Hinblick auf die Vererbungswahrscheinlichkeit und die Erkrankungsrisiken entsprach der Wissenstand einiger Frauen nicht den Informationen, die im Genbefundgespräch vermittelt wurden. Dies ist mit Studien vereinbar, die sich auf Frauen mit erhöhtem Risiko für familiären Brustkrebs oder pathogenen Varianten im *BRCA1*- oder *BRCA2*-Gen fokussieren und die Risikowahrnehmung und das Erinnern medizinischer Informationen, die von Gesundheitspersonal vermittelt werden (=Information Recall), untersucht haben[52-55]. Der Information Recall ist in der Allgemeinbevölkerung insgesamt gering: Studien legen nahe, dass nur rund 80 % der Informationen erinnert werden und der Anteil der vergessenen Informationen mit dem Umfang der Informationen zunimmt[50,51]. Insbesondere genetische Begriffe, wie z. B. ‚Gen', ‚DNS', ‚Chromosom', werden in der

Allgemeinbevölkerung laut einer qualitativen Studie von Mesters et al.[56] verwechselt und nicht verstanden. Die Gesundheitskompetenz in der Allgemeinbevölkerung in Bezug auf genetische Themen und Fragestellungen (=Genomic Literacy), wird in aktuellen Studien als sehr gering bewertet[50,57,58]. Gesundheitskompetenz bezieht sich dabei nicht nur auf das Finden und Verstehen gesundheitsbezogener Informationen, sondern umfasst auch die Bewertung und individuelle Anwendung dieser[59]. Das Verstehen und die Bewertung genetischer Informationen ist gerade in Bezug auf die prozentualen Angaben zu der Vererbungswahrscheinlichkeit und den Erkrankungsrisiken von zentraler Bedeutung und eine verständliche, laiengerechte Kommunikation dieser Zusammenhänge daher essenziell.

4.1.2. Entwickelte Überzeugungen und abgeleitete Informationsbedürfnisse

Einige Frauen entwickelten zudem eigene Konzepte und Überzeugungen hinsichtlich der Vererbung der pathogenen Variante oder der Entstehung einer Krebserkrankung. So gingen einige Frauen davon aus, dass je mehr eine Person von einem Elternteil bezüglich Aussehen oder Charakter geerbt hat, sie umso wahrscheinlicher auch die pathogene Variante geerbt hat. Dies steht im Einklang mit anderen Studien, die die Vorstellungen und Wahrnehmungen von Vererbung untersuchen[60]. Hinsichtlich der Krankheitsentstehung entwickelten einige Frauen die Überzeugung, dass Stress zum Auftreten einer Krebserkrankung oder eines Rezidivs führen könnte. Bislang liegen nur wenige Studien zum Thema Stress und Krebsrisiko vor. Wissenschaftler:innen stehen dabei stets vor der Herausforderung, das theoretische Konzept „Stress“ in eine praktisch messbare Form zu überführen. In einer Übersichtsarbeit aus dem Jahr 2006 wurde kein Zusammenhang zwischen dem Auftreten von Brustkrebs und belastenden Lebensereignissen, arbeitsbedingtem Stress oder wahrgenommenem globalen Stress festgestellt[61]. Andere, neuere Übersichtsarbeiten kamen zu dem Ergebnis, dass Stress und insbesondere stressige Lebensereignisse möglicherweise zur Krebserkrankung beitragen können[62,63]. Daher ist es noch nicht möglich, eine eindeutige Aussage über einen möglichen Zusammenhang zwischen Stress und dem Auftreten von Brustkrebs zu treffen. Außerdem beziehen sich diese Ergebnisse auf sporadischen Brustkrebs und können nicht ohne weiteres auf familiären Brustkrebs übertragen werden.

