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Review

Cumulative risk of second primary contralateral breast cancer in *BRCA1/BRCA2* mutation carriers with a first breast cancer: A systematic review and meta-analysis

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ABSTRACT

BRCA1/2 mutation carriers are at a higher risk of breast cancer and of subsequent contralateral breast cancer (CBC). This study aims to evaluate the evidence of the effect of the *BRCA1/2*-carriership on CBC cumulative risk in female breast cancer patients.

The literature was searched in Pubmed and Embase up to June 2013 for studies on CBC risk after a first primary invasive breast cancer in female *BRCA*1/2 mutation carriers. A qualitative synthesis was carried out and the methodological quality of the studies evaluated. Cumulative risks of CBC after 5, 10 and 15 years since the first breast cancer diagnosis were pooled by *BRCA1/2* mutation status.

A total number of 20 articles, out of 1324 retrieved through the search, met the inclusion criteria: 18 retrospective and 2 prospective cohort studies. Cumulative risks of up to five studies were pooled. The cumulative 5-years risk of CBC for *BRCA*1 and *BRCA*2 mutation carriers was 15% (95% CI: 9.5%e20%) and 9% (95% CI: 5%e14%), respectively. This risk increases with time since diagnosis of the first breast cancer; the 10-years risk increased up to 27% and 19%, respectively. The 5-years cumulative risk was remarkably lower in non-*BRCA* carriers (3%; 95% CI: 2%e5%) and remained so over subsequent years (5%; 95% CI: 3%e7%).

In conclusion, risk of CBC increases with length of time after the first breast cancer diagnosis in *BRCA*1/2 mutation carriers. Studies addressing the impact of treatment-related factors and clinical characteristics of the first breast cancer on this risk are warranted.

Introduction

Breast cancer is the most common cancer and cause of cancer-related death in women in Europe and the USA [1,2], in spite of having one of the highest survival rates amongst all cancers [3,2]. Thus, the number of women who overcome a breast cancer is considerably increasing along with the number of survivors after

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Abbreviations: CBC, contralateral breast cancer.

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the first diagnosis, raising the number of women at risk of developing subsequent cancers. Most of these second cancers occur in the contralateral breast [4,5]. It is well-known that BRCA mutation carriers are at higher risk of contralateral breast cancer (CBC) than non-carriers [6,7]; *BRCA* mutations have been therefore regarded as responsible for this excess risk [8,9].

A recently published meta-analysis has estimated that *BRCA*1 and *BRCA*2 mutation carriers have a 3.5 fold higher relative risk of CBC compared to non-carriers, and that CBC risk increases up to 42% in *BRCA*1 compared to *BRCA*2 carriers [10]. This study confirms that CBC risk is greater than the corresponding figure for the general population of breast cancer patients. However, risk of CBC also varies according to the time passed after the first breast cancer diagnosis. For instance, the 10-year cumulative risk of CBC in *BRCA*

Table 1
Published studies on Contralateral Breast Cancer (CBC) risk in BRCA1/2 mutation carriers.

Study [reference] Country Study design	Study period (follow-up)	Study population source	Number of CBC/ BC	Number of *BRCA* mutations in BC cases			Number of non-carriers (CBC)	Number of mutations unknown	Number of BC cases in control group**	Mean age (years) at BC diagnosis	Mean age (years) at CBC diagnosis	Mean time from BC to CBC	Clinical and pathological characteristics of the first BC
				BRCA1 (CBC)	BRCA2 (CBC)	*BRCA1/2** (CBC)							
Mavaddat *et al* 2013 [17] UK Prospective cohort	1998e2008 (10 years)	EMBRACE study	61/651 of which 2 women developed BC at follow-up	340 (42) 5 first BC cases and 3 CBC cases were DCIS.	309 (19) 24 first BC cases and 4 CBC cases were DCIS.	651[b](61)	0	0	590[b]	BRCA1: 41.6 (median 41.0) BRCA2: 45.2 (median 44.6)	BRCA1: 50.2 (median 48.6) BRCA2: 52.1 (median 54.1)	BRCA1: 3.3 years BRCA2: 2.8 years	Primary invasive breast cancer, but also some ductal carcinomas (DCIS) were included. 315 women underwent oopheroctomy
Rhiem *et al.* 2012 [15] Germany Retrospective cohort	1996e2011 (15 years)	German Consortium for Hereditary Breast and Ovarian Cancer	502/6235	213 (193)	106 (56)	319[b] (249)	4326 (253)	0	4501[a]	BRCA1: 43.5 (IQR 37.5e51.5) BRCA2: 48.1 (IQR 40.4e58.5) Non carriers: 53.6 (IQR: 45.3 e63.9)	BRCA1: 47.7 (IQR 40.1e55.5) BRCA2: 53.1 (IQR 44.7e62.6) Non carriers: 56.0 (IQR: 48.5 e66.6)	48,390 pers-years	Primary invasive breast cancer.
Metcalfe *et al* 2011 [16] Canada, USA Retrospective cohort	1975e2008 (33 years)	Genetic clinics (10 centers)	148/810	498 (?)	300 (?)	787[b], 12[a] (148)	0	0	639[b]	42.2 (range: 21 e65)	NA	5.7 range: (0.2e15)	Primary invasive breast cancer, with stage I or II. Some women underwent oopheroctomy (*n* = 47), radiotherapy (*n* = 344), used tamoxifen (*n* = 163) and chemotherapy (*n* = 321). 336 cases were estrogen positive.
Malone *et al* 2010 [37] USA, Denmark Nested case-control, population-based	1985e2001 (15 years)	WECARE study	705/1398	109 (67)	72 (41)	181 (108)[b]	597 cases, 1325 controls	0	1,398 [a] (matched on age, year of first BC diagnosis, registry, and race)	Controls: 46 (IQR: 42e50)	46 (IQR: 41 e51)	NA	Primary invasive breast cancer before the age of 55. Some women underwent oopheroctomy (*n* = 489), radiotherapy (*n* = 424), used tamoxifen (*n* = 268) and chemotherapy (*n* = 533).
Van der Kolk *et al* 2010 [24] The	1978e2003 (25 years)	Genetic clinic (Groningen)	67/300	120 (43)	72 (24)	192 (67)[b]	9	99	788[a] (matched on age, race, center)	BRCA1: 42.5 (SD 10.4) BRCA2: 46.8 (SD 10.4) Non	BRCA1: 43.8	BRCA1: 4.2	Primary

(SD 8.4) BRCA2: 51.9 (SD 9.9)	(SD 4.2) BRCA2: 4.3 (SD 4.6)	invasive breast cancer.

Netherlands Retrospective cohort										carriers: 43.9 (SD 5.6)			
Evans *et al* 2010 [25] UK Retrospective case-control	1980e1997 (17 years)	Cancer Intelligence Service	19/115 with DNA testing Or 19/288	16 (4) 2 sporadic + 14 familiar	9 (1) 1 sporadic + 8 familiar	25 (5)[b]	66 with DNA testing (14)	173	64[a] sporadic breast cancer	28 years and 3 months (range 18.5e30.9 years)	NA	NA	Primary invasive breast cancer before the age of 30.
Kirova *et al* 2010 [38] France Retrospective case-control	1981e2001 (19 years)	Institute Curie	64/131	19 (?)	8 (?)	27 (11)	53	0	261[a] sporadic breast cancer (mathed on age at diagnosis, year of treatment and follow-up)	NA	NA	NA	Primary invasive breast cancer treated with breast-conserving surgery and radiotherapy.
Garcia-Etienne et al [39] Italy Retrospective case-control	1994e2007 (13 years)	European Institute of oncology, Milan	6/216	26 (?)	28 (?)	54 (5)	0	0	162[a] sporadic breast cancer (mathed on age, size of tumor and year of surgery)	NA	NA	4 years	Primary invasive breast cancer treated with breast-conserving surgery and radiotherapy.
Bonadona *et al* 2007 [40] France Population-based prospective	1995e2004 (10 years)	Rhone breast cancer registry	18/232	15 (2)	6 (1)	21 (3)[b]	205 (15)	0	205[b]	NA	NA	BRCA1/2: 20 months Non carriers: 28 months	Primary invasive breast cancer before the age of 46. Women received radiotherapy (n = 217), tamoxifen (n = 61) and chemotherapy (n = 132).
Brekelmans *et al* 2007 [26] The Netherlands Retrospective case-control	1980e2004 (24 years)	Family Cancer Clinic (Rotterdam)	86/757	223 170 excluding index cases (25)	103 90 excluding index cases (15)	326[b] 238 excluding index cases (13)	238 with DNA testing	0	759[a] with 33 CBC sporadic breast cancer (matched on age and year of first BC diagnosis).	NA	NA	NA	Primary invasive breast cancer.
Pierce *et al* 2006 [27] USA, Canada, Israel Retrospective case-control	1976e2001 (25 years)	Genetic cancer databases (11 centers)	48/605	123 (25)	37 (15)	160 (36)[b]	0	0	445[a] with 12 CBC sporadic breast cancer (1:3, matched on age and date of first BC diagnosis)	NA	NA	NA	Primary invasive breast cancer, treated with conservation therapy, and of stage I/II. 69% of women of the carrier cohort received chemotherapy and 22% of women used tamoxifen.
Robson *et al* 2005 [28]	1992e2004 (12 years)	Hospital cancer clinic	20/87	62 (15)	25 (5)	87 (20)[b]	0	0	67[b]	BRCA1/2: 43 (range 27e82)	NA	BRCA1/2: 67.4 months	Primary invasive breast

(*continued on next page*)

Table 1 (*continued*)

Study [reference] Country Study design	Study period (follow-up)	Study population source	Number of CBC/ BC	Number of *BRCA* mutations in BC cases			Number of non-carriers (CBC)	Number of mutations unknown	Number of BC cases in control group**	Mean age (years) at BC diagnosis	Mean age (years) at CBC diagnosis	Mean time from BC to CBC	Clinical and pathological characteristics of the first BC
				BRCA1 (CBC)	BRCA2 (CBC)	*BRCA1/2** (CBC)							
USA Retrospective cohort		(Memorial Sloan-Kettering)											cancer, stage I/ II. All women received adjuvant therapy.
Robson *et al* 2004 [29] USA Retrospective cohort	1980e1995 (15 years)	Hospital cancer clinic (Memorial Sloan-Kettering and Davis-Jewish Hospital)	24/496	42	14	56[b], 1[a]	440	0	440[a]	NA	NA	NA	Primary invasive breast cancer in women under 65 years of age and undergoing breast-conserving surgery and radiotherapy.
Haffty *et al* 2002 [30] USA Retrospective cohort	1975e2000 (25 years)	Oncology database	14/127	15 (?)	7 (?)	22 (7)[b]	105 wild-type (7)	0	98[b]	BRCA1/2: 37.3 (SD 3.8) Non carriers: 33.7 (SD 4.0)	NA	NA	Primary invasive breast cancer before the age of 42, treated with conservation therapy and radiotherapy.
Eccles *et al* 2001 [31] UK Retrospective case-control	1959e1996 (37 years)	Family Cancer Clinic (Southampton)	77/304	75 (51 CBC within 142 with positive family history)	NA	NA	162 with family history negative (26)	67	49[a] (matched on age and date of first BC diagnosis)	BRCA1: 39.1 (SD: 8.8)	NA	NA	Primary invasive breast cancer in before the age of 40.
Hamann *et al* 2000 [32] Germany Retrospective cohort	1961e1994 (33 years)	Family Cancer Clinics	18/85	36 (14)	NA	NA	49 (4)	0	49[a]	BRCA1: 37.5 Non Carriers: 47	NA	BRCA1: 60 months Non Carriers: 80 months	Primary invasive breast cancer.
Verhoog *et al* 2000 [33] The Netherlands Retrospective cohort	1960e1996 (36 years)	Family Cancer Clinic (den Hoed and Rotterdam)	39/164	129 (?)	NA	NA	0	35	0	41 (range: 22 e80)	NA	57 months	Primary invasive breast cancer, histologically confirmed.
Verhoog *et al* 1999 [34] The Netherlands Retrospective cohort	1960e1996 (36 years)	Family Cancer Clinic (den Hoed and Rotterdam)	16/140	NA	22 (8)	NA	6 (?)	0	112[a] sporadic breast cancer (1:4 matched on age and date of first BC diagnosis)	NA	NA	NA	Primary invasive breast cancer. Women received adjuvant therapy.
Easton *et al* 1999 [35] Europe, Canada, USA Retrospective cohort	1960e1995 (35 years)	Family Cancer Clinics (20 centers): Breast Cancer Linkage Consortium	66/3271	NA	471 (66)	NA	390 (?)	2186	2576[b] first degree relatives	NA	NA	NA	Primary invasive breast cancer, without distant metastases. All women underwent conservation

Ford et al 1994 [36] Europe, USA Retrospective cohort	1945e1992 (47 years)	Family Cancer Clinics (18 centers): Breast Cancer Linkage Consortium	26/1327	464 (?)	NA	NA	221 (?)	642	863[a]	NA	NA	NA	therapy or mastectomy. Primary invasive breast cancer.

