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Review

Risk factors for metachronous contralateral breast cancer: A systematic review and meta-analysis

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ABSTRACT

Background: The risk of developing metachronous contralateral breast cancer (CBC) is a recurrent topic at the outpatient clinic. We aimed to provide CBC risk estimates of published patient, pathological, and primary breast cancer (PBC) treatment-related factors.

Methods: PubMed was searched for publications on factors associated with CBC risk. Meta-analyses were performed with grouping of studies by mutation status (i.e., *BRCA1*, *BRCA2*, *CHEK2* c.1100delC), familial cohorts, and general population-based cohorts.

Results: Sixty-eight papers satisfied our inclusion criteria. Strong associations with CBC were found for carrying a *BRCA1* (RR = 3.7; 95%CI:2.8–4.9), *BRCA2* (RR = 2.8; 95%CI:1.8–4.3) or *CHEK2* c.1100delC (RR = 2.7; 95%CI:2.0–3.7) mutation. In population-based cohorts, PBC family history (RR = 1.8; 95%CI:1.2–2.6), body mass index (BMI) ≥30 kg/m^2 (RR = 1.5; 95%CI:1.3–1.9), lobular PBC (RR = 1.4; 95%CI:1.1–1.8), estrogen receptor-negative PBC (RR = 1.5; 95%CI:1.0–2.3) and treatment with radiotherapy <40 years (RR = 1.4; 95%CI:1.1–1.7) was associated with increased CBC risk. Older age at PBC diagnosis (RR per decade = 0.93; 95%CI:0.88–0.98), and treatment with chemotherapy (RR = 0.7; 95%CI:0.6–0.8) or endocrine therapy (RR = 0.6; 95%CI:0.5–0.7) were associated with decreased CBC risk.

Conclusions: Mutation status, family history, and PBC treatment are key factors for CBC risk. Age at PBC diagnosis, BMI, lobular histology and hormone receptor status have weaker associations and should be considered in combination with key factors to accurately predict CBC risk.

Contents

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1. Introduction

Due to an increasing incidence of primary breast cancer (PBC) and improved breast cancer (BC) surveillance and treatment methods, an increasing number of women who have survived BC are at risk of developing a contralateral breast cancer (CBC) [1]. The annual CBC risk is around 0.5% in the general BC population and up to 3% in *BRCA1/2* mutation carriers [2,3].

A risk-reducing contralateral mastectomy minimizes the risk of developing a subsequent CBC and may improve survival in patients considered to be at high risk, i.e. hereditary BC patients [4–6]. On the other hand, the percentage of patients opting for a risk-reducing contralateral mastectomy has rapidly increased over the last decades, suggesting that more relatively low-risk BC patients are also treated [7–9]. Fear and overestimation of risk may play a role in the decision-making of these low-risk patients [10,11].

For both high-risk and low-risk PBC patients, accurate CBC risk prediction is crucial and can be achieved by taking into account the effect of patient, pathological, and treatment-related characteristics. However, CBC risk prediction as used in clinical practice is currently only based on *BRCA1/2* mutation status, family history of BC and age at PBC [2,12,13]. The association of other factors with CBC risk is either lacking or conflicting. Combinations of these factors may improve decision-making regarding surveillance, primary and risk-reducing therapies, and may enable patient-tailored counselling in both high-risk and low-risk patients.

Therefore, we aimed to quantify the association of various patient, pathological, and treatment-related characteristics with metachronous CBC risk.

2. Methods

For this systematic review we published an online protocol at Prospero including details on study design (registration number: CRD42015014381, link: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015014381) and we followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

2.1. Search strategy

In collaboration with a research librarian (EdC, see acknowledgements) a search strategy was developed. One reviewer searched PubMed for publications on search terms for metachronous CBC in combination with various predefined patient characteristics (carriership of *BRCA1, BRCA2* and *CHEK2* c.1100delC mutations, family history of (bilateral) BC, mammographic density, factors at PBC diagnosis: age, BMI, menopausal status), PBC characteristics (TN(M)-stage, tumor grade, Estrogen (ER), Progesterone (PR) and HER2 neu receptor status, histological subtype), and PBC treatment-related characteristics (radiotherapy, chemotherapy, endocrine therapy, targeted therapy, risk-reducing salpingo-oophorectomy (RRSO)). We also searched for publications on second BC risk, in the knowledge that a majority (95%) of the second breast cancers are contralateral events rather than ipsilateral breast tumors [14]. Details of the full strategy applied are provided in Supplementary Table A.1.

Abstracts were screened using the following inclusion criteria: experimental and observational studies published in English, between January 1990 and July 4, 2016, investigating CBC risk in women who have no prior history of other invasive malignancies. We included papers only from 1990 onwards to have a long-term follow-up while also being able to investigate the effects of adjuvant treatment options (which were considered mainly from the late eighties onwards). Further, we excluded papers if the reported number of second BC events was less than twenty (arbitrary cut-off), and also if no relative risk (RR) estimates (hazard ratio or odds ratio or relative risk) for CBC risk were provided.

Relevant full-text publications were considered for inclusion and critically appraised, on methodology, and comparability of groups, subgroups and their reference groups. If papers reported on specific subgroups that were non-combinable with other subgroups, these papers were excluded for the meta-analysis. In addition, potential overlap in (part of) patients due to selection from the same registries/hospitals in the same period was solved by selecting the most relevant cohort (i.e. the factor of interest for the meta-analysis was specifically published on) and/or selecting the most recent cohort with the longest follow-up. From the included papers, study design characteristics and all the available univariable and multivariable risk estimates were extracted and entered in a Microsoft Access database by four reviewers (DA, MKS, AJvdB, MJH) using a specifically designed data entry form.

2.2. Statistical analyses

We investigated the effects of carrying vs. not carrying a *BRCA1*, *BRCA2* or *CHEK2* c.1100delC mutation on the risk of developing CBC. We also investigated the effects of the aforementioned patient, pathological, and treatment characteristics separately in five different groups: 1. *BRCA1* mutation carriers; 2. *BRCA2* mutation carriers; 3. *CHEK2* c.1100delC mutation carriers; 4. Familial BC patients, i.e. patients who tested negative for a *BRCA1/2* or *CHEK2* c.1100delC mutation; 5. Population-based cohorts, i.e. patients from hospitals or official registries representing the general population, that have not been selected on gene mutation carriership or a positive family history for BC.

Papers with only combined results for *BRCA1* and *BRCA2* mutation carriers were excluded from the analyses, as these two groups represent different entities with different characteristics and should be analyzed separately (*BRCA1* mutation carriers are younger at PBC diagnosis and present more often with a triple negative BC phenotype (ER, PR and HER2 receptor negative) than *BRCA2* mutation carriers) [2,15,16]. For the analyses on carriership of a genetic *BRCA1*, *BRCA2* or *CHEK2* c.1100delC mutation, we included studies where the reference group consisted of familial patients (i.e. patients from non-*BRCA1/2*, and/or *CHEK2*-negative BC families) and excluded papers that used a sporadic population as a reference group. After all, studies that compare mutation carriers

recruited from Clinical Genetic departments with BC patients from the general population easily lead to overestimations [17]. Since this is no issue in population-based studies with genetic test results generally available, these studies were included as well.

Since various ranges for age were used in the different papers, we estimated the overall effect of age using the method described by Greenland et al. [18], typically defined in the context of dose-response studies. The requirements needed for this method are the risk estimates from every age category, the corresponding confidence levels or the standard errors, and the number of cases and controls or person-time in case of incidence rate data. If these were not given, the continuous age effect was estimated by linearly regressing the category-specific log relative risks on an age value representative for each age category. Representative values were the median age at PBC diagnosis calculated from female BC patients in the Netherlands Cancer Registry [19], with a 10-year CBC risk of 4% which is comparable with published results from studies from various western countries [20–22].

All types of relative risk estimates were log transformed and subsequently pooled for every factor of interest. The available univariable and multivariable estimates were analyzed separately (and reported as crude and adjusted analyses, respectively). If only subgroup estimates were available in a paper, we combined these estimates to generate an overall estimate. A random effects model was used to perform the meta-analyses [23]. We tested for heterogeneity using I^2 statistics and the *p*-value for heterogeneity using the Cochran's Q-statistic was reported.

