Eur Radiol (2010) 20: 2547–2556
DOI 10.1007/s00330-010-1839-y

Marijke C. Jansen-van der Weide
Marcel J. W. Greuter
Liesbeth Jansen
Jan C. Oosterwijk
Ruud M. Pijnappel
Geertruida H. de Bock

Exposure to low-dose radiation and the risk of breast cancer among women with a familial or genetic predisposition: a meta-analysis

Received: 14 January 2010
Revised: 28 April 2010
Accepted: 10 May 2010
Published online: 27 June 2010

M. C. Jansen-van der Weide (✉) · M. J. W. Greuter · R. M. Pijnappel
Department of Radiology,
University Medical Center Groningen,
University of Groningen,
Hanzeplein 1, PO Box 30.001, 9700 RB,
Groningen, The Netherlands
e-mail: m.c.jansen@rad.umcg.nl
Tel.: +31-5036-14467
Fax: +31-5036-11798

M. C. Jansen-van der Weide · G. H. Bock
Department of Epidemiology,
University Medical Center Groningen,
University of Groningen, Groningen,
The Netherlands

L. Jansen
Department of Surgery,
University Medical Center Groningen,
University of Groningen, Groningen,
The Netherlands

J. C. Oosterwijk
Department of Clinical Genetics,
University Medical Center Groningen,
University of Groningen, Groningen,
The Netherlands

Abstract *Background:* Women with familial or genetic aggregation of breast cancer are offered screening outside the population screening programme. However, the possible benefit of mammography screening could be reduced due to the risk of radiation-induced tumours. A systematic search was conducted addressing the question of how low-dose radiation exposure affects breast cancer risk among high-risk women. *Methods:* A systematic search was conducted for articles addressing breast cancer, mammography screening, radiation and high-risk women. Effects of low-dose radiation on breast cancer risk were presented in terms of pooled odds ratios (OR). *Results:* Of 127 articles found, 7 were selected for the meta-analysis. Pooled OR revealed an increased risk of breast cancer among high-risk women due to low-dose radiation exposure (OR=1.3, 95% CI: 0.9– 1.8). Exposure before age 20 (OR=2.0, 95% CI: 1.3–3.1) or a mean of ≥5 exposures (OR=1.8, 95% CI: 1.1–3.0) was significantly associated with a higher radiation-induced breast cancer risk. *Conclusion:* Low-dose radiation increases breast cancer risk among high-risk women. When using low-dose radiation among high-risk women, a careful approach is needed, by means of reducing repeated exposure, avoidance of exposure at a younger age and using non-ionising screening techniques.

Keywords Breast cancer · BRCA1/2 · Family history · Low-dose radiation · Radiation effects · Screening

Introduction

Breast cancer is a common malignancy and one of the most important causes of death among women in western countries; about one out of ten women will develop breast cancer during life [1–3]. Women with one or two affected first-degree relatives are at an increased risk of breast cancer; about one out of six will develop breast cancer [4]. About 20% of the familial aggregation of breast cancer is a result of mutations on the breast cancer susceptibility genes BRCA1 and BRCA2 [5, 6]. BRCA1/2 mutation carriers have a penetrance at 70 years of 57% and 49%, respectively [7]. Other known mutations, like TP53, ATM and CHEK2*100delC, also increase breast cancer risk. The TP53 gene is a high penetrance gene, like BRCA1 and BRCA2 [8, 9]. Mutations in the ATM gene are believed to give a lower breast cancer risk [10, 11]. The CHEK2 mutation in particular, accounting for about 6% of cases of familial breast cancer, increases the risk of contralateral breast cancer [12, 13].

Attempts are being made to reduce breast cancer mortality among women by using several screening

techniques. In several western countries, a nationwide breast cancer screening programme is available for all women from 50 to about 70 years of age, offering mammography screening generally every other year [14]. Women with familial or genetic aggregation of breast cancer in their family are often offered screening outside the population screening programme. These women are offered annual mammography screening, frequently combined with magnetic resonance imaging (MRI) and clinical breast examination, at about 25 years of age [15–17]. The Society of Breast Imaging and the Breast Imaging Commission of the ACR recommend annual mammography and MRI screening for BRCA1 and BRCA2 carriers and first-degree relatives of mutation carriers starting by the age of 30, but not before the age of 25 [18].

Breast cancer screening aims to find breast cancer at a preclinical stage, e.g., less progressed and of a smaller size, resulting in a less severe treatment and an increase in quality of life and survival. However, the possible benefit of early detection by mammography screening could be reduced due to the risk of tumour induction through radiation. Exposure to moderate and to high doses of radiation has shown to be an established risk factor for breast cancer incidence and mortality [19, 20]. Although women attending mammography screening are exposed to relatively low radiation doses (3 mSv) [21], there are concerns that these low radiation doses, when received at a younger age, and for a longer period, could increase the risk of breast cancer [22]. Furthermore, the presence of a defect in one of the breast cancer susceptibility genes could precipitate the harmful effect of radiation [23]. In this case, women with a genetic or familial predisposition for breast cancer could be at increased risk of radiation-induced tumours. Therefore, it is important to know to what extent these women could encounter adverse effects from mammography screening or other diagnostic low-dose radiation. For that, we conducted a systematic search to address the question regarding the increase in breast cancer risk through low-dose radiation exposure, in terms of relative risk or odds ratios, concerning women with a familial or genetic predisposition.