CBC: contralateral breast cancer.
BC: breast cancer.
NA: not applicable.
*BRCA1/2 refers to: a) *BRCA1* and *BRCA2*; b) *BRCA1* or *BRCA2*.
**The control group comprised women with unilateral breast cancer: a) who were considered as non carriers of *BRCA1/2* mutations; b) who were considered as carriers of *BRCA1/2* mutations but did not develop CBC during follow-up.

mutation carriers with breast cancer varies between 20 and 35%, and may even further differ by age or menopausal status at diagnosis of the first breast cancer, type of treatment and other clinical and pathological factors of the first tumor in the breast [11].

Female *BRCA* mutation carriers with breast cancer need counselling on their CBC risk so as to undergo specific surveillance programs or immediate prophylactic surgery (ooferoctomy or mastectomy), radiotherapy or drug treatment (tamoxifen, other hormonal agents or chemotherapy) [12]. Several studies have examined the effect of these options on the risk reduction of CBC [10,13,14]. To gain insight into the cumulative risk of CBC by time since diagnosis of the first breast cancer may provide a basis for determining optimal CBC surveillance and treatment strategies in these patients.

A large number of studies have evaluated the cumulative risk of CBC after an initial diagnosis of breast cancer in women carrying a BRCA mutation. A previous review that evaluated the evidence of BRCA-associated breast cancer prognosis [11] included some of these studies, and described results of CBC cumulative risks accordingly. According to this review, the estimated 10-year cumulative risk of CBC ranges from 20 to 40%, but this review did not provide a pooled estimate of this risk nor considered all the available studies on this issue. In addition to the above mentioned limitations, this review mostly included retrospective studies, subjected to the well-known selection and information biases that this kind of design entails. Since then, other studies have been published [15e17] possibly overcoming these methodological drawbacks. The latest review on risk of CBC in BRCA1/BRCA2 mutation carriers [10], did, again, not evaluate cumulative CBC risk over time in women affected with breast cancer and BRCA mutations.

The aim of the present study was to revise the current evidence on the absolute cumulative risk of CBC after a diagnosis of a first primary invasive breast cancer associated with mutations of the *BRCA*1/2 genes, and to provide for the first time a pooled estimate of this risk.

Material and methods

Search strategy

A search was carried out to find relevant studies and reviews published up to June 2013. The databases used were Pubmed and Embase.

The following MeSH terms related to "*BRCA* genes", "breast cancer", "prognosis", "multiple primary cancers" and related subcategories were selected: Neoplasms/Multiple Primary, Neoplasms/Second Primary and epidemiology. A number of key words ("second cancers", "contralateral breast cancer" and "prognosis") were also used and combined in these databases (Supplemental Table 1). The reference lists of all relevant articles were also examined.

Study inclusion and exclusion criteria

The following article types were included: (1) Original studies on risk of subsequent CBC after a first breast cancer in female *BRCA*1 and/or *BRCA*2 mutation carriers; (2) Study design: prospective and retrospective cohort studies, caseecontrol studies, and systematic reviews and meta-analyses as another source of original studies; (3) Population Characteristics: females diagnosed with a first primary invasive breast cancer and carrying *BRCA*1/*BRCA*2 mutations, as verified through genetic testing or presence of a positive family history; (4) Outcome: cumulative probability estimates of CBC risk

(probability that a women diagnosed with a breast cancer and

*BRCA*1/2 mutation will experience a CBC within a given time interval), by age at diagnosis and time after first breast cancer diagnosis (5, 10, 15 or more years actuarial risks), derived from original data.

Furthermore, we excluded: (1) Studies examining risk of ipsilateral or bilateral breast cancer in the breast in females with a first primary breast cancer and *BRCA*1/*BRCA*2 mutations; (2) Studies examining local recurrences, locoregional or distant recurrences of the first breast cancer; (3) Multiple studies on the same population. When two or more studies had overlapping study samples, we included the one assessing CBC risk within the largest and most updated study sample.

Data extraction

Two independent reviewers (EMM and BPN) read, reviewed and selected the articles. A third reviewer (MJS) decided whether or not an article would be included if the first two reviewers did not agree. In order to test the methodological quality of the studies, the questionnaire (checklists for observational studies) proposed by the SIGN50 Scottish Intercollegiate Network 2013 was used [18]. This questionnaire assesses both the methodological quality and overall quality of the studies, classifying them as high, acceptable or low. This methodology allows a critical appraisal of bias risk. The overall methodological quality of the study was assessed taking into account its design, its internal validity, consistency and precision of its results.

For each eligible study, we extracted the following data using a standardized form: country, study design, study period and follow-up, and study population source, number of breast cancer cases and CBC events, for *BRCA*1/2 mutation carriers and non-*BRCA* carriers, number of *BRCA*1/2 mutation carriers and non-carriers, number of breast cancer cases in the comparison group (controls), mean age at diagnosis of the first breast cancer and of the CBC, mean time from breast cancer to CBC, clinical and pathological characteristics of the first breast cancer, and also the cumulative probability (actuarial cumulative risk) of CBC by time elapsed between diagnosis of the first and second (contralateral) breast tumors, and the cumulative risk of CBC by age at diagnosis of the first breast cancer and by age.

The information was extracted from all studies by the same person and the results, i.e. cumulative risks, were obtained directly from the studies when available, extrapolated from the information

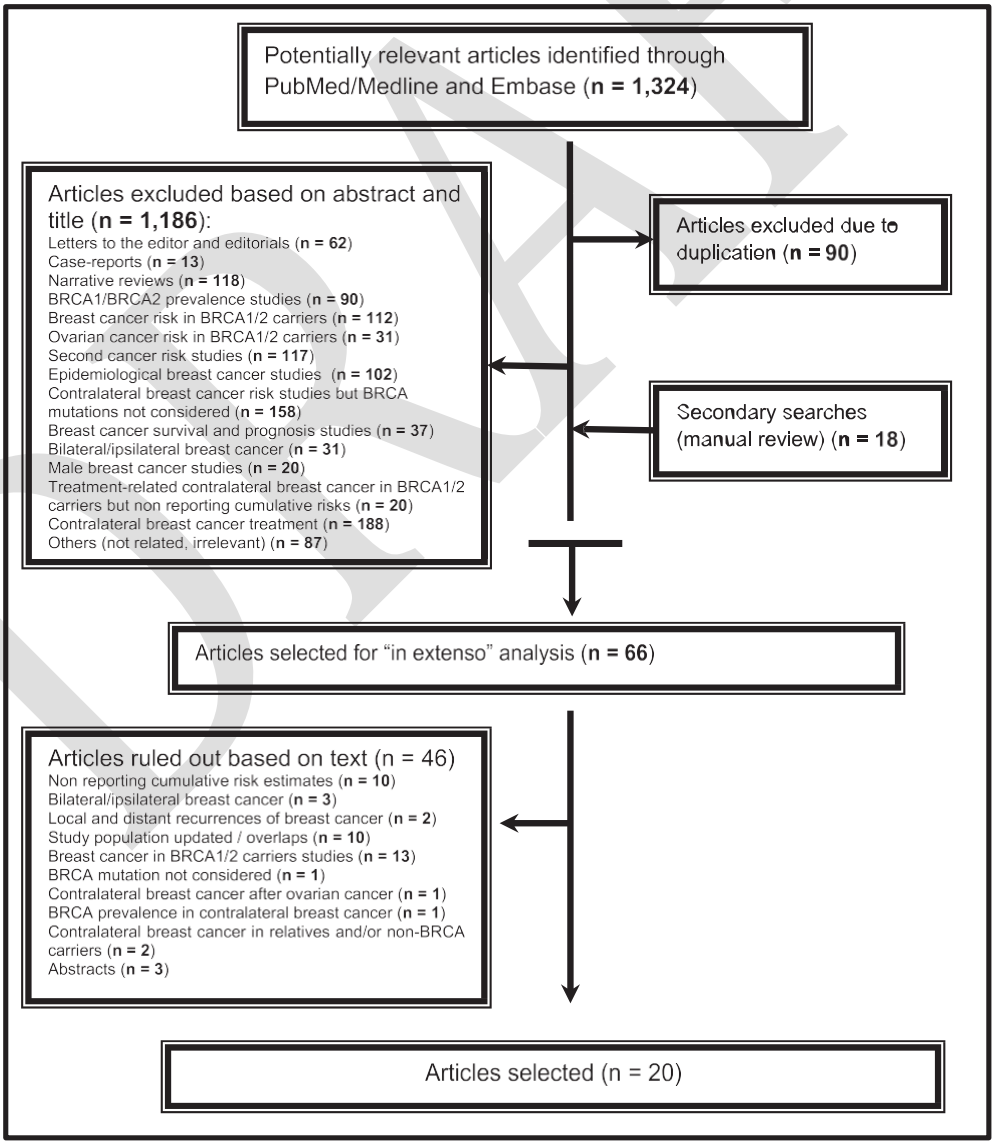

Fig. 1. Flow diagram showing the study search and selection procedure.

Table 2
Characteristics of the selected studies on Contralateral Breast Cancer (CBC) risk in BRCA1/2 mutation carriers.

Study [reference] Country	Study population	Breast cancer ascertainment	Genetic testing (methods and mutations analyzed)	Results	Limitations	Strengths	Methodological quality
Mavaddat et al. 2013 [17] UK	Cohort of 978 BRCA1 and 909 BRCA2 carriers, of which 651 (340 BRCA and 309 BRCA2 carriers) had a previous breast cancer. Inclusion: women older than 18 years and carriers of a BRCA1 or BRCA2 mutation. Breast cancer was defined as invasive or in situ carcinoma. Cases: second primary or in situ breast cancer (CBC) after more than 6 months since the first breast cancer diagnosis.	Self-reported data on: date of the CBC diagnosis and surgical procedures. The Office for National Statistics also notified CBC occurrence.	Not reported but pathogenic mutation in EMBRACE is defined as an established disease-causing mutation under the classification scheme used by Breast Cancer Information Core http://research.nhgri.nih.gov/bic/. All were positive for BRCA1/2 mutations.	BRCA1 and BRCA2 mutation carriers are at high risk of developing CBC: CBC incidence for BRCA1 carriers = 37.9 per 1000 PY (95% CI: 27.8e51.7) and for BRCA2 carriers = 21.9 (95% CI: 13.9e24.3). CBC cumulative risk by age 70 years for BRCA1 carriers = 83% (95% CI: 69%e94%) and for BRCA2 carriers = 62% (95% CI: 44% e79.5%). 10-years CBC cumulative risk for BRCA1 carriers = 33.5% and for BRCA2 carriers = 19.5%. Differences in cumulative risks by BRCA1 and BRCA2 mutation status were statistically significant (p=<0.001) After bilateral oophorectomy, the Hazar Ratio of CBC risk was: 0.77 (p = 0.42) and 0.16 (p = 0.1) in BRCA1 and BRCA2 mutation carriers, respectively.	1) Study population derived from a register of families (referred to genetic screening) (selection bias). 2) Lack of data on potential effect modifiers: tamoxifen, other therapies, and surgical procedures carried out after the diagnosis of the first primary breast cancer.	Prospective study. Average cumulative risks analysis by BRCA gene mutation. Cancer diagnosis verified through Cancer Statistics Office. Effect modification by BRCA polymorphisms and oophorectomy was also analyzed. Competing risk analysis was considered.	++ High
Rhiem et al. 2012 [15] Germany Update of [47]	Cohort of 6235 women with a first breast cancer from high risk families (1154 BRCA1 carriers, 575 BRCA2 carriers and 4501 non-carriers) and 6230 index patients (first family member affected with breast or ovarian cancer). Inclusion: index cases and their first and second-degree relatives diagnosed with a first breast cancer after 1960.	University hospitals, physician's private practice and self-reported CBC diagnosis.	BRCA gene sequencing; all exons (10 and 11) were sequenced. The method applied varied amongst the participating centers. 25% of all families included tested positive for BRCA1/2 mutations.	CRB is significantly higher in BRCA1 carriers (RR = 3; 95% CI: 2.5e3.6) and in BRCA2 carriers (RR = 1.6; 95% CI: 1.2e2.2) compared to non BRCA1/2 carriers. 25-years CBC cumulative risk for BRCA1 carriers = 44.1% (95% CI: 22.4 e44.7), for BRCA2 carriers = 33.5% (95% CI: 22.4 e44.7) and 17.2% for non BRCA1/2 carriers = 17.2% (95% CI: 14.5e19.95). CBC risk depends on age at first breast cancer diagnosis: risk was significantly increased in women with BRCA1/2 mutation and a younger age at the first breast cancer diagnosis. Differences in cumulative risks by BRCA1 and BRCA2 mutation status were statistically significant (p=<0.001) and	1) Only 16% of the relatives from BRCA1/2 positive families were proven mutation carriers. Thus, some noncarriers were included. 2) Hospital records for CBC case ascertainment were unavailable for 27% of the patients leading to plausible incomplete CBC case identification. 3) The prevalence of BRCA1/2 mutations was relatively high in this study population (25%) compared to other study populations (low external validation).	Large cohort of women. Index cases were excluded minimizing the effect of survival bias.	+ Acceptable

between BRCA1 and BRCA negative carriers ($p \leq 0.001$) and BRCA2 and BRCA negative carriers ($p = 0.01$).
Age at CBC as well as age at first breast cancer were significantly