To conduct the meta-analyses, we used Metan from the Stata

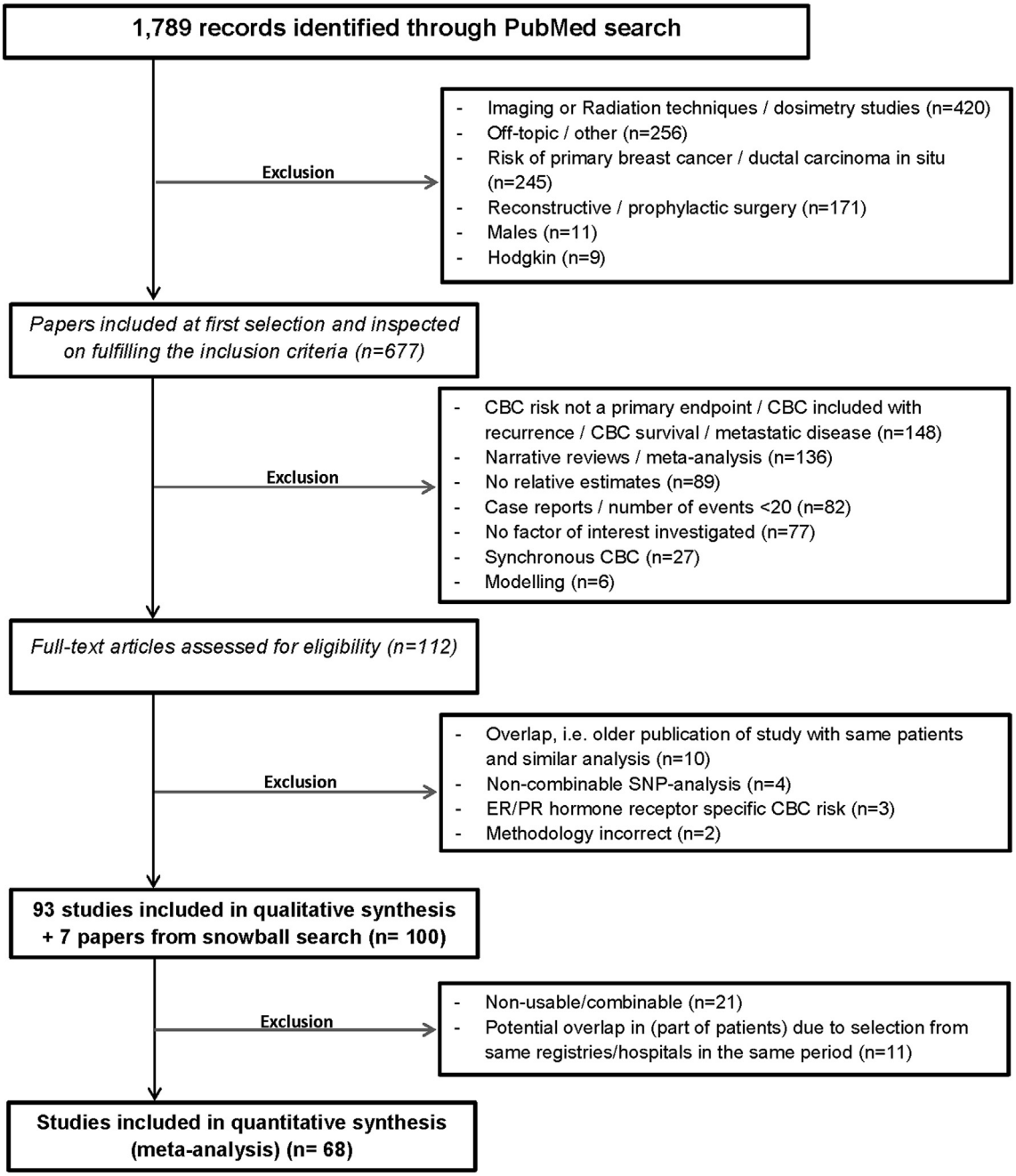

Fig. 1. PRISMA flow chart of papers on risk factors for contralateral breast cancer. Abbreviations CBC = Contralateral breast cancer; SNP= Single Nucleotide Polymorphism.

Table 1
Study characteristics of papers publishing on risk factors for contralateral breast cancer included in the systematic review.

First author, Year	Country/Continent[a]	Study Design[a]	Population	Factors[a]	Mean follow-up total group (years)[a,b]	Mean age total group (years)[a]	*N* Patients included	*N* CBCs[c]
van den Broek, 2016 [2]	Netherlands	Cohort	(non-) BRCA1/2	FamHis, Age, Ctx, DNA,	Md. 12.5	N/A	6294	578
Goss, 2016 [25],[e]	USA, Europe, Canada	RCT	Unselected	Etx	Md. 6.3	Md. 65.1	1918	43
Aalders, 2016 [26]	Netherlands	Cohort	Unselected	Age, TNM, Grade, ER,PR,HER2, His	5.0	59.0	52 626	1534
Sisti, 2015 [27]	USA, Denmark, Canada	(Nested) Case-Control	Unselected	Meno	Md Cases 6.3 Controls: 5.5 (matched)	46.0 (matched)	3733	1521
Menes, 2015 [16],[e]	USA, Australia, Canada	Cohort	BRCA1/2	Ctx, Etx, Rtx, RRSO	8.9	41.0	800	86
Kiderlen, 2015 [28]	Netherlands	Cohort	Unselected	Age	Md. 7.2	Md. 74.9	2926	75
Drooger, 2015 [29],[e]	Netherlands	Cohort	BRCA1/2	Age, Ctx, Etx, Rtx, RRSO, DNA	Md. 8.6	N/A	691	161
Basu, 2015 [30],[e]	United Kingdom	Cohort	BRCA1/2	Age, Meno, RRSO, DNA	Md. 7.8	NA	1011	202
Rasmussen, 2014 [20]	Denmark	Cohort	Unselected	Age	Md. 5.6	N/A	85 863	3120
Mellemkjaer, 2014 [31]	Denmark	Cohort	Unselected	Etx	N/A	N/A	37 533	124
Kriege, 2014 [32]	Netherlands	Cohort	(non-) CHEK2	DNA	Md. CHEK2: 6.8 Non-carriers: 7.2	N/A	3502	197
Gronwald, 2014 [33]	USA, Europe, Canada	(Nested) Case-Control	BRCA1/2	Etx	7.2	50.9 (matched)	1504	411
Calip, 2014 [34]	USA	Cohort	Unselected	BMI	Md. 6.3	Md. 63.0	4216	145 (ipsilateral: n.a.)
van de Water, 2013 [35]	USA, Japan, Europe	RCT	Unselected	Age	Md. 5.1	Md. 64.0	9766	83
Valuckas, 2013 [36]	Lithunia	Cohort	Unselected	Age, Meno, BMI, TNM, Ctx, Etx, Rtx,	Md HRtx 10.1 CRT 10.4	Md. 53.4	832	48 (ipsilateral: n.a.)
Sandberg, 2013 [37]	Sweden	(Nested) Case-Control	Unselected	BD	Cases: 8.25 Controls: 8.25 (matched)	(matched)	422	211
Reiner, 2013 [12]	USA, Denmark	(Nested) Case-Control	Non-BRCA1/2	FamHis	(matched)	(matched)	1713	594
Phillips, 2013 [15]	USA, Australia, New Zealand, Europe, Canada	Cohort	BRCA1/2	Etx	Md. 6.6	N/A	2464	520
Pacelli, 2013 [38],[e]	Italy	Cohort	Unselected	ER/PR/HER2	Md. 4.9	Md. 53.0	468	24
Metzger-Filho, 2013 [39],[e]	Australia, New Zealand, Europe, India, South-America, Africa	RCT	Unselected	ER/PR/HER2	Md. 12.5	53.9	1951	75
Mavaddat, 2013 [40]	United Kingdom	Cohort	BRCA1/2	RRSO	Md. 2.6	Md. 39.5	988	61
Maskarinec, 2013 [41],[f]	USA	Cohort	Unselected	BD	12.9	63.3	607	71
Dellapasqua, 2013 [42]	Italy	Cohort	Unselected	Age, TNM, ER/PR/HER2	Md. 6.3	Md. 52.0	6971	129
Courdi, 2013 [43]	France	Cohort	Unselected	Rtx	Md. 12.8	N/A	1630	116
Bernstein, 2013 [44]	USA, Denmark	(Nested) Case-Control	BRCA1/2	Rtx, DNA	(matched)	(matched)	1802	603
Weischer, 2012 [45]	USA, Australia, Europe, Canada	Cohort	CHEK2	DNA	Md. 6.6	N/A	25 094	647 (ipsilateral: n.a.)
Vichapat, 2012 [46]	Sweden	Cohort	Unselected	Age, TNM, His, Etx	Md. 6.7	N/A	37 393	894
Saltzman, 2012 [47],[f]	USA	(Nested) Case-Control	Unselected	ER, PR, HER2	(matched)	(matched)	1988	482
Neta, 2012 [48],[f]	USA	Cohort	Unselected	Rtx	10.0	N/A	205 316	6924
Mavaddat, 2012 [49]	USA, Australia, Europe	Cohort	BRCA1/2	ER	N/A	N/A	6893	1022
Filleron, 2012 [50]	France	RCT	Unselected	Age, TNM, Grade	Md. 4.4	Md. 49.0	2820	58
Brooks, 2012 [51]	USA, Denmark	(Nested) Case-Control	Unselected	BMI	Md. 4.2	Md. 45.0 (matched)	1510	511
Zhang, 2011 [22]	Italy	Cohort	Unselected	Rtx	8.0	54.7	5248	261
Vichapat, 2011 [52]	United Kingdom	Cohort	Unselected	FamHis, Age, Meno, TNM, Grade, ER, PR, HER2, His, Ctx, Etx, Rtx	N/A	N/A	4366	315
Metcalfe, 2011 [53]	USA, Canada	Cohort	BRCA1/2	FamHis, Age, TNM, Grade, ER, Ctx, Etx, Rtx, RRSO, DNA	11.1	Md. 42.0	846	149
Majed, 2011 [54]	France	Cohort	Unselected	FamHis, Age, Meno, BMI, TNM, Grade, ER, PR, His, Ctx, Etx, Rtx	Md. 10.0	54.0	15 166	1370
Hackshaw, 2011 [55],[e]	Europe, Asia	RCT	Unselected	Etx	Md. 10.1	Md. 62.0	3449	118
Bouchardy, 2011 [56],[f]	Switzerland	Cohort	Unselected	FamHis, Age, ER, Etx	Md. 5.2	59.8	4152	63
Rubino, 2010 [57],[e]	France	Cohort	Unselected	Age, TNM	Md. 10.6	56.0	6629	673
Rondeau, 2010 [58]	France	Cohort	Unselected	TNM, Grade, Ctx	Md. 12.7	Md. 57.0	919	69