Materials and methods

Search strategy

A systematic literature search was conducted from 1989 until 2009 aimed at finding studies on exposure to low-dose radiation and the effect on breast cancer risk among women at an increased risk of breast cancer (lifetime risk of 15% and up). Searches were conducted in PubMed and EMBASE/Medline. The following MeSH search strategy was used in PubMed: “breast neoplasms” and “mass screening/adverse effects” or “mammography/adverse effects” or “neoplasms, radiation-induced”. This search was combined with text words focusing on family history or genetic predisposition: “familial” or “heredity” or “BRCA”. In EMBASE/Medline the strategy used was: “breast cancer” and “screening” or “mammography” and “ionizing radiation”. In both search strategies only female research studies with an abstract were selected. Related articles, according to the bibliography of the selected studies, were hand-searched in order to find additional relevant reports.

Inclusion and exclusion criteria, and article selection

Studies were included in the analysis if the following inclusion criteria were met: (1) studies including women (patients or participants) having a familial or genetic predisposition of breast cancer; (2) exposure to radiation was defined as low dose, such as mammography or chest X-rays (no radiation therapy); (3) a quantification of the effect of low-dose radiation exposure was given in terms of odds ratio or relative risk; (4) studies that were published in peer-reviewed journals containing original data. In total, 127 studies were found (PubMed: 93; EMBASE/Medline: 34) (Fig. 1). After removing duplicates, 126 abstracts were screened independently by two experienced reviewers (MCJvdW/GHdB). Any discrepancies concerning the article selection were resolved by discussing the abstracts. Of the 126 abstracts, 64 papers were not eligible. Of the 62 studies left, 55 were excluded based on the inclusion criteria after reading the full text. Examples of excluded studies were: studies in which high doses of (therapeutic) radiation exposure were considered (dose >10 mSv per recording) [23, 24], studies based on cell level or animal model [25, 26] and model studies [27–35]. Finally, seven studies met the inclusion criteria (Table 1) [36–42].

Data extraction

Information was taken from each of the selected articles by two persons (MCJW and GHB). Extracted topics based on the research question were: the number of women participating, types of participants, type of comparison, study design, radiation type and the radiation dose received, and the manner of data retrieval. Odds ratios calculating the change in risk of breast cancer were registered. If the data were not available in the original papers, the authors were contacted for additional information [36].

Methodological quality assessment

Methodological quality was assessed independently by the two reviewers using the Newcastle-Ottawa Scale (NOS) [43]. Disagreement was resolved by discussion of the topics. The NOS checklist was developed as a tool for quality assessment of non-randomised studies to be used in a systematic review. In the NOS, a 'star system' was developed judging studies on eight items, based on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of

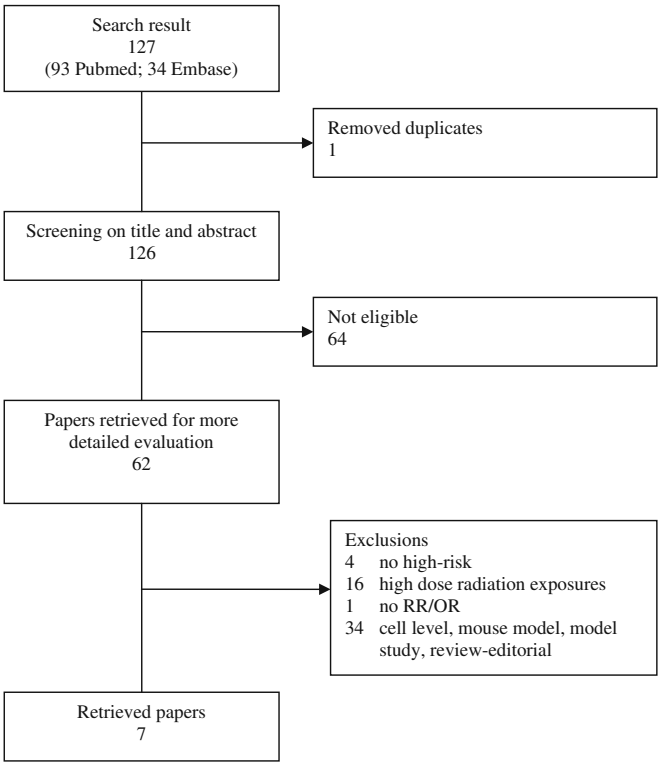

Fig. 1 Flow chart of search results

either the exposure or outcome of interest for case control or cohort studies, respectively. The maximum score that could be obtained was nine stars. The quality assessment results are summarised in Table 2.

Background

The selected research studies were carried out in ten different countries: the USA [37, 38, 40–42], Canada [36, 37, 39, 41], UK [36], Ireland [36], the Netherlands [36], Italy [41], Spain [38], Austria [41], France [36] and Israel [41]. No overlap between data was observed except for some of the data collected in Ontario, Canada [39, 41]. However, because these studies published information from other, non-overlapping countries as well, it was decided to include these data. In the case control studies, controls were obtained either through recruitment from the population matching according to age, place of residence, with place of birth, or race [39, 40, 42], by matching cases to unaffected sisters [39] or by matching BRCA mutation carriers with breast cancer with carriers without breast cancer on the basis of the date of birth, BRCA mutation or country of residence [38, 41].