(*continued on next page*)

Table 2 (*continued*)

Study [reference] Country	Study population	Breast cancer ascertainment	Genetic testing (methods and mutations analyzed)	Results	Limitations	Strengths	Methodological quality
				lower in BRCA1 mutation carriers compared with BRCA2 carriers (p=<0.001). In non-carriers, these ages were higher compared to both BRCA1 and BRCA2 mutation carriers (p=<0.001).			
Metcalfe et al. 2011 [16] Canada and USA Update of [9,45,46]	Cohort of 810 women with a first breast cancer from BRCA families, from 10 cancer genetics clinics. Inclusion: women diagnosed with a first primary stage I or II invasive breast cancer between 1975 and 2008, younger than 65 years and from high risk families with a documented BRCA1/2 mutation and at least one case of breast cancer documented.	Medical records.	Genetic testing for BRCA1 or BRCA2 performed but method is not reported. 87.2% of the study population were positive for BRCA1/2 mutations (12.2% were not tested but were from high-risk families), and all were from high risk families with a known BRCA mutation.	Women older than 50 years at first breast cancer diagnosis had a lower CBC risk (RR = 0.47; 95% CI: 0.47e0.82) than women younger than 40 years at diagnosis. CBC cumulative risks increased annually by 2.1% in both BRCA1 and BRCA2 carriers (overall, from 13.1% (95% CI: 10.3e15.9) at 5-y since breast cancer diagnosis to 33.8% (95% CI: 28.6 e39.0) at 15-y since breast cancer diagnosis), and were higher in women diagnosed with breast cancer at age younger than 50 years in both mutation carriers. The Hazard Ratio of CBC in BRCA2 carriers vs BRCA1 mutation carriers was: 0.88 (p = 0.51). Oophorectomy was associated with a significant reduction of CBC risk in BRCA1 carriers (HR: 0.48, p = 0.01), while in BRCA2 carriers, this risk reduction was not statistically significant (p = 0.51).	1) A control group of non-BRCA carriers was not considered. 2) Inclusion of women without genetic mutation confirmation (<4%); however, misclassification is unlikely since the study population had a documented mutation in each family.	Large sample size. Confirmation of CBC diagnosis in medical records. Inclusion of deceased cases to avoid the survivorship bias.	++ High
Malone *et al* 2010 [37] USA and Denmark	705 women diagnosed with CBC (cases) and 1398 women diagnosed with a unilateral breast cancer (controls) within a population cohort of 52,536 women diagnosed with a first primary breast cancer from 5 population-based cancer registries. Inclusion: first primary invasive breast cancer diagnosis before age 55 years from 1985 to 2000 and without regional lymph nodes affection. Cases: second primary or in situ breast cancer (CBC) after more	Population-based cancer registries.	HPLC and sequencing flanking intronic regions and all coding exons. 181 women were BRCA1/BRCA2 mutation carriers	BRCA1 and BRCA2 carriers had a significantly higher risk of CBC (RR = 4.5; 95% CI: 2.8-7.1 and RR = 3.4; 95% CI: 2.0-5.8, respectively) compared to non-carriers. These risks decreased with older ages at breast cancer than 1 year since the first breast cancer diagnosis. Controls: matched by year of birth and	1) Synchronous cancers and women with prophylactic contralateral mastectomy were excluded. Therefore, BRCA1/ BRCA2 mutation prevalence might be underestimated. 2) Only women who survived diagnosis in BRCA1 mutation carriers (from 11-fold among women younger	Population-based study, considering breast cancer cases from the general population and regardless of family history: an important number of cases had no first-degree familiy history and were	+ Acceptable
						than 35 years to 2.6 fold among women aged 45e54 years in BRCA1 mutation carriers, while no clear trend by age was observed for BRCA2 mutation carriers. Cumulative risks augmented as time since breast cancer diagnosis increases (i.e. from 10.9% after 5 years to 20.5%	

breast cancer were included, possibly leading to survival bias.

therefore less subject to high risk profiles. Large number of CBC cases.

	breast cancer diagnosis, registry and race. Exlusion: controls with CBC and synchronous CBC.			after 10 years since breast cancer diagnosis for BRCA1 carriers).			
Van der Kolk et al. 2010 [24] The Netherlands	Cohort of 1188 mutation carriers (755 BRCA1 and 433 BRCA2) with 94 index cases in the BRCA1 families and 58 index cases for BRCA2, all ascertained from a genetic clinic (University Medical Center Groningen). Inclusion: women with BRCA mutation and their first-degree female relatives, born between 1910 and 1987 and older than 18 years. Exclusion: mothers of mutation carriers when the mutation came from the paternal family. CBC was defined as invasive or in situ carcinoma.	Hospital or pathology records or through a first-degree family member	Denaturing gradient gel electrophoresis, protein truncation test, direct sequencing and multiplex ligation-dependent probe amplification for BRCA1 and BRCA2 genes.	The 10-year risk of a contralateral breast cancer was 34.2% (95% CI 29.4e39.0%) in BRCA1 and 29.2% (95% CI 22.9 e35.5%) in BRCA2 families. The mean time between the first breast cancer and second diagnosis (CBC) was 4 years and did not differ by BRCA mutation status (p = 0.89). Mean age at diagnosis of CBC in BRCA1 mutation carriers (43.8 years) was significantly lower compared with BRCA2 carriers (51.9 years, p = 0.01).	1) 319 and 181 women were not tested for BRCA1 or BRCA2 mutations, respectively. They were pooled with mutation carriers in CBC risk estimation analysis, assuming that women with a second cancer in the breast (n = 19) are likely to carry a mutation.	Retrospective cohort study. Cancer diagnosis was confirmed by hospital or pathology records or through a first-degree family member. Analyses were conducted including and excluding the index cases to minimize ascertainment bias. Two control groups were chosen for the mutation carrier group: proven non-carriers and not tested women.	+ Acceptable
Evans *et al* 2010 [25] UK	115 of 288 women diagnosed with breast cancer less than 30 years of age for which genetic status could be established (i.e. 173 cases were not tested). Of these, 51 cases had a positive breast cancer family history while the remaining 64 cases not (sporadic breast cancer). Inclusion: first invasive breast cancer diagnosis at or under 30 years of age between 1980 and 1997. Cases were primary tumorstumors and histologically confirmed, and screened for mutations in BRCA and TP53 genes.	Cancer Intelligence Service database.	Direct sequencing and multiple ligation-dependent probe amplification. 16 women were BRCA1 positive and 9 women were BRCA2 positive.	In women under 30 years of age at first breast cancer diagnosis, the CBC cumulative risk increased annually by 2% up to 15 years of follow-up. At 10 years since first breast cancer diagnosis, cumulative risk of CBC was about 14% in BRCA1 carriers and 10% in BRCA2 carriers. At 15 years, cumulative risk increased to about 22% in BRCA1 carriers and remained at 10% in BRCA2 carriers. In non-carriers, cumulative risk was about 15% after 10 and 15 years since breast cancer diagnosis. Cumulative risks were significantly higher in BRCA1 mutation carriers compared with BRCA2 carriers at any time since breast cancer diagnosis (p=<0.001).	1) Medical records and pathological reports were incomplete in some cases. 2) Number of CBC in BRCA1/2 mutation carriers was relatively small. 3) Genetic testing was performed in a subset of the study population (n = 115 breast cancer cases).	Population-based study. Familial cancer history was confirmed through cancer registry data (review of medical records) in all cases, including sporadic breast cancer cases.	e Low
Kirova et al. 2010 [38] France Update of [52,53]	131 women treated with breast-conserving surgery and radiotherapy (during 1981 e2000) and with family history of breast or ovarian cancer, of which 27 presented a BRCA mutation. Each case was matched to two controls without family history of breast cancer (matched for: age at diagnosis, year of treatment, and follow-up period).	Diagnoses were verified on the basis of medical and pathological records for half of the patients.	Genetic screening was applied to women complying with family history criteria. Screening for the presence of point or small mutations was performed by analysis of PCR products from genomic DNA, with denaturing gradient gel electrophoresis.	Cumulative risk rates of CBC differed significantly between BRCA1/2 mutation carriers vs non-carriers (p < 0.001). The 10-year cumulative risk estimate was approximately 40%.	1) Only few women presented a positive BRCA mutation (n = 27). Relatively few CBC case in BRCA1/2 mutation carriers. Joint BRCA1/2 mutation carriers were considered. 2) Not all the breast cancer cases were confirmed through review of medical records. 3) Control group (without family history) did not undergo genetic testing.	Controls selected from a breast cancer registry who underwent conservative treatment and with the same treatment protocols.	e Low
Garcia-Etienne	54 women with BRCA1/2	Diagnoses were	Denaturing gradient gel	Ten-year cumulative incidence	Only few CBC case in BRCA1/2	Controls selected from the same	+

et al. 2009	mutation and primary breast cancer, treated with breast	verified through medical records.	electrophoresis and direct DNA sequencing	of CBC was 25% for mutation	mutation carriers were documented. Joint BRCA1/2	institution; all underwent breast conservation therapy	Acceptable

(*continued on next page*)

Table 2 (*continued*)