Table 1 (*continued*)

First author, Year	Country/Continent[a]	Study Design[a]	Population	Factors[a]	Mean follow-up total group (years)[a,b]	Mean age total group (years)[a]	*N* Patients included	*N* CBCs[c]
Reding, 2010 [59]	USA, Denmark	(Nested) Case-Control	(non-) BRCA1/2	Ctx, Etx	(matched)	(matched)	1579	181
Poynter, 2010 [60],[e]	USA, Denmark	(Nested) Case-Control	(non-) BRCA1/2	Meno	(matched)	(matched)	2103	181
Malone, 2010 [3]	USA, Denmark	(Nested) Case-Control	BRCA1/2	DNA	(matched)	Md. 46.0 (matched)	2103	705
Cuzick, 2010 [61],[e]	Unknown	RCT	Unselected	Etx	Md. 10.0	Md. 72.0	6241	178
Buist, 2010 [62]	USA	Cohort	Unselected	FamHis, Age, BD, TNM, Ctx, Etx,	N/A	N/A	17 286	344 (ipsilateral: 54)
Berrington de Gonzalez, 2010 [63]	USA	Cohort	Unselected	Rtx	13.0	N/A	182 057	6491
Li, 2009 [64] **A**	USA	(Nested) Case-Control	Unselected	Etx	(matched)	(matched)	1094	367
Li, 2009 [65],[d] **B**	USA	(Nested) Case-Control	Unselected	BMI	(matched)	(matched)	1091	365
Graeser, 2009 [13],[e]	Germany	Cohort	BRCA1	DNA	N/A	N/A	2020	381
Bertelsen, 2009 [66]	Denmark	Cohort	Unselected	Age	8.4	N/A	8737	466
Alkner, 2009 [67]	Sweden	RCT	Unselected	Age, Etx	Md. 14.0	N/A	564	52
Stovall, 2008 [68],[d]	USA, Denmark	(Nested) Case-Control	Unselected	Rtx	Cases: 5.0 Controls: 5.0 (matched)	51.0 (matched)	1806	606
Schaapveld, 2008 [69]	Netherlands	Cohort	Unselected	Age, TNM, Ctx, Etx, Rtx	Md. 5.8	N/A	45 229	1477
Mellemkjaer, 2008 [70]	USA, Denmark	(Nested) Case-Control	(non-) CHEK2	Ctx, Rtx, DNA	5.0	(matched)	2103	708
Hooning, 2008 [71]	Netherlands	Cohort	Unselected	FamHis, Age, Ctx, Rtx	Md. 13.8	N/A	7221	503
Bertelsen, 2008 [72]	USA, Denmark	(Nested) Case-Control	Unselected	Ctx, Etx	(matched)	Md. 46.0 (matched)	1792	634
van der Leest, 2007 [73],[e]	Netherlands	Cohort	Unselected	Ctx, Etx	Md. 8.5	Md. 37.5	758	59
Trentham-Dietz, 2007 [74],[f]	USA	Cohort	Unselected	FamHis, Meno, BMI	7.1	59.4	10 953	488 (ipsilateral: n.a.)
Schmidt, 2007 [75],[d,f]	Netherlands	Cohort	CHEK2	DNA	Md. 10.1	43.0	1479	124 (ipsilateral: 13)
Rutqvist, 2007 [76]	Sweden	RCT	Unselected	Etx	Md. 18.0	N/A	2738	170
Largent, 2007 [77],[e]	USA, Denmark	(Nested) Case-Control	Unselected	Meno (at CBC diagnosis)	Cases: 5.0 Controls: 5.0 (matched)	45.0 (matched)	2107	708
Kirova, 2007 [78]	France	Cohort	Unselected	Rtx	Md. 10.5	Md. 55.0	16 705	1343
Hemminki, 2007 [79]	Sweden	Cohort	Unselected	FamHis	N/A	N/A	102 176	5495
Broeks, 2007 [80]	Netherlands	Case-Only	BRCA1/2, CHEK2	Rtx	N/A	N/A	247	247
Brekelmans, 2007 [81],[e,f]	Netherlands	Cohort	(non-) BRCA1/2	DNA	Md BRCA1/2: 4.3 NonBRCA: 4.8 Sporadic: 5.1	N/A	498	53
Tilanus-Linthorst, 2006 [82],[e]	Netherlands	Cohort	Non-BRCA1/2	FamHis	Md 6.1	(matched)	654	51
Pierce, 2006 [83],[e]	USA, Israel	Cohort	BRCA1/2, Unselected	Age, TNM, Ctx, Etx, DNA	Md BRCA1/2: 7.9 Unselected: 6.7	(matched)	605	48
Levi, 2006 [84]	Switzerland	Cohort	Unselected	Rtx	7.8	N/A	6119	222
Gronwald, 2006 [85],[d]	USA, Israel, Europe, Canada	(Nested) Case-Control	BRCA1/2	Etx	Etx: 5.7 No Etx: 7.4	N/A	1007	356
Dignam, 2006 [86]	USA	Cohort	Unselected	BMI	N/A	N/A	4077	242
Brekelmans, 2006 [87],[e,f]	Netherlands	Cohort	BRCA1	DNA	Md. 5.1	Md. 39.0 (matched)	669	75
Nordenskjold, 2005 [88],[e]	Sweden	RCT	Unselected	Etx	Md. 10.6	N/A	4610	138
Roychoudhuri, 2004 [89]	United Kingdom	Cohort	Unselected	Rtx	N/A	N/A	64 782	308
McCaskill-Stevens, 2004 [90],[d]	USA, Australia, South-America, Ireland	RCT	Unselected	Etx	N/A	Md. 50!	10 619	494
Coombes, 2004 [91],[e]	USA, Australia, Europe	RCT	Unselected	Etx	Md. 2.6	64.3	4742	29
Li, 2003 [92],[f]	USA	Cohort	Unselected		9.0	37.7	1285	77