Dose registration

As no exact information was available on the radiation dose that patients were exposed to, the cumulative radiation dose was estimated. Available information on the mean number or minimum and maximum number of mammograms or chest X-rays received was multiplied with the estimated mean dose for mammography or chest X-ray per recording (mammography mean glandular dose: 3 mSv per recording (one recording consisting of two images); chest X-ray: 0.3 mSv per recording) [21, 44].

Statistical analysis

The data in the selected studies were adjusted for different parameters. Consequently, for homogeneous pooling of the results, unadjusted data on exposed and non-exposed breast cancer cases and their controls were extracted for the calculation of crude odds ratios (OR), 95% confidence interval (CI) and a pooled estimate. The study by Andrieu

Table 1 Characteristics of the included studies

Author	Population	Study design	Measurement instrument	N (cases-controls)	Type of exposure	Time between first exposure and diagnosis (in years)	No. of examinations	Dose (mSv)	NOS quality score
Andrieu (2006)	BRCA1/2 carriers	Cohort	Questionnaire	1,601	Chest X-ray	±15-20[a]	1–7	0.3–±2[b]	5
Bernstein (2006)	CHEK2-mutation carriers	Case only	Interview	30	Chest X-ray	±15	1–≥2	0.3–≥0.6[b]	5
Goldfrank (2006)	BRCA1/2 carriers	Case control	Questionnaire	34-128	Mammography	±6.5	±8	±24[c]	4
John (2007)	women with family history	Case-control	Self-reported questionnaire	2,254-3,431	Chest X-ray	±20[a]	1–≥10	0.3–±3	8
Ma (2008)	Women with family history	Case-control	Interview	1,742-441	Mammography	Not stated	1–≥5	3–±15	7
Millikan (2005)	Mutation carriers (incl. BRCA 2)	Case control	Interview	2,045-1,818	Mammography	Not stated	1–≥11	3–±33	7
Narod (2006)	BRCA1/2 carriers	Case control	Questionnaire	1,600-1,600	Mammography	±5.2	±3-8	±9–24[c]	5

[a] Estimated on the basis of rough data

[b] ±0.3 mSv/x-ray [44]

[c] Mean glandular dose for a two-view mammogram (3 mSv) is estimated on the basis of data of the Dutch screening programme 2002–2004 [21]

Table 2 Quality rating of the included studies by the Newcastle-Ottawa Scale

Author and publication year							
Type of questions	Andrieu (2006)	Bernstein (2006)	Goldfrank (2006)	John (2007)	Ma (2008)	Millikan (2005)	Narod (2006)
Case control							
Selection							
Case definition adequate		Yes	Yes	Yes	Yes	Yes	Yes
Representativeness of cases		Possible selection bias [a]	Possible selection bias [a]	Representative	Representative	Representative	Possible selection bias [a]
Selection of controls		Community	Hospital	Community	Community	Community	Hospital
Definition of controls		No description	No history of disease	No history of disease	No history of disease	No history of disease	No history of disease
Comparability							
Control for confounding factor		2	1	14	11	17	4
Exposure							
Ascertainment of exposure		Non-blinded interview	Written self-report	Written self-report	Non-blinded interview	Non-blinded interview	Written self-report
Ascertainment of same cases/controls		Yes	Yes	Yes	Yes	Yes	Yes
Non-response rate		Rate different	Not stated	Same rate	Not stated	Rate different	Not stated
Cohort							
Selection							
Representativeness of cohort	Somewhat						
Selection of non-exposed cohort	From same source						
Ascertainment of exposure	Written self-report						
Demonstration outcome not present at the start	No						
Comparability							
Control for confounding factors	Two						
Outcome							
Assessment of outcome	Not described						
Follow-up long enough for occurrence outcome	Yes						
Adequacy of follow-up of cohorts	Not stated						
Total score	5	5	4	8	7	7	5

[a] OR not stated

et al. reported the effects of low-dose radiation in terms of hazard ratio [36]. By taking the unadjusted crude numbers of affected and non-affected women, the crude relative risk was calculated, which could then be used for the calculation of the pooled odds ratio [45]. Comparisons were made between subjects who were and who were not exposed to low-dose radiation in general, for subgroups exposed at a young age (<20), at an older age (>20–40) and subgroups that were stratified by the number of exposures received. The presence of publication bias was visually assessed through categorising the studies by sample size to get an impression of a potential relationship between sample size and effect size (Fig. 2). A test for heterogeneity was applied, using the I^2 statistic [46]. This statistic calculates the percentage of total variation across studies that can be attributed to inter-study heterogeneity, ranging from 0 (no heterogeneity) to 100% (all variance due to heterogeneity). All data were entered and analysed using Review Manager (Review Manager, version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008).

Results

Study characteristics

The characteristics of the seven selected studies are summarised in Table 1. Of the seven studies, five investigated the effect of mammography screening or chest X-rays on breast cancer risk among women with a BRCA1/2 mutation, a CHEK2*1100delC mutation or other mutations in the DNA repair genes [36–38, 41, 42]. Two studies were conducted among women with indicators of increased genetic risk (e.g., breast cancer or ovarian cancer among their first, second or third degree relatives) [39, 40]. Patients, who were exposed either to chest X-rays or mammography screening received a cumulative radiation dose ranging from about 0.3 to 33 mSv, which was calculated with the estimated mean dose for mammography or chest X-ray per recording.