4.1.3. Zusätzliche Informationsbedürfnisse

Von einigen Frauen wurde ein zusätzliches Bedürfnis nach Informationen über gesundheitsfördernde Lebensstile und vermeidbare Risikofaktoren geäußert. Beratung hinsichtlich Lebensstil und/oder Ernährung ist auch bei Frauen mit sporadischem Brustkrebs[64] und generell bei Frauen mit erhöhtem Risiko für familiären Brustkrebs[52] ein wichtiges Anliegen. Leitlinien für sporadischen Brustkrebs berücksichtigen bereits den Einfluss von körperlicher Aktivität, Ernährung, Rauchen und Körpergewicht auf die Inzidenz und Mortalität von

sporadischem Brustkrebs[12]. Darüber hinaus legen Studien zum Einfluss von Lebensstilfaktoren auf die Brustkrebsprävalenz bei Frauen mit pathogenen *BRCA1*- oder *BRCA2*-Varianten nahe, dass körperliche Aktivität mit einem verringerten Brustkrebsrisiko assoziiert ist, während Rauchen als möglicher Risikofaktor bewertet wird[12,65-67]. Aktuelle Risikokalkulationsprogramme berücksichtigen bereits den Einfluss weiterer genetischer und nicht-genetischer Risikofaktoren, wie den PRS, die Familienanamnese, Lebensstilfaktoren oder die Brustdrüsendichte bei der Berechnung des individuellen Brustkrebsrisikos[16,68]. Dies kann die Entscheidungsfindung für ein personalisiertes Screening, basierend auf dem individuellen Risiko, unterstützen[18,19]. Weitere zusätzliche Informationsbedürfnisse beziehen sich auf die Möglichkeit, Vorteile und Risiken einer RRBM und Familienplanung. Diese Punkte werden unter 4.2.2.2. genauer diskutiert.

4.2. Dimension Emotionen und Bewältigung

4.2.1. Gefühle

Das Genbefundgespräch und die durch die Mitteilung der pathogenen Variante neue Situation gehen mit den unterschiedlichsten, sowohl positiven als auch negativen Gefühlen einher.

Zum einen erlebten viele Frauen die Mitteilung des genetischen Testergebnisses während des Genbefundgesprächs als überfordernd oder überwältigend und gaben an, dass sie die medizinischen und genetischen Informationen, die ihnen während des Genbefundgesprächs mündlich mitgeteilt wurden, daher nicht richtig aufnehmen konnten. Studien zu Frauen mit pathogenen Varianten in den Hochrisikogenen *BRCA1* und *BRCA2* legen nahe, dass Überwältigung und emotionale Überforderung sowohl mit dem reinen Angebot einer genetischen Beratung und Untersuchung bei neu an Brust- oder Eierstockkrebs erkrankten Frauen als auch mit der Mitteilung des positiven Testergebnisses bei noch nicht an Brustkrebs erkrankten Frauen verbunden sein können[69,70]. Samson et al. vermuten, dass die Bekanntgabe des positiven genetischen Testergebnisses für eine pathogene *BRCA1*- oder *BRCA2*-Variante von nicht an Brustkrebs erkrankten Frauen als ebenso bedrohlich empfunden werden kann wie die Diagnose einer Brustkrebserkrankung[71].

Zum anderen empfanden einige Studienteilnehmerinnen auch eine gewisse Erleichterung, dass keine pathogene Variante in einem der Hochrisikogene *BRCA1* oder *BRCA2* vorlag, sondern in einem moderaten bis hoch-moderaten Risikogen. Grund für diese Erleichterung war, dass diese Gene mit einem geringeren Erkrankungsrisiko einhergehen und – außer *PALB2* – nicht mit einem erhöhten Risiko für Eierstockkrebs assoziiert sind. Dies entspricht den Ergebnissen von Reyes et al., die 2021 die Unsicherheit von nicht an Krebs erkrankten Frauen mit einer pathogenen Variante in den Genen *ATM* und *CHEK2* untersuchten[29]. Waltz et al.[48] weisen jedoch darauf hin, dass die Verwendung von *BRCA1* und *BRCA2* als Referenz

oder Goldstandard bei der Kommunikation anderer Risikogene für familiären Brustkrebs die Patienten verwirren und die Unsicherheit vergrößern kann.