(*continued on next page*)

Table 1 (*continued*)

First author, Year	Country/Continent[a]	Study Design[a]	Population	Factors[a]	Mean follow-up total group (years)[a,b]	Mean age total group (years)[a]	*N* Patients included	*N* CBCs[c]
				FamHis, Age, BMI, TNM, ER, PR, His				
Gao, 2003 [21],[d]	USA	Cohort	Unselected	Age, Rtx, His	Rtx: 5.7 No Rtx: 6.8	61.0	134 501	5679
Dignam, 2003 [93]	USA, Unknown	RCT	Unselected	BMI	Md. 13.8	N/A	3385	193
Fisher, 2002 [94]	USA, Canada	RCT	Unselected	Etx	Md. 7.2	N/A	1000	27
Li, 2001 [95],[d]	USA	Cohort	Unselected	Etx	Etx: 3.9 No Etx: 4.2	N/A	8981	189
Fisher, 2001 [96]	USA, Unknown	RCT	Unselected	Etx	Md. 6.8	56.0	1172	37
Vaittinen, 2000 [97]	Sweden	Cohort	Unselected	FamHis, Age	6.2	N/A	72 092	2529
Narod, 2000 [98],[d]	USA, Europe, Canada	(Nested) Case-Control	BRCA1/2	Ctx, Etx, Rtx, RRSO	9.7	40.2 (matched)	593	209
Matsuyama, 2000 [99]	Japan	Cohort	Unselected	Etx	Md Etx: 7.6 No Etx: 8.1	51.0	6148	30
Robson, 1999 [100],[e]	USA	Cohort	BRCA1/2	DNA	Md. 10.3	N/A	305	42
Newcomb, 1999 [101]	USA	Cohort	Unselected	Etx	6.4	N/A	54 821	1730
Kollias, 1999 [102]	United Kingdom	Cohort	Unselected	FamHis, Age, His	Md. 9.0	Md. 54.0	3211	83
Broet, 1999 [103]	France	Cohort	Unselected	Ctx	7.9	56.0	6185	334
Early Breast Cancer Trialists' Collaborative, 1998 [104],[d]	USA, New Zealand, Europe, South-America, Africa, Asia	RCT	Unselected	Etx	2.7	N/A	32 422	839
Swedish Breast Cancer Cooperative Group, 1996 [105],[e]	Sweden	RCT	Unselected	Etx	Md. 5.5	N/A	3545	51
Cook, 1996 [106]	USA	(Nested) Case-Control	Unselected	FamHis, Meno, BMI, ER, PR, His, Ctx, Rtx,	(matched)	N/A	640	216
Cook, 1995 [107],[d]	USA	(Nested) Case-Control	Unselected	Etx	Md. 3.3 (matched)	(matched)	673	234
Broet, 1995 [108]	Europe	Cohort	Unselected	His, Ctx	Md. 6.7	55.5	4748	282
Healey, 1993 [109]	USA	Cohort	Unselected	Age, TNM, Ctx, Etx	Md. 7.9	53.0	1624	77
Storm, 1992 [110],[f]	Denmark	(Nested) Case-Control	Unselected	FamHis, Meno, BMI, Rtx	(matched)	51.0 (matched)	56 540	529
Boice, 1992 [111],[f]	USA	(Nested) Case-Control	Unselected	Rtx	(matched)	51.7 (matched)	1844	655
Bernstein, 1992 [112],[f] **A**	USA	Cohort	Unselected	Age, Meno, BMI, His, Ctx, Rtx,	4.3	44.3	4550	136
Bernstein, 1992 [113] **B**	USA	Cohort	Unselected	FamHis	N/A	N/A	4660	136
Baum, 1992 [114]	United Kingdom	RCT	Unselected	Etx	Md. 7.8	55.1	1912	21
Andersson, 1991 [115],[d]	Denmark	RCT	Unselected	TNM, Etx	Md. 7.9	N/A	3538	143

[a] Abbreviations: Age = age at PBC diagnosis, BD = breast density, BMI = body mass index, Ctx = chemotherapy, DNA = *BRCA1*/*BRCA2*/*CHEK2* c.1100delC DNA mutation, ER = Estrogen hormone receptor status, Etx = endocrine therapy, FamHis = family history, Grade = tumor grade, HER2 = HER2 receptor status, His = histology, Md = median, Meno = menopausal status, N/A = not available, PR= Progesterone hormone receptor status, RCT = Randomized controlled trial RRSO = risk-reducing salpingo-oophorectomy, Rtx = radiotherapy, TNM = TNM-stage, USA=United States of America.

[b] Md. median if no mean was given; (matched): patients were matched on follow-up; if no mean/median follow-up for the total group was given, the mean/median follow-up for the exposed versus the reference group was given.

[c] If the number of CBC events was not provided, this was calculated from the figure in the paper; (ipsilateral): ipsilateral second breast cancers were included in the analyses.

[d] Studies not used for the analyses due to overlap in patients.

[e] Studies not used for the analyses due to reporting on subgroups that could not be combined with another estimate for the meta-analyses.

[f] Studies that included patients with metastatic disease at primary breast cancer diagnosis as well.

Statistical Software package (version 14.0). To assess the effects of age at PBC diagnosis, the dosresmeta package from R software (version 3.2.2) was used.

2.3. Quality assessment

We used the QUality In Prognostic Studies (QUIPS) tool for assessing the quality and bias in the included papers [24]. As suggested by the developers of this tool, we modified the domains to be applicable to the specific study questions in our systematic review (Supplementary Table A.2). We excluded one domain, which assessed outcome measurement, since this was performed similarly in all studies and in a following domain we already scored whether a definition for outcome was given.

Using the modified tool, two reviewers (DA, MJH) scored 11 items in five domains. Every item was assigned 0 points if bias was unlikely, 0.5 points if bias was possibly present and 1 point if bias was likely present. When in doubt, the reviewers discussed with the other authors to reach consensus. The distribution of points for potential bias following the QUIPS tool was inspected using a boxplot; the overall mean score was 1.8 points (range 0–5.5). Results were comparable for case-control (2.0), cohort studies (1.8) and randomized controlled trials (1.8). Papers that were classified as high-quality papers (i.e. on a scale of 0–11 a total bias score of <2 was assigned; Supplementary Table A.3), were analyzed separately using a random-effects model.