In spite of the relatively small number of studies, there was no indication of the presence of publication bias, as a relation between sample size and effect size was absent (Fig. 2). The median quality score was 5, ranging from 4 [38] to 8 [39] (Table 2).

Exposure in general, before or after the age of 20, frequent exposure

One study showed a significantly increased risk of breast cancer due to radiation exposure [36], whereas six studies showed no increased risk or no significantly increased risk (Table 3) [37–42]. The pooled OR revealed a non-significantly increased risk of breast cancer due to mammography or chest X-ray exposure of 1.3 (95% CI: 0.9–1.8) (Table 4).

Five studies had stratified data on the total number of exposures [36, 37, 39–42]. These studies showed that exposure to ≥2, ≥5 and ≥10 X-rays or mammograms gave a higher risk than no (or one) radiation exposure, although not all these risks were significant (Table 3). The pooled OR indicated a significantly increased breast cancer risk of 1.8 (95% CI: 1.1–3.0) for a higher number of exposures (mean ≥5) versus no (or minimal) exposure (Table 4).

Exposure before the age of 20 [36, 39] resulted in an increased risk of breast cancer (pooled OR: 2.0, 95% CI: 1.3–3.1) compared with women younger than 20 who were not exposed (Table 4).

When stratified by age >20 to 40 [36, 39, 41, 42], the risk of radiation exposure on breast cancer risk was again increased, although not significantly for all studies (Table 3). The pooled OR showed an increased risk of 1.3 (95% CI: 0.96–1.7) (Table 4).

Analysis of heterogeneity

A substantial heterogeneity was observed among the seven studies exploring the non-stratified effect of exposure to low-dose radiation on breast cancer risk among high-risk women (I^2: 92%, $p<0.0001$) and the stratified effect among women exposed before the age of 20 (I^2: 79%, $p=0.03$), between age 20 and 40 (I^2: 77%,

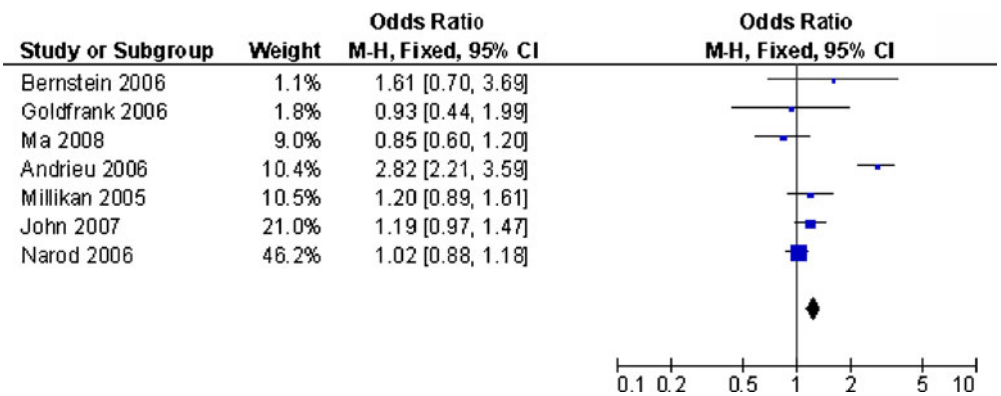

Fig. 2 Forest plot showing potential relation between sample size and effect size

Table 3 Population, comparison and main outcome of included studies

Author	Population	Comparison	Age at exposure	Exposure	Exposed with BC	Not exposed with BC	Crude OR (95% CI)
Andrieu (2006)[a]	BRCA carriers	Exposed versus not exposed	All ages	All versus not	594	143	2.8 (2.2–3.6)
			All ages	≥5 versus not	250	95	3.6 (2.6–5.0)
			<20	All versus not	296[bc]	95	2.5 (1.8–3.4)
			>20–40	All versus not	57[3c]	95	2.4 (1.5–3.9)
Author	Population	Comparison	Age at exposure	Exposure	Cases	Controls	Crude OR (95% CI)
Bernstein (2006)[d]	CHEK2 mutation carriers	Exposed versus not exposed	All ages	All versus not	10	13[e]	1.6 (0.7–3.7)
			All ages	≥2 versus <2	8	14[e]	2.0 (0.8–4.8)
Goldfrank (2006)[f]	BRCA carriers	Exposed versus not exposed	All ages	All versus not	34	128	0.9 (0.4–2.0)
John (2007)[f]	Women with family history	Exposed versus not exposed	All ages	All versus not	159	1,121	1.2 (1.0–1.5)
			All ages	≥10 versus not	20	128	1.1 (0.7–1.7)
			<20[g]	All versus not	67	359	1.6 (1.2–2.1)
			20–39[g]	All versus not	61	541	1.0 (0.7–1.3)
Ma (2008)[f]	Women with family history		All ages	All versus not	433	62	0.9 (0.6–1.2)
			All ages	≥5 versus not	134	15	1.7 (0.9–3.0)
Millikan (2005) [f]	Women with mutation in DNA repair genes (incl. BRCA2)	Exposed versus not exposed	All ages	All versus not	606	439	1.2 (0.9–1.6)
			All ages	≥10 versus not	145	91	1.4 (1.0–2.0)
				All versus not	183	132	1.4 (1.0–1.8)
Narod (2006)[f]	BRCA carriers	Exposed versus not exposed	All ages	All versus not	661[h]	729[h]	1.0 (0.9–1.2)
			31–40	All versus not	342	355	1.1 (0.9–1.3)