Study [reference] Country	Study population	Breast cancer ascertainment	Genetic testing (methods and mutations analyzed)	Results	Limitations	Strengths	Methodological quality
[39] Italy	conservation therapy and radiotherapy. Each case was mathed with a sporadic breast cancer case for age, size of tumor, and year of surgery.			carriers and 1% for sporadic controls (p = 0.03).	mutation carriers were considered for analyses.	and radiotherapy. Mutation status was verified in the entire study population.	
Bonadona et al. 2007 [40] France	Cohort of 232 women with breast cancer (21 were BRCA1 carriers and 6 were BRCA2 carriers) ascertained prospectively during 1995 and 1997. Inclusion: invasive and histologically confirmed breast cancer before age 46 years.	Population-based cancer registry.	Entire coding sequences and intron-exon junctions of BRCA1/2 genes were analyzed by heteroduplex and DHPLC mutation techiniques.	Women with breast cancer and carrying BRCA1/2 mutations had a non statistically significant lower 5-year CBC-free survival rate (90%; 95% CI: 76.8-1.00) compared to non BRCA1/2 carriers (94.4%; 95% CI: 91.2-97.6, p = 0.3). The 5-year contralateral breast cancer-free survival rate did also not reach statistical significance for BRCA1 carriers (86.7%; CI: 69.5-1.00). This rate was not significantly different to non-carriers (p = 0.4).	1) Small sample size may have limited statistical power to conduct stratified analyses. It was not possible to derive results for BRCA2 mutation carriers. 2) 230 women did not participate in the genetic testing study and were, therefore, not included.	Population-based prospective study. Breast cancer cases were ascertained several years before BRCA mutation status was assigned. Only first incident and histologically confirmed breast cancer cases were included.	++ High
Brekelmans et al. 2007 [26] The Netherlands Update of [48]	Cohort of 103 breast cancer cases from families with a BRCA2 mutation, 223 breast cancer cases from families with a BRCA1 mutation and 311 breast cancer cases without a BRCA1/2 mutation, all ascertained from the Rotterdam Family Cancer Clinic. In addition, a cohort of 759 breast cancer cases without family history (sporadic cohort) was selected through population-based cancer registries. Inclusion: women with primary invasive breast cancer and having a family history of breast or ovarian cancer. Exclusion: breast cancer cases undergoing genetic testing two or more years after breast cancer diagnosis.	Histophatology records and medical records.	Exon-intronic regions (3, 5-10, 11e23) of the BRCA1 and BRCA2 genes were screened using denaturing gradient, protein truncation test, and detection of large genomic deletions using multiplex ligation-dependent probe amplification.	The 5-year cumulative risk of contralateral breast cancer was 17%, 13%, 5% and 3% for in BRCA2, BRCA1, non BRCA1/2 mutation carriers and in the sporadic breast cancer control group, respectively. Cumulative risk estimates for 10 years were: 20%, 25%, 6% and 5%, respectively. The HR for CBC development was 5.83 (95% CI: 3.32e10.26) for BRCA1 mutation carriers, 6.09 (95% CI: 3.14e1.67) for BRCA2 mutation carriers and 1.67 (95% CI: 0.85e3.27) for non-BRCA mutation carriers. Difference in 5 and 10 year cumulative CBC risks between BRCA2-associated tumours and BRCA1 was not statistically significant (p = 0.72).	1) Matched control group with unknown mutation status (only history family records were reviewed). 2) Although CBC is less frequent in the non-BRCA mutation group compared with the sporadic breast cancer control group, selection bias might be present.	Control group (sporadic breast cancer cases) selected from population-based cancer registries. All were free of breast cancer family history as verified through medical records. Including cases with a breast cancer occurred long before the mutation testing has possibly leaded to longevity bias (preferential selection of long-living cases). To minimize this, all cases of hereditary breast cancer were included and a distinction was made for index patients undergoing genetic testing 2 years after their breast cancer diagnosis and unselected cases for the remaining cases. Cases undergoing genetic testing after two or more years since breast cancer diagnosis were excluded.	+ Acceptable
Pierce et al. 2006 [27] USA, Canada, Israel	Cohort of 160 women carrying a BRCA1/2 mutation and treated with breast conservation therapy, matched	Medical records.	Protein-truncating testing, conformation-sensitive electrophoresis, allelic discrimintation assay and direct	The 10-year cumulative risks of CBC were 26% (95% CI:22% e30%) in BRCA1/2 mutation carriers compared with 3% (95%	1) Matched control group with unknown mutation status (genetic testing was not applied to the control group and only	Competing risks were accounted for (mastectomy, ovarian cancer and death) to estimate cumulative risks.	+ Acceptable

Update of [49]	by age and date of diagnosis with 445 sporadic controls, which were randomly selected from the oncology databases of each participating institution. Inclusion: women with primary and invasive stage I/II breast	sequencing of DNA. Controls did not underwent genetic testing.	CI: 2%e4%) in sporadic controls, whilst the 15-year cumulative risk was 39% (95% CI: 31%e47%) in mutation carriers and 7% (95% CI: 5%e10%) in sporadic controls. [Pierce et al., 2000: the 5-year cumulative risks of CBC	history family records were reviewed). 2) Factors influencing CBC ocurrence, such as tamoxifen use and bilateral oophorectomy, were not considered.	Selection bias was minimized by selecting patients randomly from the radiation oncology database of each participating center.

	cancer, a proven BRCA1/2 mutation and treated with breast conservation therapy. In addition, for controls only those with no more than one postmenopausal relative with breast cancer and no family history of ovarian cancer were included.			were: 20% for the BRCA1/2 mutation carriers and 5% for the sporadic controls]. Differences in CBC rates between the BRCA1/2 mutation carriers and the non-carriers (controls) were greater among mutation carriers who had not undergone oophorectomy compared with controls, with 5-, 10-, and 15-year estimates of CBC in mutation carriers of 16%, 34%, and 45% v 1%, 4%, and 9% in controls, respectively.			
Robson et al. 2005 [28] USA	Cohort of 87 women carrying a BRCA1/2 mutation and with a positive family history. Inclusion: women diagnosed with invasive breast cancer, carrying a BRCA1/2 mutation, and treated with breast-conserving therapy.	Genetic counseling record, clinical records and self-reported by the patient if needed.	Mutations identified through complete coding sequence analysis or analysis of specific founder mutations, and further verified through direct DNA sequencing.	The 5-, 10-, and 15-year probability of remaining free of CBC were 88.1% (cumulative risk = 11.9%), 62.4% (cumulative risk = 37.6%) and 46.8% (cumulative risk = 53.2%), respectively, overall in BRCA1/2 mutation carriers. Estimated crude annual incidence of CBC was 39.3 per 1000 women-years.	1) A control group of non-BRCA carriers was not considered. 2) Small sample size. 3) Competing cause of death was not considered in data analysis. 3) Women who have survived breast cancer were more prone to undergo genetic testing and cancer surveillance (survival bias).	Unknown mutation carriers were excluded from the study population. Effect of treatment (breast conserving therapy and use of tamoxifen or chemotherapy) was considered.	e Low
Robson et al. 2004 [29] USA Update of [50,51]	Cohort of 584 Jewish women with breast cancer. Final study sample was of 496 women in whom genotyping was completed. Inclusion: Jewish women diagnosed with invasive breast cancer less than 65 years of age and undergoing breast-conserving surgery and radiotherapy, with or without axilary node dissection. Available paraffin-embedded tissue and follow-up information. Exclusion: women with unknown mutation status (failed genetic tests).	Clinical databases from the Departments of Patholology Surgery, and Radiation Therapy were used.	DNA was isolated from the tissue blocks (paraffin-embedded) and analyzed by PCR amplification of the regions surrounding the Ashkenazi founder mutations 185delAG and 5382insC in BRCA1 and 6174delT in BRCA2). Variant bands were confirmed by direct sequencing or and independent PRC amplification of the sample.	The 10-year cumulative risks of CBC were 27% in BRCA1 carriers and 32% in BRCA2 carriers ($p > 0.05$), while in non-carriers the risk was of 8% ($p < 0.0001$).	1) Only known deleterious BRCA1/2 mutations were tested; other mutant alleles that also may confer risk were not tested. 2) The increased CBC risk could be attributed to radiation-therapy.	Competing risk analysis was accounted for (chemotherapy, tamoxifen and death). The population study of Ashkenazi Jewish origin harbours more frequently BRCA1/2 mutations. All women underwent genetic testing. Unknown mutations status was an exclusion criteria. Genetic testing was performed on tissue blocks; thus, CBC risk could be estimated for all women regardles of vital status	+ Acceptable
Haffty et al. 2002 [30] USA	Cohort of 127 women with breast cancer, of which 22 harboured a mutation in BRCA1/2 genes, while the remaining 105 women were classified as sporadic cases (including wild-type, known polymorphisms and variants of unknown significance). Inclusion: women diagnosed at age 42 years or younger with invasive breast cancer and undergoing conservative	Not stated. Cases were recruited through Radiology Department at University School.	Sequencing of BRCA1/2 through PCR and sequencing reactions. There were 22 women with deterious mutations in the study population (15 in BRCA1 and 7 in BRCA2).	After 10 years of follow-up, 31% of women carrying a BRCA1/2 mutation developed a CBC with respect to 7% of women in the sporadic group ($p = 0.001$). The	1) Women who died were excluded (survival bias). 2) The study population was comprised by women with breast cancer and treated with surgery and radiotherapy. Participants who agreed to	All women underwent complete genetic testing. Unclear genetic variants were classified in both the genetic and the sporadic group in	+ Acceptable
					proportion of women free of relapse in the contralateral breast was about 80% (cumulative risk about 20%)	after 10 years of follow-up. In the sporadic group,	this proportion reached about 95% (cumulative risk about 5%).

conservative surgery followed by radiotherapy. Other treatments were not considered.

separate analyses for comparison.

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Table 2 (*continued*)

Study [reference] Country	Study population	Breast cancer ascertainment	Genetic testing (methods and mutations analyzed)	Results	Limitations	Strengths	Methodological quality
	participate and alive at recruitment were included.						
Eccles et al. 2001 [31] UK	Cohort of 180 women with familial breast cancer (breast cancer diagnoised under 40 years of age); 75 women had a BRCA1 mutation. 49 women with sporadic breast cancer and without a documented family history, matched by age and year of diagnosis (±5 years), were ascertained as a control group. Inclusion: women diagnosed at 40 years or younger with invasive breast cancer between 1959 and 1996, with clinical notes and a full pedigree constructed.	Not stated. Cases were recruited through breast clinics and a hospital surgical database (controls).	PCR (185delAG and 5382insC for BRCA1). Only samples that were positive on at least two independent PCRbased assays were considered positive. All women, except those of the sporadic control group, underwent genetic testing.	The 5- and 10-year cumulative risks of CBC in women with a known BRCA1 mutation and positive family history was of 22% and 40%, respectively, while in family history negative women the cumulative risk was 6% and 11%, respectively.	1) Matched control group with unknown mutation status and considered as family history negative (genetic testing was not applied to the control group). 2) Invasive and non-invasive breast cancer was considered for CBC case ascertainment.	Risk estimates were calculated for known BRCA1 carriers and unknown mutation carriers separately. Treatment outcomes (bilateral mastectomy and breast conserving surgery) were analyzed in relation to CBC risk.	e Low
Hamann et al. 2000 [32] Germany	Cohort of 36 breast and/or ovarian cancer high-risk families of which 85 women developed a breast cancer (36 BRCA1 carriers from 13 families and 49 non-carriers from 23 families). Inclusion: women diagnosed with a first primary invasive breast cancer between 1961 and 1994.	Pathology records in most cases (n = 70) and self-reports if unavailable (15 cases). CBC was documented through medical records,physicians or reported by the affected woman or her relatives.	Single strand conformational polymorphism analysis, protein truncation test, heteroduplex analysis, sequencing analysis and PCR amplification detection. Genetic testing for BRCA1 performed for some but not all breast cancer cases. BRCA1 mutation status was also assesed through their relation to familiar tested carriers. For those who died, genetic testing was performed in children of affected patients.	The 5- and 10-year cumulative risks of CBC was of 24% and 42% in BRCA1 carriers, respectively, while in non-carriers the cumulative risk was 6% at both 5 and 10 years since breast cancer diagnosis (p = 0.04 between BRCA1 carriers and non-carriers).	1) The study sample was ascertained from high-risk families. 2) Synchronous and metachronous CBC were both included.	All women who were BRCA1 carriers were included idenpendently of vital status to minimize longevity bias. The index patient was excluded in sensitivity analyses.	e Low
Verhoog et al. 2000 [33] The Netherlands	Cohort of 164 women with breast cancer ascertained from 83 high-risk families. 129 of these cases had a proven BRCA1 mutation. Inclusion: women with histologically confirmed invasive breast cancer and from high-risk families. Exclusion: women with synchronous bilateral breast cancer, women who were proven non-BRCA1 carriers and women who underwent bilateral mastectomy after breast cancer diagnosis.	Pathology reports and hospital records.	BRCA1 mutation was tested through protein truncation test, allele-specific oligonucleotide hybrization and by PCR analysis.	Cumulative risk after 5 and 10 years of follow up was: 21% and 27% in women under 40 years at breast cancer diagnosis, respectively, 33% and 52% in women aged 41e50 years, respectively, and 4% and 15% in women aged 51-50 years, respectively. In the group of women younger than 50 years, the cumulative risks were 30% after 5 years of follow-up and 40% after 10 years of follow-up.	1) A control group of non-BRCA carriers was not considered. 2) The study population was ascertained through a Family Cancer Clinic. 2) Genetic testing was not applied to the entire study population. Non mutation carriers were excluded but those with unknwon mutation status were still kept in the study population (selection bias).	Diagnosis of breast cancer was confirmed. Analyses were restricted to knwon BRCA1 mutation status analyses.	e Low
Verhoog et al. 1999 [34] The	Cohort of 28 women with breast cancer ascertained from 14 high-risk families (Family	Pathology reports and hospital records.	BRCA2 mutation was tested through protein truncation test, allele-specific oligonucleotide	CBCefree probability for patients with BRCA2-associated (n = 27) or sporadic	1) Small sample size. 2) Matched control group with unknown mutation status	Histologically confirmed cases were included only. Probands were excluded in sensitivity	e Low