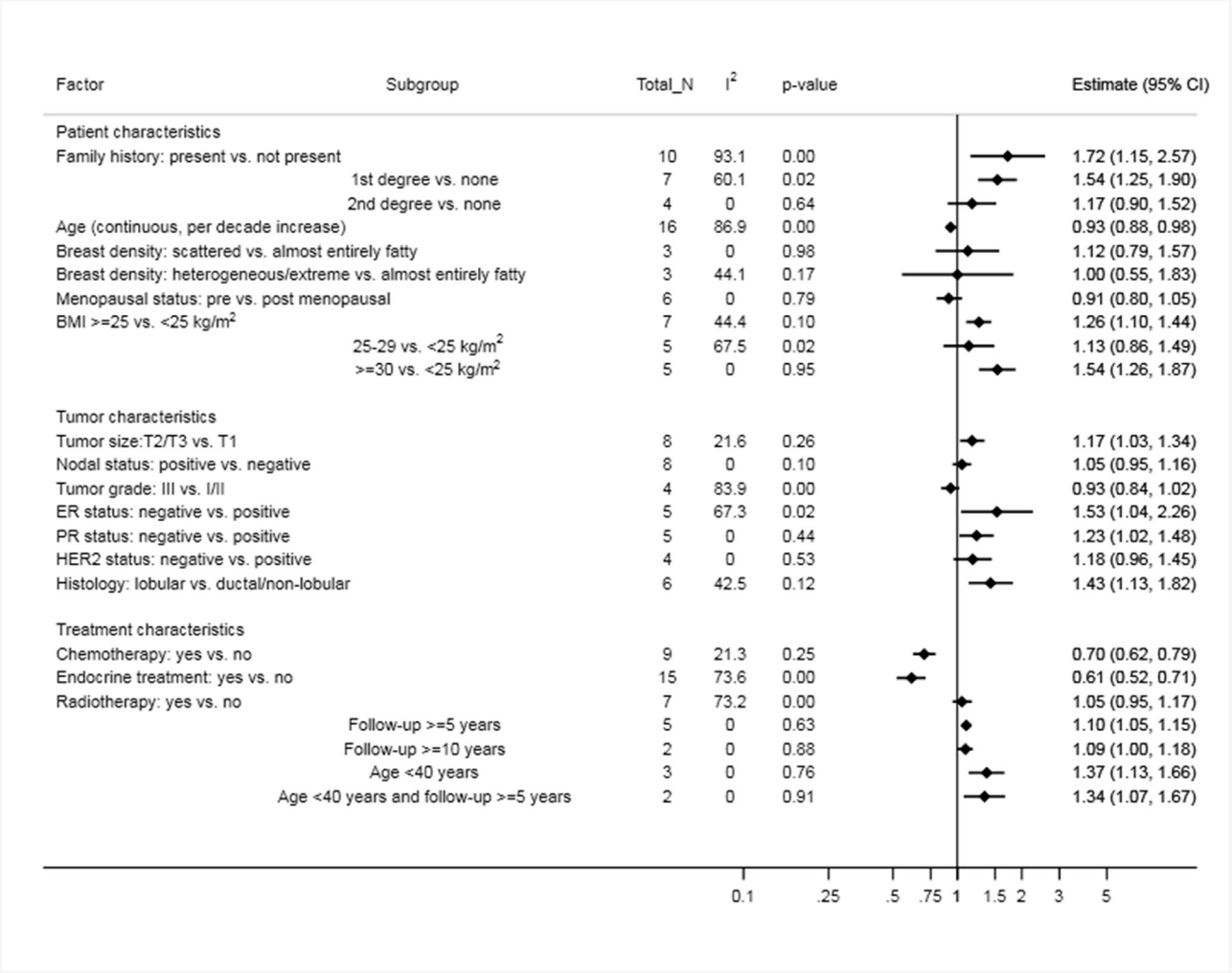

Fig. 2. Forest plot of the adjusted meta-analyses per patient, pathological and treatment-related characteristic on the risk of developing contralateral breast cancer in population-based cohorts; Abbreviations: BMI = body mass index per kg/m^2; ER = Estrogen hormone receptor; PR=Progesterone hormone receptor; T1 = tumor size ≤2 cm; T2 = tumor size 2.1–5.0 cm; T3 = tumor size >5.0 cm; Total_N = number of papers used for the analysis.
Age concerns the age at primary breast cancer diagnosis; family history concerns the family history of breast cancer; estimate is a relative risk estimate combining hazard ratios, odds ratios and relative risks; I^2 test for heterogeneity; *p*-value for heterogeneity: $p < 0.05$ considered significant; patient and pathological factors are assessed at primary breast cancer diagnosis; treatment-related characteristics concern primary breast cancer treatment.

3. Results

In total, 100 papers out of 1789 identified records fulfilled the inclusion criteria (Flow diagram, see Fig. 1) [2,3,12,13,15,16,20–22,25–115]; study characteristics are depicted in Table 1. Eligibility was validated for 10% of the titles and abstracts by a second reviewer. Subsequently, potential overlap in patients included in different papers was evaluated and we selected either the most relevant (i.e. on topic) or most recent paper (n = 11 excluded). In addition, we evaluated whether risk estimates in their given form were usable and/or combinable (n = 21 excluded).

Eventually, 68 papers were used for the meta-analyses and these included between 247 and 205 316 PBC patients and 21 and 6924 second BCs per study. Twenty studies used data from patients diagnosed in Northern America (USA/Canada) solely, versus 24 European studies. The risk estimates mainly concerned population-based cohorts; for the specific genetic groups of interest and the familial BC group the number of estimates was limited (Supplementary Table A.4).

In the summary estimates reported below, the adjusted estimates are reported (Figs. 2–5). Crude estimates are only provided in the main paper if the number of multivariable estimates was insufficient to perform a meta-analysis. An overview of the results from the crude analyses can be found in Supplementary Figure (S Fig.) B.1. Study-specific estimates per factor and per group of interest are provided in S Figs. B.2-B.40.

Population-based cohorts: Patient characteristics (Fig. 2; S Figs. B.2-B.12).

For the analyses concerning patient characteristics we reviewed 30 papers. Having a positive family history of BC was associated with an increased risk of CBC, but heterogeneity was substantial (RR = 1.72; 95% CI: 1.15–2.57; I^2 93.1%; S Fig. B.2). The study performed by Hemminki et al. [79] was the main outlier. They used a non-conventional method to determine CBC risk, by doubling the risk, leading to overestimation. Heterogeneity as well as the relative risk estimate decreased when ignoring this study (RR = 1.43; 95% CI: 1.22–1.68; I^2 41.6%).

CBC risk appeared to be higher in first than in second degree relatives (RR = 1.54; 95% CI: 1.25–1.90 and RR = 1.17; 95% CI: 0.90–1.52, respectively; S Figs. B.3 and B.4). Heterogeneity was also