[a] Cohort study

[b] Data provided by authors

[c] The patients who were both exposed at an age younger than 20 as well as at the age of 20 and over (n=262) are not shown in the table. Number of missing values is 24

[d] Case-only study

[e] As this is a case-only study, controls were breast cancer patients who had not been exposed to radiation

[f] Case control study

[g] The patients who were exposed at an age of 40 and older were not shown in the table (without family history, cases n=4, controls n=9; with family history, cases n=2, controls n=9)

[h] Number of missing values; cases 102, controls 255

p=0.004) or receiving repeated exposure (I^2: 82%, p=0.0002). Selection of studies among mutation carriers did not change heterogeneity (I^2: 92%, p<0.0001, pooled OR: 1.4, 95% CI: 0.9–2.3) [36–38, 41, 42]. Selection of case control studies lowered heterogeneity (I^2: 0%, p=0.44, pooled OR: 1.1, 95% CI: 0.96–1.2) [37–42]. Because of heterogeneity and possible unmeasured variance at the study level, a random-effects model was used to obtain all pooled estimates, as this model interprets the available data with more caution and uses broad confidence intervals [47].

Table 4 Results of pooled OR (95% CI) for breast cancer risk due to low-dose radiation in general, stratified for the number of exposures, age <20 and age >20–40 (RANDOM effects model)

Outcome or subgroup	Studies	Participants	OR (95% CI)
Breast cancer	7[a]	11,814	1.3 (0.9–1.8)
Breast cancer, >exposures	5[b]	5,708	1.8 (1.1–3.0)
Breast cancer, age <20	2[c]	3,772	2.0 (1.3–3.1)
Breast cancer, age >20–40	4[d]	6,822	1.3 (0.96–1.7)

[a] Andrieu, Bernstein, Goldfrank, John, Ma, Millikan, Narod

[b] Andrieu, Bernstein, John, Ma, Millikan

[c] Andrieu, John

[d] Andrieu, John, Millikan, Narod

Discussion

This meta-analysis analysed the data from seven studies in order to evaluate the effects of low-dose radiation exposure, such as mammography, on breast cancer risk in women with a familial or genetic predisposition. Our findings show that there is indeed a relation between exposure to low-dose radiation and an additional increase in breast cancer risk among high-risk women. Exposure to radiation results in a 1.3 times increased breast cancer risk (OR=1.3, 95% CI: 0.9–1.8). Subsequently, breast cancer risk is higher among high-risk women exposed before the age of 20 (OR=2.0 95% CI: 1.3–3.1) or who are frequently exposed (≥2, ≥5 or ≥10; OR=1.8, 95% CI: 1.1–3.0). Women exposed between 20 and 40 years of age are also at increased risk (OR=1.3, 95% CI: 0.96–1.7).

This meta-analysis evaluated the current evidence on the role of low-dose radiation concerning breast cancer

risk. Like other meta-analyses, it has potential limitations resulting from the availability, quality and heterogeneity of the published data. For example, we were able to include seven studies on this subject only, according to our inclusion criteria. Moreover, the selected studies were somewhat heterogeneous with respect to the type of participants, type of study and selections. Therefore, we used a random effects model. Nevertheless, the determinants that increase breast cancer risk in our pooled analysis are in accordance with literature on moderate to high radiation exposure in the general population. In the literature, it was shown that higher doses of radiation evoke a higher risk of radiation-induced tumours than do lower doses [19, 48]. The observed inverse relation between age at exposure and risk of radiation-induced breast tumours resembled the results in other studies [19, 22].

Most selected studies were of average quality; none of the studies had a low quality. In addition, no relation was seen between quality and radiation effect. According to Fig. 2, there was no suggestion of publication bias, which indicates that we did not likely miss studies with a negative outcome. Therefore, it is expected that our analysis did not overestimate the effect of low-dose radiation on breast cancer risk. However, because of the relatively small number of studies, conclusions should be interpreted with caution.

The study by Bernstein et al. [37] was based on a population of CHEK2*1100delC mutation carriers. The baseline risk of developing breast cancer in women with such a mutation is lower compared with women with a BRCA1 or BRCA2 mutation. Women with a CHEK2*1100delC mutation in particular are at increased risk of developing a contralateral breast cancer [12, 13]. The combination of different baseline risks could have influenced heterogeneity and the effect estimate. However, because no substantial difference was seen regarding heterogeneity and pooled OR, this study was not excluded from the analysis.

Three studies addressed the effect of chest X-rays on breast cancer risk of women at elevated risk [36, 37, 39]. John et al. categorised all common types of diagnostic chest X-rays [39]. Although all three studies found an effect of chest X-rays on breast cancer risk, the study by John et al. only found this effect for diagnostic chest X-rays for pneumonia and tuberculosis. It is not clear what caused the difference in effect, as for these types of radiation exposure the dose lies in the same order of magnitude. The association of diagnostic radiation for tuberculosis with increased breast cancer risk is consistent with other studies [49, 50]. John et al., however, reported that the results from the reported diagnostic radiation for pneumonia could be recalled differently by cases and controls and could have caused an overestimation of the effect. Taking into account the other two studies that did find an overall effect of diagnostic chest X-rays, it is thus important to collect more detailed information on the type of exposure and radiation dose in future investigations with a prospective setting.