Netherlands	Cancer Clinic). 22 had a proven BRCA2 mutation and six were considered probands. Control	hybrization and by PCR analysis. All women, except	breast cancer (n = 109) since 10 years after first breast cancer diagnosis was about 73%	(genetic testing was not applied to the control group). 3) Non mutation carriers were	analysis to evaluate the presence of longevity bias. Synchronous contralateral	

	group of 112 breast cancer cases was matched by (1:4) for age and date of breast cancer diagnosis (population-based cancer registry). Inclusion: Families with an identified mutation in the BRCA2 gene and complete follow-up data. Each family included one or more patients with histologically confirmed breast cancer for whom data was available through hospital records.		those of the control group, underwent genetic testing.	(cumulative risk = 27%) and about 90% (cumulative risk = 10%), respectively. After 20 years since breast cancer diagnosis, CBC-free probability was of about 62.5% in BRCA2 carriers (cumulative risk = 37.5%) while was kept around 90% in the control group.	excluded but those with unknwon mutation status were still kept in the study population (selection bias).	breast cancer cases were excluded for CBC risk estimates.	
Easton et al. 1999 [35] Europe, Canada and USA	Cohort of 173 high-risk families with BRCA2 mutations. Three cohorts were considered: 1) women with breast cancer under age 60 years (n = 800, of which 363 were known mutation carriers); 2) unaffected known mutation carriers (n = 622); 3) first-degree relatives of affected individuals of the first group or of known carriers (n = 3271, of which 471 were known carriers, 390 were non-carriers and 2186 had an unknown mutation status). Inclusion: families with positive BRCA2 genetic testing or with breast cancer cases among women under age 30 years or with one or more affected individuals with breast cancer diagnosed under age 60 years, depending on the center of ascertainmnent.	Self-reported by the families. 48% of the cases were confirmed by pathology reports, clinical records or death certificate.	Method not stated but it is reported that genetic testing was performed by direct mutation testing or segregation of linked haplotypes.	Cumulative risk by age 70 years was 52.3% (95% CI: 41.7e61.0), and of 17.7% (95% CI: 6.5e27.5) by age 40 years, of 37% (95% CI: 25.7e46.6) by age 50 and of 57.1% (95% CI: 46.4e65.6) by age 80 years. Incidence rates were of 2e3% per year between the ages of 30 and 60 years.	1) Study population constituted by high-risk families. 2) An important number of cases did not underwent genetic testing but were considered as mutation carriers based on carrier probability of each relative. 3) Cases with unknown mutations status were included in data analysis. 4) An important proportion of second cancer cases (CBC) were not confirmed through pathology or medical records.	Large study population of BRCA2 high-risk families. The first breast cancer documented in each individual was considered to minimize ascertainment bias.	e Low
Ford et al. 1994 [36] Europe and USA	Cohort of 33 high-risk families with BRCA1 mutations, contributing with 1327 BRCA1 women with breast cancer and evidence of BRCA1 mutation. Inclusion: 1327 invasive breast cancer cases and their first degree relatives of which 464 were proven BRCA1 carriers by marker typing or age 60 years or younger at breast cancer diagnosis, 221 were non BRCA1 carriers by marker typing and 642 cases had an unknown mutation status. Second cancers in the breast occurring within 3 years of the first were excluded.	Some cases were histopathologically confirmed, others were validated through clinical records or death ceritificates, and others were self-reported by the families.	Genetic testing not performed. Probability of linkage to BRCA1 was assesed through a risk score (LOD) and typing of markers closely linked to BRCA1. Individuals from high risk families were assumed to be BRCA1 carriers provided that marker typing resulted negative or if they had breast cancer before age 60 years and an unknown mutation status.	Cumulative risk in BRCA1 carriers was 48% by age 50 years and 64% by age 70 years. CBC risk was estimated as age-specific incidence rates.	1) Genetic testing was not consistently applied. 2) A large proportion of individuals with an unknown mutation carrier status were included (selection bias).	Breast cancer diagnosis was confirmed in almost all breast cancer and CBC events.	e Low

available in the study (text or curves) and/or through additional data requested to the authors in some cases (authors of all selected studies were contacted to complete data not available in the published manuscript).

Synthesis of results

The 5, 10, 15 or more cumulative probabilities (actuarial cumulative risk) of CBC for women who were *BRCA1/BRCA2* mutation carriers after the occurrence of the first primary breast tumor.

Cumulative risks were estimated from KaplaneMeier survival curves for studies reporting free CBC survival as this denotes the probability of staying free of contralateral breast cancer after a specified duration of time (age or time interval between the first and second cancer in the breast). Results with a $p > 0.05$ or 95% confidence intervals (CI) including 1 were deemed not significant. Cumulative probabilities by age at first breast cancer diagnosis and by age were also extracted.

Meta-analysis

Meta-analyses were performed for risk of CBC by time (5, 10 and 15 years) since diagnosis of the first breast cancer. We carried out separate analyses in *BRCA1* and *BRCA2* mutation carriers as well as in women who carried either *BRCA1* or *BRCA2* mutations, and non-carriers. Insufficient data on cumulative risks of CBC beyond 15 years since the first breast cancer diagnosis or by age groups impeded the calculation of pooled effect estimates for these strata.

In addition, we extracted or calculated standard errors, which were derived from confidence limits, applying the formula Standard Error (SE) = log (upper limit of 95% CI/lower limit of 95% CI)/(1.96*2). Based on the SE, we estimated the weight of each study and pooled risks in our analysis using both fixed-effects and random effects-models. We used the summary estimates from the random effects models of meta-analyses as the main results because they tend to give a more conservative estimate when between-study heterogeneity is present.

The SE could be only derived when the *p*-value or the CI was reported in the study or provided by the author. Therefore, only studies with this information available could be pooled.

Statistical heterogeneity of data included in the pooled analysis was estimated by calculation of the Cochran's Q statistic value. Besides, sources of heterogeneity attributable to study characteristics were further explored [19]. Meta-regression was applied to analyze the effect of age at diagnosis of the first breast cancer, age at diagnosis of the contralateral breast cancer, treatment (yes vs no, adjuvant and/or prophylactic treatment), women with unknown mutation status (yes vs no), duration of follow-up, study design (retrospective vs prospective) and study quality (high vs acceptable) on the estimates. The influence of one study on the overall meta-analysis estimate was also analyzed. Publication bias was investigated using funnel plots [20], and evaluated through Begg's [21] and Egger's [22] tests.

We used STATA (12.0; College Station, TX) and R (3.0.1) statistical software for the data analysis.

The PRISMA guidelines (27 item checklist and a four phase flow diagram) to report systematic reviews and meta-analyses were followed [23].

Results

Results of the bibliographical search

A total number of 1324 articles were retrieved through the search. Secondary searches in reference lists of selected studies

retrieved other 18 studies. Ninety were ruled out because of duplication. 1186 studies were also excluded based on their abstracts or titles, leaving a total of 66 articles for the "*in extenso*" analysis. Of these, 46 articles were again ruled out for different causes (Fig. 1). The final selection was made up of 20 articles: 18 retrospective studies [15,16,24e39], including twelve cohort studies [15,16,24,27e30,32e36], five caseecontrol studies [25,26,31,38,39], and a nested caseecontrol study [37], and 2 pro- spective cohort studies [17,40]. Two systematic reviews related to the risk of CBC in *BRCA1/2* mutation carries were also found, although they did not specifically address cumulative risk of CBC [10,41]. Besides, we identified three congress abstracts potentially eligible for inclusion, which were excluded because no further details on the study population or results other than those reported in the abstracts could be retrieved [42e44]. We also excluded ten studies with study populations and study periods that overlapped with the selected studies: 3 studies [9,45,46] that overlapped with the study of Metcalfe et al. [16]; 1 study [47] that overlapped with the study of Rhiem et al. [15]; 1 study [48] that overlapped with the study of Brekelmans et al. [26]; 1 study [49] that overlapped with the study of Pierce et al. [27]; 2 studies [50,51] that overlapped with the studies of Robson et al. [28,29] and 2 studies [52,53] that overlapped with the study of Kirova et al. [38], so as to include the study analyzing the highest number of women with BRCA muta- tions. Other plausible overlaps between the studies were explored (e.g. references 27, 28, 29 and 15) but the study centers and/or study periods did not exactly coincide. However, it might be possible that a few participants of these studies had participated in more than one study.

Description of the studies

Details and characteristics of the studies are shown in Tables 1 and 2. Of the studies included, 15 were conducted by ascertain- ment of *BRCA* carriers among high risk families or genetic clinics [15e17,24,26e29,31e36,38]. Two were population-based [37,40], whereas the remaining were hospital-based series. Ascertainment of breast cancer cases was restricted by age at diagnosis in six studies [25,29e31,37,40]. The study populations differed with re- gard to sample size and characteristics of the study. The retrospective, multicenter, cohort study of Rhiem et al. included 6235 women with unilateral breast cancer from high risk families and was the study with the greatest sample size [15].

Five of the studies did not include non-carriers [16,17,27,28,33], nine studies included breast cancer cases with unknown mutation status [24e27,31,33e36], and all except three studies [16,28,33] presented a control group comprised by non-*BRCA* carriers with breast cancer [15,24e27,29,31,32,34,36e39], or *BRCA* carriers with unilateral breast cancer [17,28,30,35,40]. For example, the nested caseecontrol study of Malone et al. [37], compared patients with CBC diagnosed 1 year or more after a first primary breast cancer (n = 705) and controls with unilateral breast cancer(n = 1398), who were ascertained from an underlying population-based cohort of 52,536 women diagnosed with a first invasive breast cancer before age 55 years.

Among the non-*BRCA* carrier control group, there were six studies that included sporadic breast cancer cases [25e27,34,38,39], but only of them performed a genetic testing in this subgroup [39]. Other four studies used a matched control group for comparison with an unknown mutation status [24,31,35,36]. Only one of the selected studies did not use a control group [16].

There were several clinical characteristics of the first breast cancer that varied widely between the studies, such as stage of the tumor (whether restricted to stage I/II or not), or the type of treatment that

women with breast cancer received. Breast cancer was defined as invasive cancer in all studies, except in three studies that also considered ductal carcinomas in situ as CBC events [17,24,37]. A variety of mutation-screening techniques and targets were also used. Fourteen studies screened for mutations in both genes [15,16,24e30,37e40], four screened for mutations in *BRCA1* only [31e33,36], and two for BRCA2 mutations [34,35]. Only one study investigated specific founder mutations (in an Ashkenazi Jewish population) [29]. In two two of the selected studies, it was established that the entire study population underwent genetic testing [17,37]. One of these studies, a prospective cohort of 978 BRCA1 and 909 BRCA2 mutation carriers, reached the highest methodological [17].

Cumulative risks of CBC

Published actuarial cumulative risk estimates by *BRCA1/2* mutation status are summarized in Table 3. Most of the selected studies found a statistically significant higher risk of CBC for BRCA1/2 mutation carriers as compared to non-carriers (5-year cumulative risk of CBC ranging from 5% to 21% for BRCA1/2 mutation carriers and from 2% to 6% for non-carriers; 10-year cumulative risk of CBC ranging from 14% to 27% for BRCA1/2 mutation carriers and from 5% to 10% for the non-carrier cases).