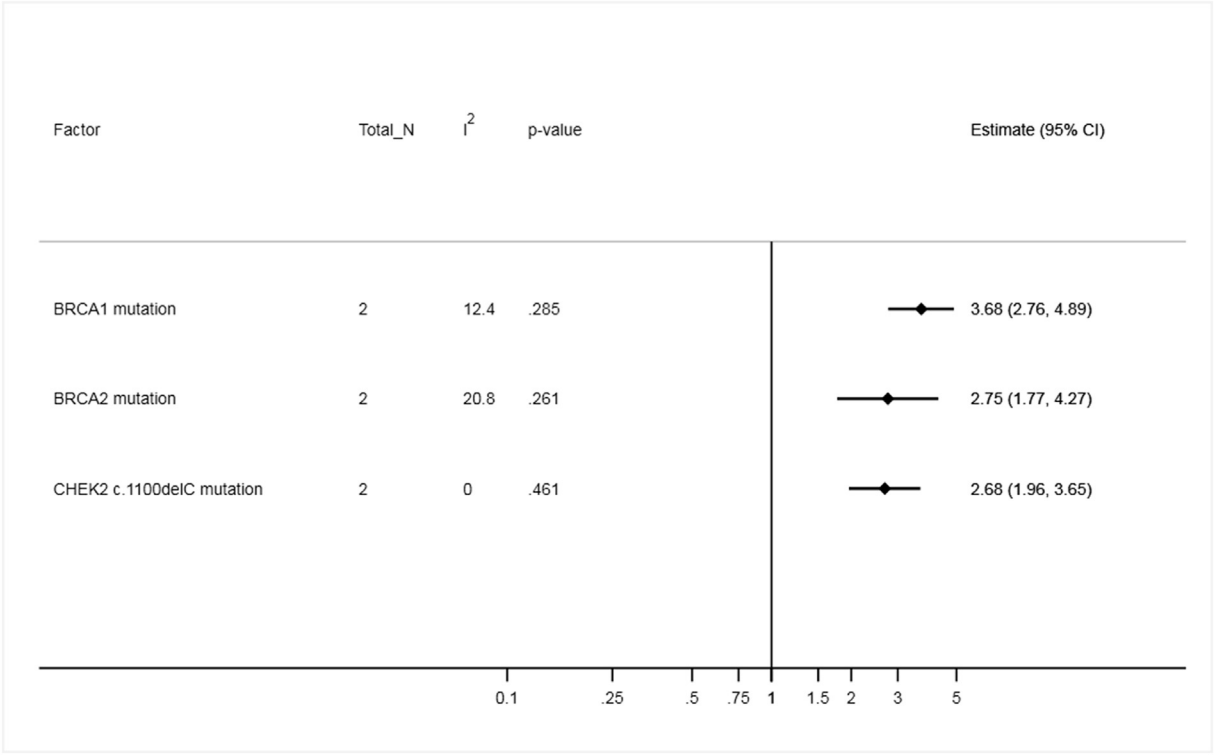

Fig. 3. Forest plot of the adjusted meta-analyses comparing carrying a *BRCA1*, *BRCA2* or *CHEK2* c.1100delC mutation with patients who did not have the genetic mutation on the risk of developing contralateral breast cancer; Abbreviations: Total_N = number of papers used for the analysis. Estimate is a relative risk estimate combining hazard ratios, odds ratios and relative risks; I^2: test for heterogeneity; *p*-value for heterogeneity: $p < 0.05$ considered significant.

present in the meta-analysis concerning first degree relatives (I^2 60.1% vs. 0% in second degree relatives). Excluding the results from Buist et al. [62], which was the main outlier in this analysis, resulted in a decrease in heterogeneity and small increase in CBC risk (RR = 1.61; 95% CI: 1.41–1.85; I^2 15.3%).

Age at PBC diagnosis was associated with a 7% decrease in CBC risk per decade (RR = 0.93; 95% CI: 0.88–0.98, I^2 86.9%; S Fig. B.5). Although heterogeneity between studies was substantial, the estimates from the individual papers did not seem to vary widely.

For mammographic breast density (S Figs. B.6 and B.7) and menopausal status (S Fig. B.8) no association with CBC risk was observed.

Being overweight or obese (BMI ≥25 kg/m^2) or being obese (BMI ≥30 kg/m^2) compared to having normal weight (BMI <25 kg/m^2), was associated with an increased risk of developing CBC (RR = 1.26; 95% CI: 1.10–1.44; I^2 44.4% and RR = 1.54; 95% CI: 1.26–1.87; I^2 0%, respectively; S Figs. B.9 and B.11).

Population-based cohorts: Pathological characteristics (Fig. 2; S Figs. B13-B.19).

For the analyses concerning pathological characteristics we analyzed 15 papers. Having a PBC with a larger size was associated with increased CBC risk (tumor size >2 cm vs. ≤2 cm; RR = 1.17; 95% CI: 1.03–1.34; I^2 21.6%; S Fig. B.13). For nodal status and tumor grade no association with CBC was observed (S Fig. B.14 and B.15, respectively). Both negative ER and PR hormone receptor status (vs. positive) were associated with an increased risk of CBC as well (RR = 1.53; 95% CI: 1.04–2.26; S Fig. B.16; and RR = 1.23; 95% CI: 1.02–1.48; S Fig. B.17, respectively), although for ER status there was evidence of substantial heterogeneity (I^2 67.3% vs. 0% for PR status). Excluding the outlying estimate reported by Filleron et al. [50] (possibly large effect size due to a small study population available for this factor), resulted in a decrease in heterogeneity and a non-significant association between ER status and CBC risk (RR = 1.32; 95% CI: 0.99–1.76; I^2 38.5%). For Her2 status no association with CBC risk was observed (S Fig. B.18).

Lobular morphology vs. ductal/non-lobular morphology was also associated with an increased risk of developing CBC, which in the forest plot was observed mainly in the older publications (RR = 1.43; 95% CI: 1.13–1.82; I^2 42.5%; S Fig. B.19).

Population-based cohorts: Treatment-related characteristics (Fig. 2; S Figs. B.20-B.27).

Nine papers were included on treatment with adjuvant chemotherapy and 15 studies on adjuvant endocrine therapy; both factors were associated with a lower CBC risk (RR = 0.70; 95% CI: 0.62–0.79; I^2 21.3%; S Fig. B.20 and RR = 0.61; 95% CI: 0.53–0.72; S Fig. B.21, respectively). Results for patients aged below and above 50 years at PBC diagnosis were similar (data not shown). Heterogeneity was high in the meta-analysis concerning endocrine therapy (I^2 73.6%), but decreased substantially (I^2 19.4%) when we selected papers including only patients with ER-positive tumors (RR = 0.57; 95% CI: 0.49–0.66; S Fig. B.22).

Treatment with radiotherapy (vs. no radiotherapy) was analyzed in 8 papers and associated with a modestly increased CBC risk when diagnosed at least five years after PBC (RR = 1.10; 95% CI: 1.05–1.15; I^2 0%; S fig. B.24). In patients aged below 40 years at PBC diagnosis this risk appeared to be higher, both for CBCs occurring any time after PBC and for CBCs occurring at least 5 years after PBC diagnosis (RR = 1.37; 95% CI: 1.13–1.66; I^2 0% and RR = 1.34; 95% CI: 1.07–1.67; I^2 0%, respectively; S Figs. B.26 and B.27). The association appeared to attenuate when the age cut-off was raised to 45 years at PBC diagnosis (RR = 1.22; 95% CI: 1.09–1.36, I^2 0.0% and RR = 1.20; 95% CI: 1.06–1.35, I^2 0.0%, respectively, data not shown).

Mutation carriers vs. patients from mutation-negative BC families (Fig. 3, S Figs. B.28-B.30).