Schließlich thematisierten einige Frauen Gefühle in Bezug auf die Trägerschaft der pathogenen Variante und im Hinblick auf die Vererbung der pathogenen Variante an die Kinder: Schuldgefühle, die Last, das Gen vererbt zu haben, das schlechte Gewissen der Eltern und die Schuldzuweisung gegenüber Verwandten wurden von den Teilnehmerinnen beschrieben. Dies deckt sich mit Studien, die sich auf Frauen mit einer pathogenen *BRCA1*- oder *BRCA2*-Variante konzentrieren. In einer Studie von Lynch et al.[72] berichteten die Teilnehmenden über Schuldgefühle aufgrund der Weitergabe der pathogenen Variante an ihre Kinder und über die Sorge, dass ihre Kinder an Krebs erkranken könnten. Die Autor:innen identifizierten diese Sorgen als zwei der vier Hauptbelastungen von Trägerinnen pathogener Varianten. Auch in der vorliegenden Studie wurde von den Teilnehmerinnen die Sorge um das Erkrankungsrisiko der Kinder als eines der zentralen Probleme und Anliegen in Bezug auf die Genveränderung und/oder die Gesamtsituation genannt. Hallowell[73] und Grant et al.[53] verwenden den Begriff der „genetic responsibility“, also der genetischen Verantwortung, um diese besondere Situation und das Gefühl, für die Gesundheit anderer verantwortlich zu sein, zu beschreiben. Fisher et al.[74] konzentrierten sich auf die Perspektive der Nachkommen und beschrieben, wie die Tochter ihrer Mutter die Schuld dafür gab, dass sie ihr erhöhtes Risiko weitergegeben hatte.

4.2.2. Bewältigungsverhalten

Das Bewältigungsverhalten (=Coping) wurde nach dem transaktionalen Stressmodell von Lazarus und Folkmann[75] bewertet und in emotionsorientiertes Coping (= emotion-focused coping) und problemorientiertes Coping (=problem-focused coping) unterteilt. Zusätzlich wurden bei bereits an Brustkrebs erkrankten Teilnehmerinnen Strategien identifiziert, die dem sinnzentrierten Coping (=meaning-focused coping) zugeordnet werden können.

4.2.2.1 Emotion-focused coping

Alle Teilnehmerinnen dieser Studie verwendeten Bewältigungsstrategien, die nach der Definition von Lazarus und Folkman[75] als emotion-focused coping eingestuft werden können. Emotion-focused coping wird auch „intrapsychisches Coping“ genannt und bezieht sich auf Gedanken und Handlungen, die Menschen zur Regulierung oder Reduzierung von Stress und der durch den Stressor ausgelösten negativen Gefühle einsetzen[76]. Dazu gehört die Suche nach Unterstützung durch Familie und Freunde oder auch die Anwendung von Strategien der Selbstfürsorge und Achtsamkeit. Die vorliegenden Ergebnisse entsprechen der Annahme von Folkmann[76], dass emotion-focused coping eher in Situationen eingesetzt wird, die nicht zu ändern sind und akzeptiert werden müssen, wie beispielsweise chronische Krankheiten.

Verschiedene quantitative und qualitative Studien untersuchten das Bewältigungsverhalten von Frauen mit erhöhtem Risiko für familiären Brustkrebs und kamen zu vergleichbaren Ergebnissen. Pieterse et al.[77] fanden heraus, dass die Suche nach sozialer Unterstützung ein vorteilhafter Bewältigungsstil ist, da er mit einem geringeren Maß an psychischer Belastung verbunden ist. Dukes Holland und Holahan[78] stellten fest, dass ein hohes Maß an sozialer Unterstützung zu einem höheren Maß an emotionalem Wohlbefinden bei Brustkrebspatientinnen führte. In einer Studie von Ozdemir und Tas Arslan[79] sagte die soziale Unterstützung eine effektive Stressbewältigung bei Frauen mit Brustkrebs voraus.