Risk over time and absolute risk

In general, the risk of developing breast cancer increases with age. For women with a familial aggregation or genetic predisposition for breast cancer, this risk is highest between 60 and 70 years of age [7]. A meta-analysis regarding the penetrance of breast cancer among high-risk women revealed that BRCA1 mutation carriers who were 20 years old were at a risk of developing breast cancer at age 50 of 29% [7]. If women are exposed to low-dose radiation before the age of 20, then, according to our study, the risk of breast cancer at age 50 is increased to 58%. In addition, at age 50, the risk of developing breast cancer at 70 years increases from 37% to 74%. The same is the case when these women are exposed to a larger number of low-dose radiation recordings. As this is common practice among women with a familial or genetic predisposition, it is important to be careful with the use of radiation among high-risk women, especially at a young age, and also to avoid repeated exposure.

Estimated dose

None of the selected studies contained detailed information on the dose the patients received. Therefore, a cumulative dose estimate was not available. As a consequence, it was not clear in which studies patients received the highest cumulative dose. Furthermore, two studies did not provide data on the total number of exposures [38, 41]. This could have influenced the outcome, i.e., on the magnitude of the actual effect of radiation on breast cancer risk. For instance, five studies used the total number of chest X-ray or mammography exposures in their analysis to give an estimate of the effect of a higher level of radiation on breast cancer risk [36, 37, 39, 40, 42]. The radiation effect when using this comparison was substantially higher than the general effect. Instead, the two studies only used the age at first exposure in their analysis [38, 41]. If the number of mammograms and the estimated cumulative dose had been taken into account, they might have seen an effect as well.

It is known that the effect of exposure to radiation has a latency period of at least 10 to 15 years [19, 48]. For studies investigating the effect of radiation on breast cancer risk, it is thus important that the follow-up time is long enough to observe a possible effect. Not all studies presented a clear timeline from first exposure to diagnosis; however, in most cases it was possible to obtain an estimation of the time between the first exposure and the age at diagnosis. In three studies this period was estimated to be 15 to 20 years [36, 37, 39]. Two other studies had a mean time of approximately 6 years [38, 41], which is expected to be too short to find a radiation effect on breast cancer risk. Actually, these two studies did not see any effect of radiation. Therefore, it is conceivable that the current short-term studies underestimated breast cancer risk. Recalculation after exclusion of these two studies resulted in an increased pooled OR (OR: 1.4, 95% CI: 0.9–2.2). Incorporation of future studies with a prospective design and a long follow-up period may lead to a higher and more accurate pooled radiation effect.

All data from the selected studies on radiation exposure were retrieved from patients and controls in a retrospective way. The reliability of self-reported radiation data raises concern about potential exposure misclassification. Because it is generally known that exposure to radiation increases the risk of cancer, it is possible that cases over-reported their exposure to radiation. However, three studies comparing self-assessment with medical records data showed that the disagreement between medical data and interview data on exposure measures among patients and controls could largely be classified as non-differential [51–53]. In our meta-analysis, we think the received dose is not expected to be overestimated by the patients. However, to overcome this type of bias, prospective future studies on this subject are recommended.

Comparison between high- and low-risk women

Some studies compared the risk of radiation-induced breast cancer among women with familial aggregation or genetic predisposition of breast cancer with that among women without such a family history [23, 24, 39]. Other studies addressed this comparison on an animal or cellular level [25, 26]. Of these studies, no pooled results were calculated as the study types were too different or higher doses of radiation were used. However, most studies showed similar results. One study, investigating both diagnostic and therapeutic radiation, showed an increased risk among women with familial aggregation compared with women without a family history of breast cancer [24]. Another study showed that BRCA1 or BRCA2 carriers with breast cancer were at increased risk of contralateral breast cancer compared with non-carriers after receiving radiotherapy [23]. However, John et al. [39] saw no difference between women with and without a positive family history after radiation exposure. Two experimental studies (one mouse model and one in-vitro study), in which BRCA1/2 mutated mice or cells were used, showed elevated radiosensitivity among those with a defect in the BRCA genes [25, 26]. The current results suggest an increased breast cancer risk among high-risk women compared with those women without a familial or genetic predisposition due to radiation.

Risks and benefits

Once it is known what risks high-risk women encounter with low-dose radiation such as mammography screening, attempts could be made to balance these risks against the benefits of screening. In this case model, studies in which all risks and benefits are accounted for could give a good estimate of which screening strategy is adequate for high-risk women. For example, Berrington de Gonzalez et al. used an excess relative risk model to calculate the lifetime risk of radiation-induced breast cancer from five annual mammographic screenings among mutation carriers aged 40 years or younger from three cohorts [54]. They found that there was no benefit of annual mammography screening between the ages of 25 and 34, and some net benefit from the age of 35. With the results of our meta-analysis, it might be possible to fine-tune these recommendations regarding the guidelines for optimal screening for mutation carriers. The use of non-ionising imaging techniques for the screening of high-risk women, such as magnetic resonance imaging (MRI), could also contribute to an adequate balance between risks and benefits.