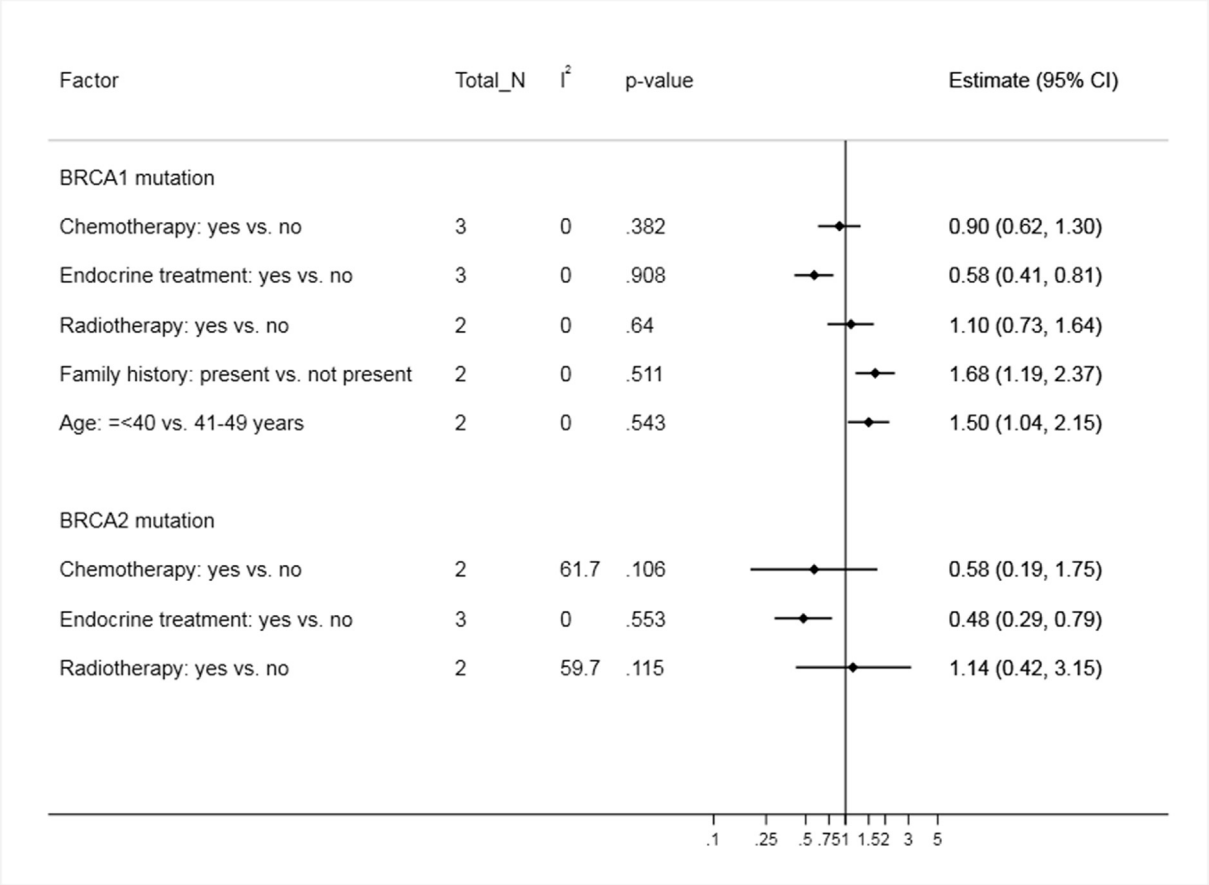

Fig. 4. Forest plot of the overall adjusted meta-analyses per patient, pathological or treatment-related characteristic on the risk of developing contralateral breast cancer in *BRCA1* and *BRCA2* mutation carriers Abbreviations: Total_N = number of papers used for the analysis. Age concerns the age at primary breast cancer diagnosis; family history concerns the family history for breast cancer; estimate is a relative risk estimate combining hazard ratios, odds ratios and relative risks; I^2: test for heterogeneity; *p*-value for heterogeneity: $p < 0.05$ considered significant; treatment-related characteristics concerns primary breast cancer treatment.

The effect of mutation status on CBC risk was analyzed in 5 papers [2,3,32,45,70]. Carriership of a *BRCA1*, *BRCA2* or *CHEK2* c.1100delC mutation vs. non-carriership was associated with an increased risk of CBC (RR = 3.68; 95% CI: 2.76–4.89; I^2 12.4%; RR = 2.75; 95% CI: 1.77–4.27; I^2 20.8%; RR = 2.68, 95% CI: 1.96–3.65; I^2 0%; S Figs. B.28-B.30; respectively).

BRCA1 and *BRCA2* mutation carriers (Fig. 4; S Figs. B.31-B.40).

Seven papers reported on risk factors in both *BRCA1* and *BRCA2* mutation carriers [3,15,33,40,53,59,80], and one in *BRCA1* mutation carriers only [2]. Although the number of papers was limited for *BRCA1* and *BRCA2* mutation carriers, effects of the meta-analyses pointed in the same direction as in the population based cohorts for family history of BC, age at PBC diagnosis and endocrine therapy. RRSO was associated with a decreased CBC risk in *BRCA1* mutation carriers (crude RR = 0.56; 95% CI: 0.32–0.99; I^2 46.8%; S Fig. B.36).

3.1. Quality assessment

Results from the boxplot on the distribution of points for potential bias following the QUIPS tool are shown in S Figure B.41. We classified 46 out of 68 papers as being high quality which were subsequently used for the sensitivity analysis (S Table A.3).

Following the sensitivity analysis, heterogeneity became 0% in the meta-analysis concerning ER status and BMI (25–29.9 vs < 25 kg/m^2) and decreased for age at PBC diagnosis (I^2 58.4%). Further, a significant association between BMI and CBC risk was observed (BMI 25–29.9 vs < 25 kg/m^2: RR = 1.39; 95% CI: 1.14–1.69), but we no longer observed an association between T2 vs. T1/T0 PBC and CBC risk (Fig. 5). Concerning *BRCA1* and *BRCA2* mutation carriers, an insufficient number of papers remained to perform meta-analyses, especially due to evidence for selection bias.

Funnel plots were generated for the factors with multiple papers available (i.e. family history, age at PBC diagnosis, TNM-stage, treatment); we observed no evidence for publication bias (Supplementary Figures B.42-B.48).

4. Discussion

In this systematic review with meta-analyses, we aimed to quantify the association of several patient, pathological, and treatment-related characteristics and their influence on CBC risk. For the general BC population, confirming current clinical practice, we observed that carrying a *BRCA1*, *BRCA2* or *CHEK2* c.1100delC mutation comprises the strongest predictors for CBC risk. Family history of BC was also associated with increased CBC risk. In addition, a moderately increased risk was observed following lobular PBC, ER/PR negative PBC, radiotherapy for PBC (at young age) or having a high BMI at PBC diagnosis. Administration of adjuvant chemotherapy or endocrine therapy was associated with decreased CBC risk, as well as older age at PBC diagnosis, although to a lesser extent. For *BRCA1*, *BRCA2* and *CHEK2* c.1100delC mutation carriers,