4.2.2.2 Problem-focused coping

Neben dem emotion-focused coping definierten Lazarus und Folkman das problem-focused coping. Sie verstehen darunter Strategien, die Menschen anwenden, um das zu Stress und Belastung führende Problem an sich zu bewältigen oder zu lösen[75]. Die wichtigste Strategie, die diesem Coping zugeordnet werden kann und die von 75 % der Teilnehmerinnen der vorliegenden Studie genannt wurde, ist die Teilnahme am iFE. Sie erlebten das iFE überwiegend als hilfreich und positiv. Es gibt jedoch auch qualitative Studien, die darauf hinweisen, dass die Teilnahme an einem iFE bei jungen Frauen mit pathogenen *BRCA1-* oder *BRCA2*-Varianten zu Ängsten und Sorgen führen kann, die durch (falsch-positive) auffällige Befunde und dadurch erforderliche Nachuntersuchungen und Biopsien verursacht werden[80,81]. Dies entspricht den Schilderungen und Bedenken der einzigen kinderlosen und unter 30 Jahre alten Teilnehmerin der vorliegenden Studie, die sich mit der Frage konfrontiert sah, wann der richtige Zeitpunkt für eine Schwangerschaft sei und Interesse an einer RRBM äußerte und sich diesbezüglich mehr Informationen gewünscht hätte. Werner-Lin[81] und Hoskins und Greene[80] verwenden die Begriffe „surveillance fatigue“ und „screening fatigue“, um diese sehr spezielle Situation junger Frauen mit hohem Risiko für familiären Brustkrebs zu beschreiben, die regelmäßig an einem iFE teilnehmen und das ständige Screening als stressig, unangenehm und beängstigend erleben. In diesen Studien war die „surveillance fatigue“ einer der Gründe dafür, dass sich junge Frauen bereits in jungen Jahren für eine RRBM entschieden. Werner-Lin et al[81,82] stellten fest, dass die Dringlichkeit, einen Partner zu finden und Kinder zu bekommen einerseits und die Minimierung des Krebsrisikos durch risikoreduzierende Operationen andererseits eine Belastung für die Frauen darstellt. Nach Metcalfe et al.[83] nahm bei nicht an Brustkrebs erkrankten Frauen mit einer pathogenen *BRCA1-* oder *BRCA2*-Variante die empfundene Belastung sowohl nach einer RRBM als auch nach einer RRSO deutlich ab. Bislang gibt es keine allgemeine Empfehlung für eine RRBM für Frauen mit pathogener Varianten in moderaten bis hoch-moderaten Risikogenen. Die Ergebnisse lassen jedoch annehmen, dass vor allem junge Frauen mit einer pathogenen Variante in einem moderaten bis hoch-moderaten Risikogen dennoch einen Informationsbedarf in Bezug auf

risikoreduzierende Operationen und Familienplanung haben. Dies entspricht auch der Studienlage zu den Informationsbedürfnissen von Frauen mit pathogenen *BRCA1* oder *BRCA2*-Varianten[43-45,84].

Weitere Copingstrategien, die dem problem-focused coping zuzuordnen sind, sind die Meidung von Risikofaktoren und der Wandel des Lebensstils.

4.2.2.3 Meaning-focused coping

Bereits an Brustkrebs erkrankte Frauen wählten zusätzlich Bewältigungsmechanismen, die dem meaning-focused coping zugeordnet werden können. Darunter versteht man Gedanken, Handlungen und Strategien, die Menschen einsetzen, um ihr Wohlbefinden aufrechtzuerhalten und eine Situation auf positive Weise umzudeuten oder neu zu bewerten. Meaning-focused coping scheint eher in unveränderlichen Situationen, wie beispielsweise bei chronischen Krankheiten, zum Einsatz zu kommen und wird angewandt, wenn die initialen Bewältigungsversuche fehlschlagen[76]. Studien mit Krebspatient:innen ergaben, dass meaning-focused coping zu einer Wiederherstellung des Wohlbefindens führte und mit einer höheren Lebensqualität verbunden war[85,86]. Darüber hinaus fanden Vehling et al.[87] heraus, dass der Glaube an „a global sense of meaning" ein wichtiger Schutzfaktor für die Entwicklung von Stress bei Krebspatient:innen ist.