For meta-analyses in *BRCA1/2* mutation carriers and in non-carriers by 5, 10 and 15-years of cumulative risk of CBC we pooled those studies with sufficient information [15e17,24,27,37,40] (Fig. 2). The pooled estimates revealed that cumulative risk of CBC increases over time in women with breast cancer if they are *BRCA1* mutation carriers (5-years = 15%; 95% CI: 9.5%e20%; 10-years = 27%; 95% CI: 21%e33%; 15-years = 33%; 95% CI: 28%e38%), or *BRCA2* carriers (5-years = 9%; 95% CI: 5%e14%; 10-years = 19%; 95% CI: 15%e23%; 15-years = 23%; 95% CI: 16%e29%). When BRCA1/2 mutations were combined, the cumulative risk of CBC also increases to a similar extent and proportionally to the time since the first breast cancer diagnosis (5-years = 14%; 10-years = 22%; 15-years = 33%). By contrast, the 5-year cumulative risk was remarkably lower in non-*BRCA* mutation carriers (3%) and remained so during the following 5 years (5%). We lacked the data necessary to evaluate the 15 years cumulative risk in non-carriers.

Meta-analysis restricted to prospective studies [17,40] revealed that the CBC cumulative risk is 23.4% (95% CI: 9.1%e39.5%) in BRCA1 carriers and 17.5% (95% CI: 9.1%e39.5%) in BRCA1/2 carriers after 5 years of the initial breast cancer diagnosis. In pooled analyses of the retrospective studies, these risks were lower and of similar magnitude in both carriers (11.5% and 11.1%, respectively). Interestingly, heterogeneity between studies was not statistically significant. In the remaining subgroup analyses there was only one prospective study available for analyses. Therefore, meta-analyses restricted only to retrospective studies could be performed. The results showed that CBC cumulative risks did not substantially change (e.g. BRCA1 at 10 years: 25%; 95% CI: 18.8%e31.6% and BRCA2 at 10 years: 18.9%; 95% IC: 13.6%e24.5%) (data not shown).

Heterogeneity was found to be statistically significant in pooled analyses for 5 and 10 years of cumulative risks. Meta-regression analysis revealed a statistically significant effect of study design ($p = 0.001$) on the estimates in BRCA1 and BRCA1/2 carriers at 5 years since the first breast cancer. No further variables affected the cumulative CBC risk estimates. We found no evidence of publication bias (data not shown).

The pooled estimates did not differ greatly between random- and fixed-effects models (e.g. considering fixed-effects model for 5-year cumulative risk in *BRCA*1 and *BRCA*2 mutations carriers: 12% (95% CI: 10e14% and 8% (95% CI: 6e9%), respectively).

Table 4 shows cumulative risk of CBC by age and age at diagnosis of the first breast cancer. Seven studies evaluated cumulative risk of

CBC by age [15e17,33,35e37]. As shown in these studies, CBC risk for BRCA mutation carries increases as age of first diagnosis de- creases [15,16,33,37].. Women carrying BRCA1/2 mutations and diagnosed with breast cancer between 25 and 54 years showed a 10-years CBC risk of 18.4% with this risk being increased at earlier ages (e.g. cumulative CBC risk at age 35e39 years = 23.7%) [37]. According to the study by Metcalfe et al., the cumulative risk of CBC at 5, 10 and 15 years was 14.2%, 23.9% and 37.6% for women <50 at
diagnosis, and 8.6%, 14.7% and 16.8% for women >50 at diagnosis [16]. This was also supported by the study of Rhiem et al.: the 10- years risk for BRCA1/2 mutation carriers was lower in women diagnosed with breast cancer at menopausal ages (10.4%), followed by women at perimenopausal ages (13.4%), while it was notably increased in women at premenopausal ages at first breast cancer diagnosis (18.4%) [15]. It was not possible to perform a meta- analysis by age groups due to lack of data.

Discussion

This systematic review and meta-analysis is the first quantifying the cumulative risk of CBC in breast cancer patients who are *BRCA1/ 2* mutation carriers. Our results suggest an increased cumulative risk of CBC in women with breast cancer and carrying mutations in *BRCA1* or *BRCA2* genes with this risk increasing as time since diagnosis of the first breast cancer passes. The pooled cumulative risk of CBC since breast cancer diagnosis increases from 15% at 5 years to 27% at 10 years and to 33% at 15 years in BRCA1 carriers, and from 9% at 5 years to 19% at 10 years and to 23% at 15 years in *BRCA2* carriers. In contrast, breast cancer patients who were non- carriers present a substantially lower cumulative risk of CBC (3% at 5 years) that remained so over time (5% at 10 years). The con- sistency of these findings is supported by a previous systematic review on prognosis of BRCA-associated breast cancer, which re- ported an estimated 10-year cumulative CBC risk ranging from 20 to 42% in BRCA carriers and from 5 to 6% in non-carriers [11]. These results are roughly in the region of our pooled cumulative CBC risk estimates (10-year cumulative CBC risk of 22% in BRCA1/2 carriers and of 5% in non-carriers), although it has to be taken into consideration that we provide pooled estimates of cumulative CBC risk, for BRCA1, BRCA2 and BRCA1/2 carriers, and that more recently published studies were included in our review.

BRCA-associated CBC after a first breast tumor can be attributed to genetic predisposition, but it can also be related to the same external factors that cause CBC among non-carriers, including hormonal and reproductive factors [8]. The fact that CBC risk is greater for women diagnosed with first breast cancer at younger ages (i.e. 10-year cumulative CBC risk in women younger than 50 years ranges from 18.4% to 23.9% [16,37] versus 14.7% in women of older ages [16]) reflects their stronger genetic predisposition [8]. Regarding factors that may predispose to breast cancer in *BRCA1/2* mutation carriers, some of them namely early age at first birth and smoking-have been established as modifiers of breast cancer risk in a recent meta-analysis of 44 studies [54]. These factors may in turn also confer a higher risk of CBC in *BRCA*1/2 mutation carriers.

The higher lifetime risk of CBC in *BRCA*1 mutation carriers compared to *BRCA*2 carriers is not surprising given that the magnitude of breast cancer risk differs depending on whether the germline mutation is in the *BRCA*1 or *BRCA*2 gene [55]. It could be moreover attributed to the different pathological features of the tumors caused by *BRCA*1 and *BRCA*2 mutations. As such, *BRCA*1- associated breast cancer usually presents a more aggressive phenotype (commonly medullary-like, triple negative ER-, PgR- and Her2-and showing a “basal” phenotype), while tumors in *BRCA*2 mutation carriers do not show a specific morphological

Table 3
Actuarial cumulative risk estimates by time after Breast Cancer Diagnosis (years).

Study [Reference]	Years after first BC	*BRCA1* Mutation Carrier		*BRCA2* Mutation Carrier		*BRCA1/2* Mutation Carrier		Noncarriers	
		Cumulative Risk (%)	95 % CI	Cumulative Risk (%)	95 % CI	Cumulative Risk (%)	95 % CI	Cumulative Risk (%)	95 % CI
Mavaddat et al. 2013 [17]	5	29.1[x]	23.2e36.6	12.6[x]	8.6e18.5	21.7[x]	17.8e26.4	NA	NA
	10	33.5[x]	25.8e41.2	19.5[x]	14.2e24.8	27.1[x]	17.3e36.9	NA	NA
	15	35.3[x]	28.1e42.4	19.2[x]	10.3e28.1	28.0[x]	22.4e33.6	NA	NA
Rhiem et al. 2012 [15]	5	10.4[¶]	8.3e12.5	4.5[¶]	2.5e6.5	e	e	3.9[¶]	3.2e4.6
	10	20.4[¶]	17.1e23.7	13.2[¶]	9.2e17.2	e	e	7.1[¶]	6.0e8.2
	15	28.7[¶]	24.4e32.9	19.0[¶]	13.5e24.4	e	e	9.9[¶]	8.5e11.4
	20	e	e	e	e	e	e	e	e
	25	44.1[¶]	37.6e50.6	33.5	22.4e44.7	e	e	17.2[¶]	14.5e19.9
Metcalfe et al. 2011 [16]	5	13.7[¶,a]	10.9e16.5	12.0[¶,a]	9.2e14.8	13.1[¶]	10.3e15.9	NA	NA
	10	23.8[¶,a]	21.0e26.6	18.7[¶,a]	15.9e18.7	22.0[¶]	19.2e26.8	NA	NA
	15	36.1[¶,a]	30.9e41.3	28.5[¶,a]	23.3e33.7	33.8[¶]	28.6e39.0	NA	NA
Malone et al. 2010 [37]	5	10.9[¶]	6.7e17.5	8.3[¶]	4.8e14.2	9.7[¶]	8.4e11.2	2.5[¶]	2.3e2.7
	10	20.5[¶]	12.7e33.0	15.9[¶]	9.2e27.2	18.4[¶]	16.0e21.3	4.9[¶]	4.5e5.4
	15	e	e	e	e	e	e	e	e
Van der Kolk et al. 2010 [24]	5	e	e	e	e	e	e	e	e
	10	34.2	29.4e39.0	29.2	22.9e35.5	e	e	e	e
	15	e	e	e	e	e	e	e	e
	20	42.8	e	49.8	e	e	e	e	e
Evans et al. 2010 [25]	5	0[x]	0e6	0[#]	e	4.2[x]	0e12.3	6.3[x]	0.9e11.6
	10	13.8[x]	0e32.4	10[#]	e	13.9[x]	0e29.1	9.0[x]	0.3e15.5
	15	22.5[x]	0e46.2	30[#]	e	21.7[x]	1.1e42.3	9.0[x]	0.3e15.5
	20	41.8[x]	0e83.8	30[#]	e	37.4[x]	2.6e72.2	14.1[x]	0.5e23.3
Kirova et al.. 2010 [38]	5	e	e	e	e	25[#]	e	5[#]	e
	10	e	e	e	e	40[#]	e	10[#]	e
	15	e	e	e	e	50[#]	e	20[#]	e
Garcia-Etienne et al.. 2010 [39]	5	e	e	e	e	0	e	1	e
	10	e	e	e	e	25	e	1	e
	15	e	e	e	e	e	e	e	e
Bonadona et al. 2007 [40]	5	13.3[¶]	0e30.5	e	e	10[¶]	0e23.2	5.6[¶]	2.4e8.8
	10	e	e	e	e	e	e	e	e
	15	e	e	e	e	e	e	e	e
Brekelmans et al. 2007 [26]	5	13[¶]	e	17[¶]	e	e	e	5[¶]	e
	10	25[¶]	e	20[¶]	e	e	e	6[¶]	e
	15	e	e	e	e	e	e	e	e
Pierce et al. 2006 [27]	5	e	e	e	e	e	e	e	e
	10	e	e	e	e	26[¶]	22e30	3[¶]	2e4
	15	e	e	e	e	39[¶]	31e47	7[¶]	5- 10
Robson et al. 2005 [28]	5	e	e	e	e	11.9	e	NA	NA
	10	e	e	e	e	37.6	e	NA	NA
	15	e	e	e	e	53.2	e	NA	NA
Robson et al. 2004 [29]	5	e	e	e	e	e	e	e	e
	10	27[¶]	e	32[¶]	e	e	e	e	e
	15	e	e	e	e	e	e	e	e
Haffty et al. 2002 [30]	5	e	e	e	e	e	e	e	e
	10	e	e	e	e	20[¶]	e	5[¶]	e
	15	e	e	e	e	e	e	e	e
Eccles et al. 2001 [31]	5	22[¶]	e	NA	NA	NA	NA	6[¶]	e
	10	40[¶]	e	NA	NA	NA	NA	11[¶]	e
	15	e	e	NA	NA	NA	NA	e	e
Hamann et al. 2000 [32]	5	24[¶]	e	NA	NA	NA	NA	6[¶]	e
	10	42[¶]	e	NA	NA	NA	NA	6[¶]	e
	15	e	e	NA	NA	NA	NA	e	e
Verhoog et al. 2000 [33]	5	24[¶]	e	NA	NA	NA	NA	NA	NA
	10	34[¶]	e	NA	NA	NA	NA	NA	NA
	15	e	e	NA	NA	NA	NA	NA	NA
Verhoog et al. 1999 [34]	5	NA	NA	12[¶]	e	NA	NA	2[¶]	e
	10	NA	NA	28[#]	e	NA	NA	10[#]	e
	15	NA	NA	37[#]	e	NA	NA	10[#]	e

Only studies reporting actuarial cumulative CBS risks are shown.
e: not stated.
NA: not applicable if non-carriers or BRCA1/2 carriers were not accounted for.
[¶]Cumulative risk was reported in tables and text.
[#]Cumulative risk was approximately extrapolated from incidence or disease free survival curves.
[x]Cumulative risk was reported by the author (previously contacted).
[a] Confidence intervals were calculated from the information provided in the article.

phenotype [56]. Triple negative tumors cannot benefit from any type of hormone therapy, which may also contribute to the increased risk of CBC in women with breast cancer and carrying a BRCA1 mutation [13]

A substantial body of literature is available on the effect of *BRCA*1/2 mutation on the CBC lifetime risk in women previously diagnosed with a first primary breast cancer, but only two of the studies published so far are prospective cohorts [17,40].