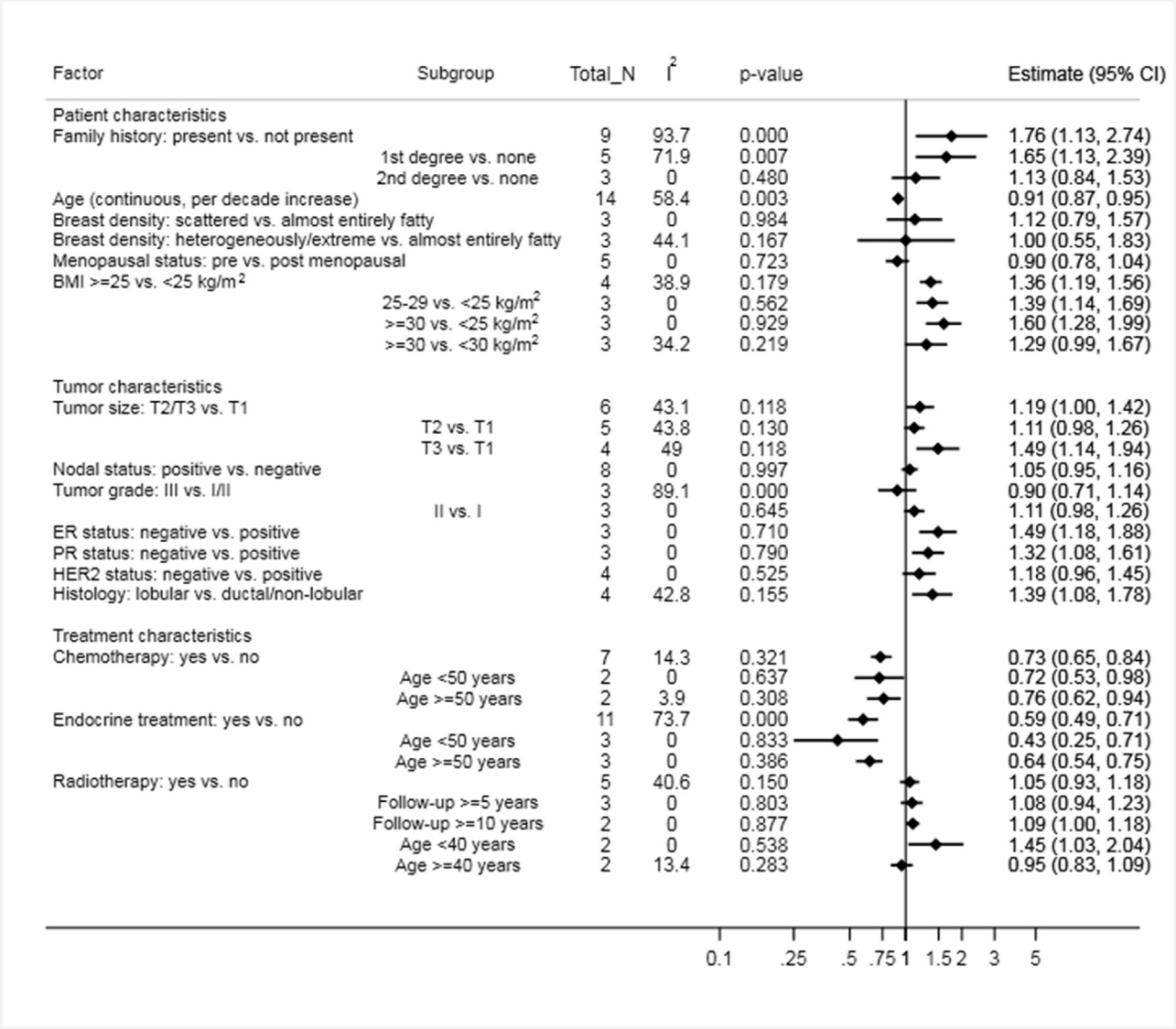

Fig. 5. Forest plot of the overall adjusted meta-analyses per patient, pathological or treatment-related characteristic on the risk of developing contralateral breast cancer in population-based cohorts using only high-quality papers following the QUIPS bias scoring tool Abbreviations: BMI = body mass index per kg/m^2; ER = Estrogen hormone receptor; PR=Progesterone hormone receptor; Total_N = number of papers used for the analysis. Age concerns the age (years) at primary breast cancer diagnosis; family history concerns the family history of breast cancer estimate is a relative risk estimate combining hazard ratios, odds ratios and relative risks; I^2: test for heterogeneity; *p*-value for heterogeneity: $p < 0.05$ considered significant; patient and pathological characteristics are assessed at primary breast cancer diagnosis; treatment-related characteristics concerns primary breast cancer treatment.

all estimates on risk factors went in the same direction. However, the number of papers was insufficient to draw strong conclusions. Most importantly, we confirmed the protective effect of adjuvant chemotherapy and endocrine therapy on CBC risk in population-based studies, as reported in large consortia such as the Early Breast Cancer Trialists' Collaborative Group [104,116]. In addition, the protective effect of adjuvant endocrine therapy was also found in *BRCA1/2* mutation carriers, specifically.

Radiotherapy for primary BC was associated with an increased risk of CBC, especially in patients irradiated at younger age (<40 years). This negative effect of radiotherapy is likely a consequence of scattered radiation dose in the contralateral breast [68]. In addition, in younger patients the cells are at higher risk of damage after radiotherapy due to a higher breast cell proliferation and increased DNA synthesis [117]. The late adverse effects of radiotherapy occur at least 10–12 years after PBC diagnosis, as has been shown by Land et al. who studied atomic bomb survivors, and by Ronckers et al. who investigated the effects of x-rays for spine deformities [118,119]. Interestingly, we observed an increased risk of CBC already 5 years following radiotherapy for PBC.

We observed an increased CBC risk in patients with large tumors, and ER/PR negative PBC. Although we cannot deny these associations, both features are also associated with worse prognosis of BC, raising the question whether some CBCs were distant PBC metastases. Only recently it became possible to genetically distinguish a true CBC from recurrent disease. In the latter case, we might misclassify a malignant tumor in the contralateral breast as a new entity, while in fact we are dealing with recurrent disease (misclassification of outcome) [120–123]. This can lead to overestimation of CBC risk for these features. Furthermore, some studies did not rule out the ascertainment of CBCs in the presence of distant metastasis [47,56,112] or did not mention this.

Misclassification of outcome may then occur more often, especially when considering tumor features with high recurrence rate. We can thus not rule out that part of the CBCs were in fact recurrences.

We observed an increased association with CBC risk for lobular PBC, which is in line with some older studies [112,124]. In the papers published before 2000 lobular PBC appeared to be associated with a higher risk of CBC. The effect of lobular histology on CBC risk was less observed in the papers published after 2000, an era in which adjuvant systemic therapy was more widely given (S Fig. B.19). The latter phenomenon has also been reported for CBC in general [20]. In our opinion, this reflects the risk reducing effect of adjuvant systemic therapy, and is in line with our earlier mentioned results on the impact of systemic therapy for PBC on CBC risk.

Results from the QUIPS underscored the importance of interpreting the results of studies in *BRCA1/2* mutation carriers with caution because of several potential forms of bias. In particular, survival bias was observed, which was mainly due to the retrospective design with inclusion of only mutation carriers who were still alive at the time of genetic testing [125]. Additionally, selection bias played a role specifically in the papers published on factors associated with the DNA test result, such as RRSO. These studies showed a protective effect from RRSO in the meta-analyses, but were potentially biased and led to an overestimation of the protective effect.

Our study had some limitations. First, we used reported results rather than individual patient data for the meta-analyses. Nonetheless, for most factors we observed acceptable levels of heterogeneity, which make our results reliable. Second, we cannot completely exclude the possibility of some publication bias, although the funnel plots did not provide evidence for the factors where we had enough papers to inspect this. Last, we only included papers with relative risk estimates, excluding 89 papers which reported cumulative incidences or standardized incidence rates only. However, those papers presented univariable estimates (factors were sometimes only stratified for a potential effect modifier), while we preferred multivariable estimates since these results are potentially less biased.

4.1. Implications for future research

Results from our meta-analyses have provided information on multiple CBC risk factors that should be incorporated in a CBC risk prediction model, but have also identified several topics needing further attention. First, although we observed considerable bias according to the QUIPS tool in the studies on *BRCA1*, *BRCA2* or *CHEK2* c.1100delC mutation carriers, the effect of carrying either one of these mutations has the largest impact on CBC risk and remains, therefore, the most important factor in estimating CBC risk. We will need more data on the effects of other risk factors within these groups to provide more personalized CBC risk estimates. This also accounts for familial BC cohorts. Second, concerning treatment, the effects of various adjuvant chemotherapy regimens, various targeted therapies and the long-term effects of radiotherapy (in young patients) should be investigated more extensively. Third, the effects of breast density on CBC risk should be investigated in large and prospective studies to determine the effects of breast density at PBC diagnosis and changes in density over time, also in relation to adjuvant systemic treatment. Fourth, we propose to investigate SNPs and polygenic risk scores within one large international dataset. This will enable researchers to explore interaction between different SNPs (and between SNPs and other factors) and to further personalize CBC risk estimates. In general, large cohorts (i.e. multicenter/international studies) with individual patient data and sufficiently long follow-up of at least 10–15 years are needed to accurately predict the risk of CBC.

4.2. Clinical implications

CBC risk is a growing concern in patients diagnosed with PBC, not only resulting in a psychological burden, but also determining survival in certain cases [126,127]. Risk-reducing mastectomy may be offered to those at high risk of developing CBC. On the other hand, overtreatment and exposing patients to side-effects of such radical surgery should be avoided as long as survival benefit has not been demonstrated. Especially in low-risk patients, where the number of patients opting for contralateral risk-reducing mastectomy is increasing, but no survival benefit has been observed, more thorough discussion on the individual CBC risk estimation considering various risk factors is important. This also includes discussing potential alternative risk-reducing options [128].

For example, extended endocrine treatment (beyond 5 years of initial/standard therapy) has been recently associated with a reduced risk of CBC as well [25]. In specific subgroups where the benefit from contralateral mastectomy is undecided, (extended) endocrine treatment as an alternative to reduce the risk of CBC may be advised. Nonetheless, the side-effects of (extended) endocrine treatment should also be considered.

For young PBC patients it is important to take into consideration the long-term side-effects of radiotherapy. Although local recurrence rates are decreased by more than 50% after radiotherapy in young PBC patients [129], CBC risk after radiotherapy is quite substantial in this group, and options to further reduce the scattered radiation dose towards the contralateral breast, as is done with more recent techniques, should thus be focused on.

Having a high BMI is one of the few modifiable risk factors that we have identified. Physicians should inform overweight patients about weight loss intervention programs that already have gained some success in BC patients [130,131].

5. Conclusion

Based on this review with meta-analyses, key prognostic factors for CBC risk are mutation status, family history of BC, and treatment for primary BC. Age at primary BC diagnosis, BMI, lobular histology and hormone receptor status of the primary BC have a weaker association and should be considered in combination with key factors to accurately predict CBC risk.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.breast.2018.11.005.

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