4.2.3. Unterstützungsbedürfnisse

Die Teilnehmerinnen der vorliegenden Studie hatten sehr unterschiedliche und heterogene Ansichten zu den Themen psychoonkologische Unterstützung und Selbsthilfe. Während einige an beidem interessiert waren und einen entsprechenden Bedarf äußerten, waren andere eher zurückhaltend und bevorzugten ihre Familie als primären Ansprechpartner. Derart unterschiedliche Bedürfnisse wurden auch in einer qualitativen Studie von Hughes und Phelps[88] über die Unterstützungsbedürfnisse von Frauen mit einer pathogenen *BRCA1*- oder *BRCA2*-Variante festgestellt. Die Autor:innen schlussfolgerten, dass verschiedene Menschen in den verschiedenen Phasen ihres Lebens und während ihrer gesamten „genetischen Reise" verschiedene Dinge wollen[88]. Sie schlugen ein Unterstützungsmodell vor, das aus mehreren Elementen besteht, wie z. B. Veranstaltungen, einer 24-Stunden-Telefonhotline, einem Chat-Forum und einer zentralen, von Fachleuten und Betroffenen gleichermaßen geleiteten Organisationsstelle. Farrely et al.[89] untersuchten die Einführung einer telefonischen „peer support intervention" für Frauen mit einer pathogenen *BRCA1*- oder *BRCA2*-Variante. Sie regten die Teilnehmerinnen an, zusätzlich zu den Anrufen auch Textnachrichten und/oder E-Mails zu verwenden, und schlussfolgerten, dass eine Intervention mit mehreren verschiedenen Medien am wirksamsten sein könnte. Segal et al.[90] untersuchten das Interesse von Frauen mit einer pathogenen *BRCA1*- oder *BRCA2*-Variante an Maßnahmen zur Unterstützung der

Kommunikation von genetischen Testergebnissen mit den Kindern und vermuteten daraufhin, dass eine einzige Art der Unterstützung möglicherweise nicht für alle Frauen gleichermaßen geeignet ist. Eine quantitative Studie über den Unterstützungsbedarf nicht erkrankter Frauen mit einer Brustkrebserkrankung in der Familie ergab, dass demografische Variablen das Interesse an der Teilnahme an einer Selbsthilfegruppe nicht vorhersagen konnten[52].

4.3. Frauen mit Brustkrebserfahrungen

In dieser Studie waren sowohl Frauen, die bereits selbst an Brustkrebs erkrankt waren, als auch Frauen mit einer Brustkrebserfahrung in der Familie eingeschlossen. Für die Teilnehmerinnen beider Subgruppen konnten Hinweise auf ganz spezielle Bedürfnisse, Ansichten und Herausforderungen gefunden werden.

4.3.1. Persönliche Brustkrebserfahrungen

Frauen, die bereits an Brustkrebs erkrankt waren, waren nicht nur mit den Informationen über ihre Erkrankung und Therapie konfrontiert, sondern auch mit den genetischen und medizinischen Informationen über die pathogene Variante. Die klare Unterscheidung zwischen Informationen über die pathogene Variante und Informationen über die Brustkrebserkrankung wurde von den Frauen als schwierig beschrieben. Metcalfe et al. [44] stellten in einer Studie mit an Brustkrebs erkrankten und nicht erkrankten Frauen mit einer pathogenen *BRCA1*- oder *BRCA2*-Variante fest, dass bereits erkrankte Frauen mehr Informationen über die Brustkrebsbehandlung benötigten. Ein weiterer Aspekt, der die Informationsaufnahme erschwert, ist, dass bereits erkrankte Frauen in der Regel eine operative und medikamentöse Tumortherapie erhalten haben und mit etwaigen Langzeit- und Spätfolgen konfrontiert sein können. „Cancer-related cognitive impairments“ (CRCI) – definiert als wahrgenommene oder objektive Beeinträchtigungen des Gedächtnisses, der Aufmerksamkeit, der Klarheit des Denkens, der Geschwindigkeit der Informationsverarbeitung und der Konzentration – sind häufig eine Folge der Chemotherapie, insbesondere bei Brustkrebpatientinnen[91,92].
Im Hinblick auf die Gefühle war auffällig, dass bereits erkrankte Frauen ruhiger und gelassener auf die Genbefundmitteilung reagierten als nicht erkrankte Frauen.