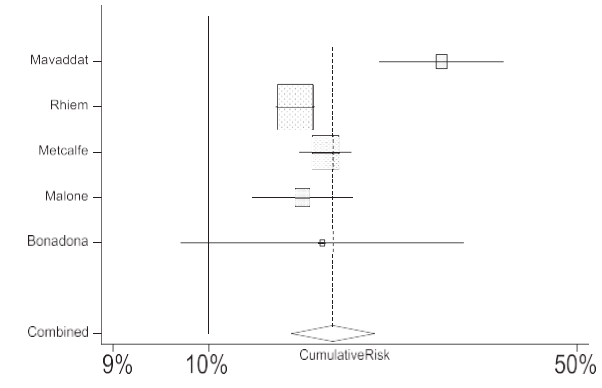
Retrospective cohort studies are subjected to the well-known selection and information biases. Apart from the study design, other differences confined to methodological issues (study design, study population and selection criteria, definition of breast cancer, definition of family history of breast cancer, genetic testing applied to the entire study sample or to a subset or even analysis of specific mutations) also limited the comparability of the selected studies and may account for the statistically significant heterogeneity in the estimates of combined CBC cumulative risks. Another source of heterogeneity between the studies could be related to differences in the type of adjuvant treatment that women received, as well as to differences in treatment protocols for breast cancer or variations in these protocols over time. Some studies also included an important proportion of women undergoing prophylactic treatments, which may also contribute to this heterogeneity. However, the meta-regression analyses revealed that there was no statistically significant effect of these variables on this risk except for study design (retrospective vs prospective studies). Since meta-regression was limited by the number of studies combined [57], a cautious interpretation of these results is required.

The studies also differed with respect to the inclusion or exclusion of index patients, population source, completion of cancer ascertainment and proven mutation status in the entire study populations or in a subsample. Most of the studies included female patients from genetic counselling clinics [15e17,24,26e29,31e36,38], which makes selection bias plausible because breast cancer is more prevalent among mutation carriers included in genetic screening programs [58,59]. Also, high-risk families are more likely to be diagnosed with breast cancer earlier because they are usually included in cancer surveillance programs [58]. The majority of the studies only included women who survived breast cancer and who had undergone a *BRCA* genetic testing [15,24,26e30,32e37]. Longevity bias is therefore another issue. Also, survival bias may have affected the results of the studies included in this review as women with a better prognosis (such as those with tumors of lower aggressiveness) survived sufficiently long to be eligible for the studies. Thus, findings reported in these studies are relevant for high-risk families but may not be extrapolated to the general population. Since the index cases are more likely selected based on clinical criteria (i.e. patients with younger age at breast cancer diagnosis and with clinical phenotypes that are more commonly related to *BRCA* mutations are those who usually undergo DNA testing) some studies excluded the index cases in sensitivity analyses so as to minimize these biases and to confirm the lifetime risk of CBC in affected carriers [15,24,26,32]. The inclusion of sporadic breast cancer cases is important to compare and contrast longevity bias, but only six studies accounted for this control group [25e27,34,38,39]. Despite a restrictive definition for negative family history in some sporadic control groups, a potential for misclassification of mutation carriers in this group was possible in these studies because mutation status was not verified. This may imply that some hereditary cases might have been included, tending to attenuate any differences between the two groups (cohort/cases and control group). However, absence of family history suggestive of hereditary breast cancer was checked in these studies through the review of medical records, so as to presume that the presence of *BRCA* mutation carriers was unlikely. Other studies used other control groups, either proven non-carriers [17,28e30,37,40] or uncertain non-carriers (i.e. not DNA tested) [24,27,31,35,36]; the latter one may lead to misclassification of mutation carriers in the control group too. It is unlikely that *BRCA*1/2 carriers affected with ovarian cancer were included in those studies that specified ascertainment of first primary breast cancer cases [15e17,25e27,29,34,37,40]. Women with *BRCA*-associated ovarian cancer have a lower risk of developing subsequent CBC than mutation carriers without ovarian cancer [60]. Studies that did not account for a first primary ovarian cancer might be therefore subjected to diluted effects of CBC cumulative risk.

Thus, the main methodological drawbacks of the selected studies are: 1) limited sample size (except in two studies that included more than 500 CBC cases [15,37]; 2) survival/longevity bias because being alive after the first breast cancer diagnosis is required in order to be included; 3) dilution bias as a consequence of the lack of genetic analysis among the study population or due to the inclusion of previous ovarian cancer events; 4) limited generalizability to the general population in studies of breast cancer families attending genetic counselling centres (although generalizable to mutation carriers in the general population). Prospective cohort studies and population-based studies would overcome these limitations, but would also request large sample sizes due to the low prevalence of *BRCA* mutations in the general population, and an extended follow-up in order to accrue a sufficient number of CBC events. Two population-based studies have examined the lifetime risk of CBC in *BRCA*1/2 mutation carriers [37,40], but both are still subjected to some limitations. The study by Malone et al. [37] included a large number of CBC cases but the prevalence of *BRCA1/2* mutations in the study population was not representative of the general population because, as in other retrospective studies [33], women with prophylactic mastectomy were excluded. These women are no longer at risk of CBC but risk estimates might differ from the general population of breast cancer patients. On the other hand, the study by Bonadona et al. [40] used a small sample size with an insufficient number of *BRCA*2 carriers, and did not prove mutation status in the entire study population. Selection bias in this study is, however, unlikely due to the prospective identification of CBC in a cohort of breast cancer cases ascertained long before *BRCA* status was assigned. The study by Mavaddat et al. [17] presented the highest methodological quality. This study presented, however, selection and information biases driven by the recruitment of the study population from high-risk families who self-reported data on their cancer diagnoses.

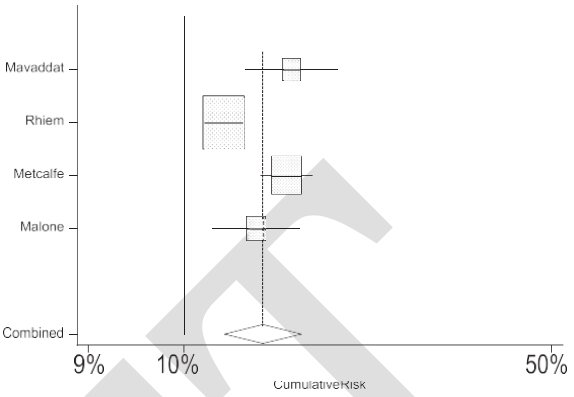
The effect of clinical and pathological characteristics of the first breast cancer on risk of CBC by *BRCA* mutation status was analyzed in seven studies [16,17,26,27,31,37,40]. Only two of these studies analyzed the influence of treatment-related factors, namely oophorectomy, on the lifetime risk of CBC [17,27]. Prophylactic breast-conserving surgery and oophorectomy in women carrying *BRCA* mutations reduce their lifetime risk of breast cancer and CBC [17,27]. This fact could also explain the higher lifetime risk of CBC in women who carry *BRCA*1 mutations in whom the effect of preventive surgery is weaker compared to *BRCA*2-carriers due to the higher rate of triple negative tumors in *BRCA1*-carriers. Hormone or anti-Her2 therapy could contribute to reduce the risk of CBC in breast cancer patients [61,62] but, as stated before, a lower preventive effect of CBC could be expected in BRCA1-carriers. However, studies that evaluated adjuvant tamoxifen treatment and risk reduction of CBC found similar results by mutation status [13,63e65]. A number of studies have given attention to risk reduction of breast cancer and CBC by treatment methods, such as salpingo-oopheroctomy [66e68], breast conserving therapy [66,10], radiotherapy [14] and chemotherapy or other adjuvant treatments [65] but their effect on CBC risk needs to be explored further with regard to the cumulative risk of CBC by BRCA1/2 mutation status, and the influence of factors that alters risk of CBC. Other factors that may affect CBC lifetime risk, such as age of menopause (natural or surgical) or hormone receptor status, amongst other factors, have not been explored.

Some limitations and strengths of the present study warrant consideration. Our study includes different study populations and study periods with varying treatment protocols for breast cancer,



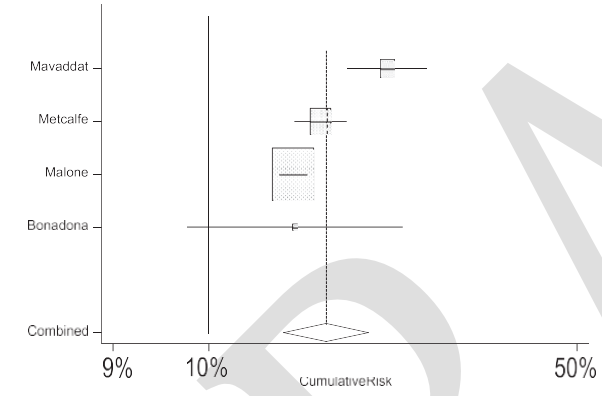
A1

Cumulative risk = 15%; 95% CI: 9.5%-20%
Test for heterogeneity: Q = 20.716 (p=<0.001)



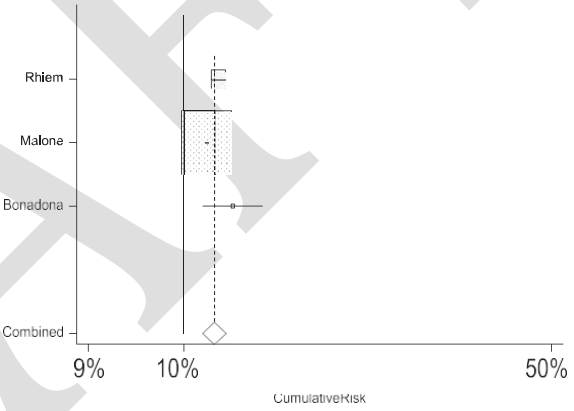
A2

Cumulative risk = 9%; 95% CI: 5%-14%
Test for heterogeneity: Q = 18.599 (p=<0.001)



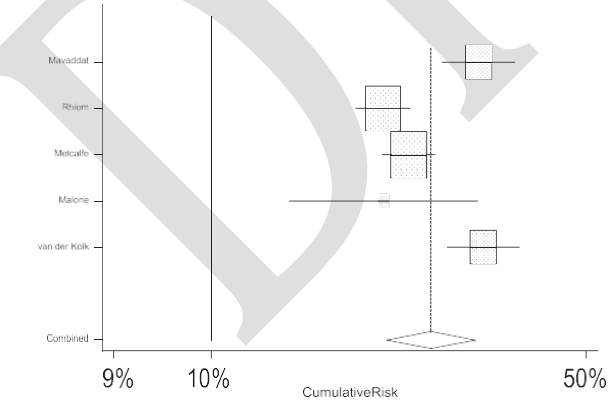
A3

Cumulative risk = 14%; 95% CI: 9%-19%
Test for heterogeneity: Q = 21.079 (p=<0.001)



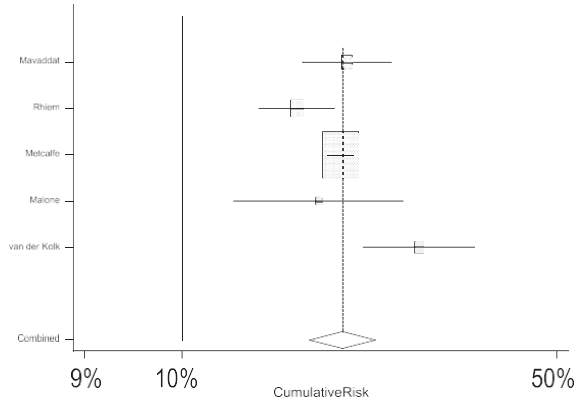
A4

Cumulative risk = 3%; 95% CI: 2%-5%
Test for heterogeneity: Q = 14.597 (p=0.001)