Overall, we observed that exposure to low-dose radiation does increased breast cancer risk among high-risk women. The effect of radiation is even larger among women who are exposed more frequently (≥2, ≥5 or ≥10 exposures) or at a younger age (<20). As for women who have a greater chance of developing breast cancer, this radiation effect increases the breast cancer risk considerably.

Therefore, adaptation of the screening programme to a more careful approach by using other, non-ionising screening techniques at a younger age, reducing the number of mammograms and the glandular dose per exam needs serious consideration. Finally, future prospective studies with a long follow-up time and detailed information on radiation dose could be useful for obtaining a more accurate and probably larger effect of low-dose radiation.

Acknowledgements We thank Mr. David Goldgar on behalf of the IBCCS study for providing additional information for the subgroup analysis.

References

1. Dutch Cancer Registry (2006) Available via IKCnet. http://www.ikcnet.nl. Accessed 28 April 2010
2. Jemal A, Murray T, Ward E et al (2005) Cancer statistics. CA Cancer J Clin 55:10–30
3. Loman N, Johannsson O, Kristoffersson U et al (2001) Family history of breast and ovarian cancers and BRCA1 and BRCA2 mutations in a population-based series of early-onset breast cancer. J Nat Cancer Inst 93:1215–1223
4. Collaborative Group on Hormonal Factors in Breast Cancer (2001) Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. Lancet 358:1389–1399
5. Nathanson KN, Wooster R, Weber BL (2001) Breast cancer genetics: what we know and what we need. Nat Med 7:552–556
6. Verhoog LC, van den Ouweland AM, Berns E et al (2001) Large regional differences in the frequency of distinct BRCA1/BRCA2 mutations in 517 Dutch breast and/or ovarian cancer families. Eur J Cancer 37:2082–2090

7. Chen S, Parmigiani G (2007) Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 25:1329–1333
8. Cui J, Antoniou AC, Dite GS et al (2001) After BRCA1 and BRCA2—what next? multifactorial segregation analyses of three-generation, population-based Australian families affected by female breast cancer. Am J Hum Genet 68:420–431
9. Antoniou AC, Pharoah PD, McMullan G et al (2002) A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes. Br J Cancer 86:76–83
10. de Jong MM, Nolte IM, Te Meerman GJ et al (2002) Genes other than BRCA1 and BRCA2 involved in breast cancer susceptibility. J Med Genet 39:225–242
11. Goode EL, Dunning AM, Kuschel B et al (2002) Effect of germ-line genetic variation on breast cancer survival in a population-based study. Cancer Res 62:3052–3057
12. Vahteristo P, Bartkova J, Eerola H et al (2002) A CHEK2 genetic variant contributing to a substantial fraction of familial breast cancer. Am J Hum Genet 71:432–438
13. de Bock GH, Schutte M, Krol-Warmerdam EMM et al (2004) Tumour characteristics and prognosis of breast cancer patients carrying the germline CHEK*1100delC variant. J Med Genet 41:731–735
14. Shapiro S, Coleman EA, Broeders M et al (1998) Breast cancer screening programmes in 22 countries: current policies, administration and guidelines. international breast cancer screening network (IBSN) and the European network of pilot projects for breast cancer screening. Int J Epidemiol 27:735–742
15. Kriege M, Brekelmans CT, Boetes C et al (2004) Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 351:427–437
16. Leach MO, Boggis CR, Dixon AK et al (2005) The MARIBS study group. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 365:1769–1778
17. Warner E, Messersmith H, Causer P et al (2008) Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. Ann Int Med 148:671–679
18. Lee CH, Dershaw DD, Kopans D et al (2010) Breast cancer screening with imaging: recommendations from the Society of breast imaging and the ACR on the use of mammography, breast MRI, breast ultrasound, and other technologies for the detection of clinically occult breast cancer. J Am Coll Radiol 7:18–27
19. Preston DL, Mattson A, Holmberg E et al (2002) Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. Radiat Res 158:220–235
20. Ronckers CM, Erdmann CA, Land CE (2005) Radiation and breast cancer: a review of current evidence. Breast Cancer Res 7:21–32
21. Zoetelief J, Veldkamp WJH, Thijssen MAO, Jansen JTM (2006) Glandularity and mean glandular dose determined for individual women at four regional breast cancer screening units in the Netherlands. Phys Med Biol 51:1807–1817
22. Wakeford R (2004) The cancer epidemiology of radiation. Oncogene 23:6404–6428
23. Broeks A, Braaf LM, Huseinovic A et al (2007) Identification of women with an increased risk of developing radiation-induced breast cancer: a case only study. Breast Cancer Res 9:106–114
24. Hill DA, Preston-Martin S, Ross RK, Bernstein L (2002) Medical radiation, family history of cancer, and benign breast disease in relation to breast cancer risk in young women, USA. Cancer Causes Control 13:711–718
25. Rothfuss A, Schutz P, Bochum S et al (2000) Induced micronucleus frequencies in peripheral lymphocytes as a screening test for carriers of a BRCA1 mutation in breast cancer families. Cancer Res 60:390–394
26. Tutt ANJ, Van Oostrom CTM, Ross GM et al (2002) Disruption of BRCA2 increases the spontaneous mutation rate in vivo: synergism with ionizing radiation. EMBO Rep 31:255–260
27. Berrington de Gonzalez A, Reeves G (2005) Mammographic screening before age 50years in the UK: comparison of the radiation risks with the mortality benefits. Br J Cancer 93:590–596
28. Chakraborty R, Sankaranarayanan K (1995) Cancer predisposition, radiosensitivity and the risk of radiation-induced cancers II. A Mendelian single-locus model of cancer predisposition and radiosensitivity for predicting cancer risks in populations. Radiat Res 143:293–301
29. Chakraborty R, Sankaranarayanan K (1998) Mutations in the BRCA1 gene: implications of inter-population differences for predicting the risk of radiation-induced breast cancers. Genet Res 72:191–198
30. Chakraborty R, Little MP, Sankaranarayanan (1998) Cancer predisposition, radiosensitivity and the risk of radiation-induced cancers. IV. prediction of risks in relatives of cancer-predisposed individuals. Radiat Res 149:493–507
31. Den Otter W, Merchant TE, Beijerink D et al (1993) Exclusion from mammographic screening of women genetically predisposed to breast cancer will probably eliminate mammographically induced breast cancer. Anticancer Res 13:1113–1116
32. Den Otter W, Merchant TE, Beijerink D et al (1996) Breast cancer induction due to mammographic screening in hereditarily affected women. Anticancer Res 16:3173–3176
33. Law J, Faulkner K (2001) Cancers detected and induced, and associated risk and benefit, in a breast screening programme. Br J Radiol 74:1121–1127
34. Law J, Faulkner K (2002) Concerning the relationship between benefit and radiation risk, and cancers detected and induced, in a breast screening programme. Br J Radiol 75:678–684
35. Law J, Faulkner F, Young KC (2007) Risk factors for induction of breast cancer by X-rays and their implications for breast screening. Br J Radiol 80:261–266
36. Andrieu N, Easton DF, Chang-Claude J et al (2006) Effect of chest X-rays on the risk of breast cancer among BRCA1/2 mutation carriers in the international BRCA1/2 carrier cohort study: a report from the EMBRACE, GENEPSO, GEO-HEBON, and IBCCS Collaborators' Group. J Clin Oncol 24:3361–3366
37. Bernstein JL, Teraoka SN, John EM et al (2006) The CHEK*1100delC allelic variant and risk of breast cancer: screening results from the breast cancer family registry. Cancer Epidemiol Biomark Prev 15:348–352
38. Goldfrank D, Chuai S, Bernstein JL et al (2006) Effect of mammography on breast cancer risk in women with mutations in BRCA1 or BRCA2. Cancer Epidemiol Biomark Prev 15:2311–2313
39. John EM, Phipps AI, Knight JA et al (2007) Medical radiation and breast cancer risk: findings from the breast cancer family registry. Int J Cancer 121:386–394