4.3.2. Brustkrebserfahrungen in der Familie

Neben der eigenen Brustkrebserkrankung kann auch eine Brustkrebserfahrung in der Familie – vor allem in der Kernfamilie – einen Einfluss auf Frauen mit moderat bis hoch-moderat erhöhtem Risiko für familiären Brustkrebs haben. Im Hinblick auf die mit dem Genbefundgespräch verbundenen Gefühle berichteten Frauen mit einer positiven Familienanamnese in der vorliegenden Studie von Trauer und Schmerz durch das Erinnern an Familienmitglieder, die an (Brust-) Krebs verstorben sind. Des Weiteren erwähnten einige Frauen die Bewältigungsmechanismen ihrer Mütter und wie sie den Umgang der Mutter mit

der Brustkrebserkrankung bewertet und empfunden haben. Die Einschätzung und Bewertung der Bewältigung der Mutter kann einen Einfluss auf den eigenen Bewältigungsstil und das eigene Verhalten der Frauen haben. Diese Ergebnisse der vorliegenden Studie sind im Einklang mit weiteren Studien, die darauf hindeuten, dass die Gefühle und Einstellung von Frauen mit erhöhtem Risiko für familiären Brustkrebs im Hinblick auf präventive Optionen durch Brustkrebserfahrungen in der Familie beeinflusst werden können[74,93-95]. Singh et al.[96] sind sogar der Meinung, dass die familiären Brustkrebserfahrungen einen starken Einfluss auf das von den Frauen wahrgenommene Krebsrisiko haben und in Hinblick auf präventive Entscheidungen für oder gegen risikoreduzierende Operationen als stärkerer Motivator fungieren als die tatsächlichen Risiken selbst.

4.4. Stärken, Limitationen und wissenschaftliche Implikationen

Eine Stärke dieser Studie ist der qualitative Ansatz, der es ermöglichte, ein breites Spektrum an Themen, Gefühlen, Erfahrungen und Lebensumständen zu erforschen. Dank des geschützten Rahmens der Einzelinterviews konnten die Teilnehmerinnen sehr private Gedanken und Erfahrungen mitteilen und die Interviewerin konnte spontan auf Aussagen und Gefühle reagieren und gegebenenfalls genauer nachfragen. Eine weitere Stärke ist die Heterogenität der Studienstichprobe: Die Teilnehmerinnen hatten pathogene Varianten in drei verschiedenen Risikogenen, repräsentierten sowohl bereits an Brustkrebs erkrankte als auch nicht erkrankte Frauen und einige hatten ihre Familienplanung abgeschlossen, während andere dies nicht getan hatten. Dies ermöglichte einen ersten detaillierten Einblick in ein breites Spektrum unterschiedlicher persönlicher Perspektiven, Lebenssituationen, Gefühle und Meinungen dieser speziellen Zielgruppe.

Die vorliegende Studie hat verschiedene Limitationen. Unter den Studienteilnehmerinnen war jeweils nur eine Frau ohne Kinder und eine Frau ohne eine Brustkrebsvorerkrankung und -erfahrung in der Familie. Weitere Studien sind wünschenswert, um tiefere und umfassendere Einblicke in die Bedürfnisse, Situation und Erfahrungen dieser Untergruppen zu gewinnen. Darüber hinaus sind quantitative Studien erforderlich, um die aufgezeigten Unterschiede zwischen den verschiedenen Untergruppen zu untersuchen und bestätigen. Dies gilt auch für potenzielle Unterschiede zwischen den mit den verschiedenen Risikogenen verbundenen Situationen und Erfahrungswelten. Eine weitere Limitation ist die Stichprobenverzerrung bzw. der Selection Bias: Da die Frauen gezielt angesprochen und ausgewählt wurden, waren die Teilnehmerinnen möglicherweise bereits sehr daran interessiert, ihre Erfahrungen mitzuteilen. Eine weitere mögliche Limitation ist die geringe Stichprobengröße mit nur zwölf Teilnehmerinnen und dadurch fragliche Generalisierbarkeit der Ergebnisse. Da die Datenerhebung jedoch auf dem Prinzip der theoretischen Sättigung von Glaser und Strauss basiert, ist davon auszugehen, dass die Datengrundlage generalisierte Aussagen für Frauen

mit pathogenen Varianten in moderaten bis hoch-moderaten Risikogenen, die in einem Zentrum des Deutschen Konsortiums Brust- und Eierstockkrebs betreut werden, erlaubt[97]. Nachfolgende Studien, die dies an einer größeren Stichprobe quantitativ untersuchen, wären dennoch wünschenswert. Die Generalisierbarkeit und Gültigkeit der Empfehlungen für die Beratung in anderen (universitären) Zentren, Beratungsstellen und Settings mit anderen Beratungsstandards sollte ebenfalls anhand von größeren, quantitativen Studien überprüft werden. Die hier erhobenen Daten könnten die Grundlage bilden für die Entwicklung entsprechender Erhebungsinstrumente, die in der quantitativen Forschung bei der Überprüfung der Ergebnisse an größeren Studienpopulationen eingesetzt werden könnten.