B1

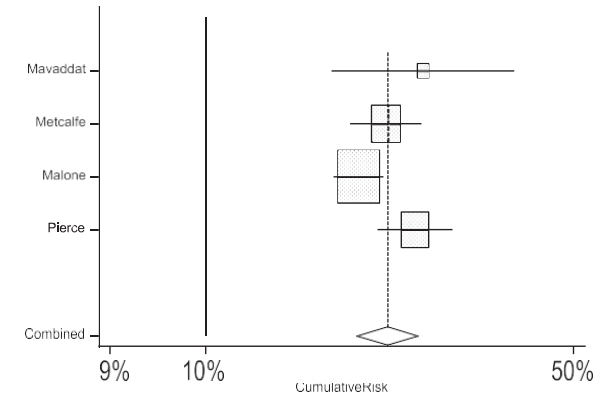
Cumulative risk = 27%; 95% CI: 21%-33%
Test for heterogeneity: Q = 29.677 (p=<0.001)

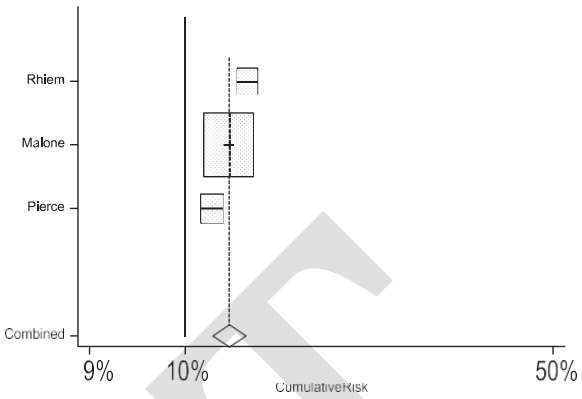


B2

Cumulative risk = 19%; 95% CI: 15%-23%
Test for heterogeneity: Q = 13.090 (p=0.011)

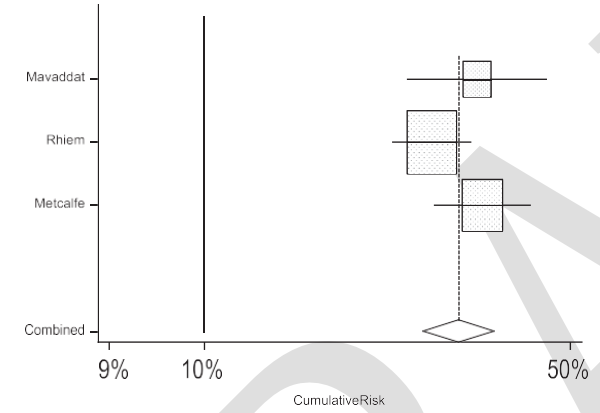
Fig. 2. Meta-analysis of CBD cumulative risk by time after diagnosis of the first primary breast cancer. A) Cumulative risk at 5 years after the diagnosis in BRCA1 (A1), BRCA2 (A2), BRCA1/2 (A3) mutation carriers and non-carriers (A4). B) Cumulative risk at 10 years after the diagnosis in BRCA1 (B1), BRCA2 (B2), BRCA1/2 (B3) mutation carriers and non-carriers (B4). C) Cumulative risk at 15 years after the diagnosis in BRCA1 (C1), BRCA2 (C2), and BRCA1/2 (C3) mutation carriers. The dashed vertical line represents the combined estimate, and the shaped box the size of the squares in terms of weight of each study in the meta-analysis. Error bars indicate 95% confidence interval.





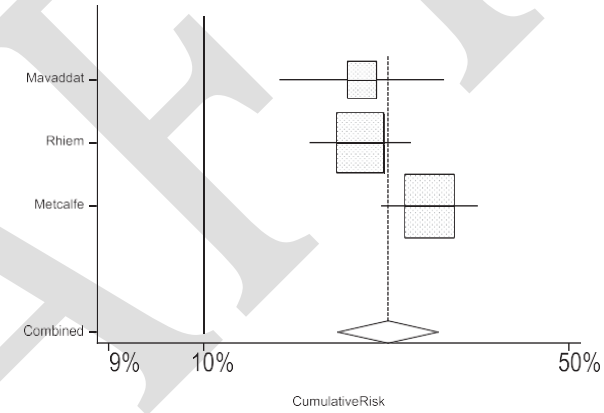
B3

Cumulative risk = 22%; 95% CI: 18%-27%
Test for heterogeneity: Q = 7.792 (p=0.051)



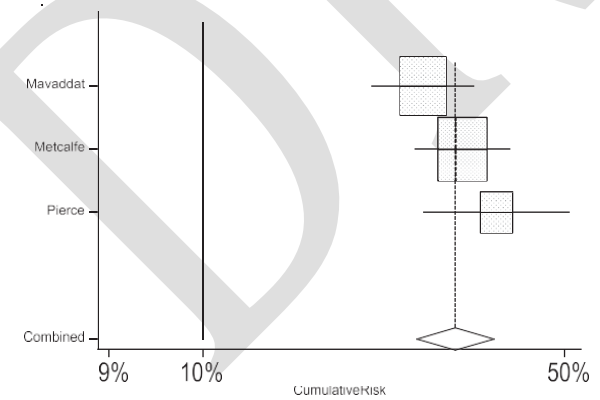
B4

Cumulative risk = 5%; 95% CI: 3%-7%
Test for heterogeneity: Q = 25.466 (p=<0.001)



C1

Cumulative risk = 33%; 95% CI: 28%-38%
Test for heterogeneity: Q = 3.186 (p=0.203)



C2

Cumulative risk = 23%; 95% CI: 16%-29%
Test for heterogeneity: Q = 4.510 (p=0.105)

C3

Cumulative risk = 33%; 95% CI: 27%-39%
Test for heterogeneity: Q = 4.071 (p=0.131)

Fig. 2. (*continued*).

from both hospital (mainly genetic counselling clinics) and population-based settings; these circumstances may contribute to the heterogeneity observed. Stratification of the analyses according to CBC prognostic factors may reduce this heterogeneity. However,

this could not be performed given the absence of data necessary to evaluate the effects of birth cohort, treatment methods of the first breast cancer, or other influencing factors on the lifetime risk of CBC. Furthermore, the studies found through the bibliographic

Table 4
Cumulative risk of CBC by age or by age at diagnosis of the first breast cancer (BC).

Study [Reference]	Age	BRCA1 mutation carrier		BRCA2 mutation carrier		BRCA1/2 mutation carrier		Noncarriers	
		Cumulative risk (%)	95 % CI	Cumulative risk (%)	95 % CI	Cumulative risk (%)	95 % CI	Cumulative risk (%)	95 % CI
Mavadat et al. 2013 [17]	by 70 years of age	83	69e94	62	44e79.5	e	e	NA	NA
Rhiem et al. 2012 [15]	at <40 years at first BC								
	5	14.1	10.1e18.0	2.9	0.0e6.3	e	e	4.8	2.6e6.9
	10	30.1	24.0e36.2	18.2	7.9e28.5	e	e	10.6	6.8e14.4
	15	40.8	33.2e48.3	20.9	9.7e32.1	e	e	15.3	10.4e20.3
	25	55.1	45.4e65.9	38.5	18.5e58.2	e	e	28.4	20.5e36.3
	at 40e49 years at first BC								
	5	9.2	5.8e12.5	6.9	2.7e11.1	e	e	4.2	2.9e5.5
	10	16.7	11.7e21.7	13.4	7.0e19.8	e	e	8.4	6.3e10.5
	15	23.2	16.9e29.6	22.0	12.1e31.9	e	e	10.7	8.1e13.3
	25	44.5	33.2e55.7	40.5	22.4e58.6	e	e	18.1	13.9e22.3
	at >50 years at first BC								
	5	7.1	3.8e10.5	3.5	0.9e6.1	e	e	3.6	2.7e4.5
	10	11.4	6.5e16.3	10.4	4.9e16.0	e	e	5.5	4.3e6.7
	15	18.7	11.0e26.3	15.5	7.8e23.3	e	e	8.1	6.3e9.9
	25	21.6	12.3e30.8	15.5	7.8e23.3	e	e	12.9	8.9e17.0
Metcalfe et al. 2011 [16]	at <50 years at first BC								
	5	e	e	e	e	14.2	e	NA	NA
	10	e	e	e	e	23.9	e	NA	NA
	15	e	e	e	e	37.6	e	NA	NA
	at >50 years at first BC								
	5	e	e	e	e	8.6	e	NA	NA
	10	e	e	e	e	14.7	e	NA	NA
	15	e	e	e	e	16.8	e	NA	NA
Malone et al. 2010 [37]	All ages combined:								
	at 25e54 years at first BC								
	5	10.9	6.7e17.5	8.3	4.8e14.2	9.7	8.4e11.2	2.5	2.3e2.7
	10	20.5	12.7e33.0	15.9	9.2e27.2	18.4	16.0-21.3	4.9	4.5e5.4
	at 35e39 years at first BC								
	5	13.2	7.4e23.5	12.0	5.6e26.0	12.8	7.7e21.3	2.6	2.2e3.1
	10	24.4	13.7e43.4	22.3	10.3e48.2	23.7	14.3e39.3	5.1	4.2 to 6.1
	at 40e44 years at first BC								
	5	9.8	5.5e17.4	8.9	4.1e19.3	9.5	5.8e15.8	1.9	1.6e2.3
	10	20.0	11.3e35.5	18.3	8.5e39.4	19.4	11.8e32.1	4.1	3.4e4.9
	at 45e49 years at first BC								
	5	7.3	2.7e19.7	6.5	2.9e11.9	6.7	3.6e12.6	2.8	2.6e3.1
	10	13.1	4.8e35.7	11.7	5.3e26.1	12.2	6.5e22.9	5.3	4.8e5.8
	at 50e54 years at first BC								
	5	6.0	2.2e16.3	5.3	2.4e11.9	5.6	2.9e10.3	2.3	2.1e2.6
	10	11.7	4.3e31.8	10.4	4.7e23.2	10.8	5.8e20.3	4.7	4.2e5.1
Verhoog et al. 2000 [33]	at <40 years at first BC								
	5	30	e	NA	NA	NA	NA	NA	NA
	10	40	e	NA	NA	NA	NA	NA	NA
	at >50 years at first BC								
	5	4	e	NA	NA	NA	NA	NA	NA
	10	12	e	NA	NA	NA	NA	NA	NA
Easton et al. 1999 [35]	by 50 years of age	NA	NA	37	25.7e46.6	NA	NA	NA	NA
	by 70 years of age	NA	NA	52.3	41.7e61.0	NA	NA	NA	NA
Ford et al. 1994 [36]	by 50 years of age	48	e	NA	NA	NA	NA	NA	NA
	by 70 years of age	64	e	NA	NA	NA	NA	NA	NA

Only studies reporting cumulative CBS risks by age or age at diagnosis of the first breast cancer are shown.
e: not stated.
NA: not applicable if non-carriers or BRCA1/2 carriers were not accounted for.

search may be a biased selection of all studies carried out. Although we did not found evidence for publication bias, it is impossible to rule out its presence.

The main strength of our study is the inclusion of prospective studies not considered in previous reviews, together with the quantification of cumulative CBC risk separately for *BRCA*1 and *BRCA*2 mutation carrier patients at different time intervals since diagnosis of a first breast cancer.

Conclusion

In view of the findings of this study, risk of CBC in *BRCA1* and *BRCA2* mutation carriers increases with length of time after the first breast

cancer diagnosis. The magnitude of this risk emphasizes the impor- tance of prevention and control policies aimed at reducing the inci- dence of CBC in *BRCA*1/2 mutation carriers. Despite the consistency of the data in the literature as reflected in our study, some uncertainties remain about how characteristics of women with BRCA mutations and an initial breast cancer diagnosis influences cumulative risk of CBC. Therefore, data from large prospective studies, addressing the impact of treatment-related factors as well as clinical and patholog- ical characteristics of the first breast cancer are warranted.

Conflict of interest statement

The authors declare that they have no conflict of interest

Disclosures

None.

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Author's contributions

EMM and MJS carried out the review and drafted the manuscript. MJS participated in its coordination. EMM, MJS and BPN participated in the selection of studies and extraction of data. MP provided expert advice, reviewing the paper and the selected studies, and helped in the drafting of the manuscript. EMM and ESC analyzed the data. JE contributed in the critical revision of the paper and of all the selected studies. All authors read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at

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