40. Ma H, Hill CK, Bernstein L, Ursin G (2008) Low-dose medical radiation exposure and breast cancer risk in women under age 50years overall and by estrogen and progesterone receptor status: results from a case-control and case-case comparison. Breast Cancer Res Treat 109:77–90
41. Narod SA, Lubinski J, Ghadirian P et al (2006) Screening mammography and risk of breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Lancet Oncol 7:402–406
42. Millikan RC, Player JS, Decotret AR et al (2005) Polymorphisms in DNA repair genes, medical exposure to ionizing radiation, and breast cancer risk. Cancer Epidemiol Biomark Prev 14:2326–2334
43. Wells GA, Shea B, O'Connell J et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm
44. Schaefer-Prokop C, Neitzel U, Venema HW et al (2008) Digital chest radiography: an update on modern technology, dose containment, and control of image quality. Eur Radiol 18:1818–1830
45. Vandenbroucke JP, Hofman A (1999) Principles of epidemiology. Reed Business, Amsterdam
46. Higgins JP, Thompson SG, Deeks JJ et al (2003) Measuring inconsistency in meta-analyses. BMJ 327:557–560
47. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188
48. Land CE, Tokunaga M, Koyama K et al (2003) Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950-1990. Radiat Res 160:707–717
49. Boice JD Jr, Preston D, Davis FG, Monson RR (1991) Frequent chest X-ray fluoroscopy and breast cancer incidence among tuberculosis patients in Massachusetts. Radiat Res 125:214–222
50. Hrubec Z, Boice JD Jr, Monson RR, Rosenstein M (1989) Breast cancer after multiple chest fluorscopies: second follow-up of Massachusetts women with tuberculosis. Cancer Res 49:229–234
51. Berrington de Gonzalez A, Ekboom A, Glass A et al (2003) Comparison of documented and recalled histories of exposure to diagnostic X-rays in case-control studies of thyroid cancer. Am J Epidemiol 157:652–663
52. Pagoda JM, Preston-Martin S (2002) Radiation exposure from diagnostic imaging: agreement between self-report and medical records. Health Phys 83:907–917
53. Preston-Martin S, Bernstein L, Maldonado AA et al (1985) Comparison of information from patient interviews and dental charts. Am J Epidemiol 121:430–439
54. Berrington de Gonzalez A, Berg CD, Visvanathan K, Robson M (2009) Estimated risk of radiation-induced breast cancer from mammographic screening for young BRCA mutation carriers. J Natl Cancer Inst 101:205–209