4.5. Schlussfolgerung und praktische Implikationen

Die genetische Beratung von Frauen mit pathogenen Varianten in moderaten bis hoch-moderaten Risikogenen für familiären Brustkrebs in Bezug auf mit der Variante assoziierte Erkrankungsrisiken und verfügbare präventive Handlungsoptionen gewinnt zunehmend an Bedeutung für die klinische Versorgung. Beratende stehen derzeit vor der kommunikativen Herausforderung, über weniger sicher belegte Risiken und weniger evidenzbasierte präventive Handlungsoptionen zu informieren, als es bei Trägerinnen der schon länger bekannten pathogenen *BRCA1*- und *BRCA2*-Varianten möglich ist. Aus den hier gewonnenen Erkenntnissen können verschiedene Empfehlungen für eine stärkere Patientenorientierung in der Kommunikation mit betroffenen Frauen und das persönliche ärztliche Genbefundgespräch abgeleitet werden.

Gleichzeitig lassen sich die Ergebnisse als eine erste Grundlage nutzen, um für betroffene Frauen schriftliche, strukturierte, evidenzbasierte und laiengerechte Informationen in deutscher Sprache zu entwickeln. Evidenzbasierte Gesundheitsinformationen sind die Voraussetzung für Partizipation und informierte Entscheidungen und können Entscheidungen nachweislich verbessern[2]. Gemäß der aktuellen Leitlinie evidenzbasierte Gesundheitsinformation[98] ist die Identifikation der Informationsbedürfnisse der Zielgruppe ein essentieller und wichtiger Schritt für die Erstellung evidenzbasierter Informationsmaterialien.

4.5.1. Relevanz für die klinische Versorgung und Patientenorientierung

Die gewonnenen Einblicke in die persönlichen Sichtweisen von Frauen mit einer pathogenen Variante in einem moderaten bis hoch-moderaten Risikogen für familiären Brustkrebs können helfen, die Beratungssituation weiter zu verbessern und das persönliche ärztliche Genbefundgespräch bedürfnis- und patientenorientierter zu gestalten. So konnten medizinische Informationslücken und Missverständnisse aufgezeigt werden, insbesondere hinsichtlich der mit der pathogenen Variante verbundenen Erkrankungs- und Vererbungswahrscheinlichkeiten. Diesen Missverständnissen könnte während des

Genbefundgesprächs mit laiengerecht vermittelten Informationen darüber, dass die Vererbung nicht beeinflusst werden kann und das Vorliegen einer pathogenen Variante nicht mit anderen Merkmalen des Elternteils korreliert, begegnet werden. Darüber hinaus wäre es hilfreich, während des Genbefundgesprächs zu erklären, dass die mit den moderaten bis hoch-moderaten Risikogenen assoziierten und im Gespräch kommunizierten Erkrankungsrisiken den Stand der aktuellen Forschung wiedergeben, jedoch in laufenden Studien stetig weiter erforscht werden und sich daher in Zukunft ändern können. Zusätzlich identifizierte Informationsbedürfnisse betrafen unter anderem die Themen Stress, Lebensstiländerungen, vermeidbare Risikofaktoren, risikoreduzierende Operationen und Familienplanung. Diesen sollte, ebenso wie den Bedenken, Fragen, Erfahrungen und Ängsten in Bezug auf die Familienplanung und den eigenen Überlegungen, Wünschen oder Fragen in Bezug auf risikoreduzierende Operationen während des Genbefundgesprächs ausreichend Raum gegeben werden.

Genetische Berater:innen und behandelnde Ärzt:innen sollten außerdem für mögliche Herausforderungen und Unterschiede durch die individuellen Brustkrebserfahrungen der betroffenen Frauen sensibilisiert werden. Zum einen sollten die Folgen der Tumortherapie für die Konzentration und Aufnahmefähigkeit (Cancer-related cognitive impairments) der Frauen bei der Kommunikation komplexer Themen während oder kurz nach der Krebsbehandlung berücksichtigt werden. Zum anderen ist zu bedenken, dass Brustkrebserfahrungen in der Familie einen Einfluss auf das Bewältigungsverhalten der Frauen und auch auf die persönlichen präventiven Entscheidungen haben können.

Die mit der Genbefundmitteilung und der pathogenen Variante verbundenen Gefühle können sehr komplex und vielfältig sein. Genetische Berater:innen und Ärzt:innen sollten darauf vorbereitet sein, aufkommende Gefühle und Überzeugungen während des Genbefundgesprächs und/oder der Folgetermine zu erkennen und bei Bedarf adäquat darauf reagieren und eingehen zu können. Die Verwendung von *BRCA1* und *BRCA2* als Referenz oder Goldstandard bei der Kommunikation moderater bis hoch-moderater Risikogene für familiären Brustkrebs kann bei den betroffenen Frauen einerseits ein Gefühl der Erleichterung auslösen, andererseits jedoch auch zu Verwirrung führen und die Unsicherheit vergrößern. Dies sollte bei der Beratung bedacht und sensibel behandelt werden. Zusätzlich kann aufgrund der Gefühle der Überwältigung und Überforderung, die durch die Genbefundmitteilung ausgelöst werden können, die Aufnahmefähigkeit für medizinische/genetische Informationen während des Genbefundgesprächs eingeschränkt oder nicht vorhanden sein.

Schriftliches Informationsmaterial speziell für Frauen mit pathogenen Varianten in moderaten bis hoch-moderaten Risikogenen für familiären Brustkrebs könnte die ärztliche Beratungssituation zusätzlich unterstützen und das Verständnis der Frauen fördern.

Schriftliche, strukturierte, evidenzbasierte, laiengerechte Informationen könnten außerdem im Anschluss an das Genbefundgespräch offen gebliebene Informationslücken schließen, das Verständnis für Zusammenhänge unterstützen und somit Missverständnisse mindern. Dies könnte eine realistische Risikoeinschätzung und -bewertung fördern, Schuldgefühlen oder -zuweisungen entgegenwirken und der Entwicklung eigener Überzeugungen aufgrund von Fehlinterpretationen vorbeugen. Die zusätzlichen Informationsbedürfnisse, die identifiziert wurden, könnten ebenfalls in einer schriftlichen Information adressiert werden.

Zu den Themen psychoonkologische Unterstützung und Selbsthilfe hatten die Teilnehmerinnen der vorliegenden Studie eine sehr heterogene Haltung. Für einen Teil der Frauen stellt ein psychoonkologisches Angebot eine wichtige Unterstützung dar, so dass die bereits etablierten Angebote im Bereich Psychoonkologie und Selbsthilfe Frauen mit pathogenen Varianten in moderaten bis hoch-moderaten Risikogenen sowohl beim Genbefundgespräch als auch bei den Nachsorgeterminen weiterhin vorgestellt und angeboten werden sollten.

Zusammenfassend können die Erkenntnisse der vorliegenden Studie die Patientenorientierung in der Beratung und Betreuung von Frauen mit pathogenen Varianten in moderaten bis hoch-moderaten Risikogenen für familiären Brustkrebs weiter fördern und optimieren. Für betroffene Frauen sind eine patientenorientiertere Beratung und ein bedürfnisorientierteres Informationsangebot wichtige Schritte auf dem Weg zu mehr Gesundheits- und Entscheidungskompetenz. Die Implementierung der sich kontinuierlich ändernden wissenschaftlichen Datenlage in den Versorgungskontext und die laiengerechte Kommunikation dieser Änderungen und sich stetig wandelnden Risikoeinschätzungen mit den betroffenen Frauen bleibt eine Herausforderung für die genetische Beratung.

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6. Anhang

6.1. Abbildungsverzeichnis

6.2. Tabellenverzeichnis