Cancer Effects of Low to Moderate Doses of Ionizing Radiation in Young People with Cancer-Predisposing Conditions: A Systematic Review

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ABSTRACT

Moderate to high doses of ionizing radiation (IR) are known to increase the risk of cancer, particularly following childhood exposure. Concerns remain regarding risks from lower doses and the role of cancer-predisposing factors (CPF; genetic disorders, immunodeficiency, mutations/variants in DNA damage detection or repair genes) on radiation-induced cancer (RIC) risk. We conducted a systematic review of evidence that CPFs modify RIC risk in young people. Searches were performed in PubMed, Scopus, Web of Science, and EMBASE for epidemiologic studies of cancer risk in humans (<25 years) with a CPF, exposed to low–moderate IR. Risk of bias was considered. Fifteen articles focusing on leukemia, lymphoma, breast, brain, and thyroid cancers were included. We found inadequate evidence that CPFs modify the risk of radiation-induced leukemia, lymphoma, brain/central nervous system, and thyroid cancers and limited evidence that *BRCA* mutations modify radiation-induced breast cancer risk. Heterogeneity was observed across studies regarding exposure measures, and the numbers of subjects with CPFs other than *BRCA* mutations were very small. Further studies with more appropriate study designs are needed to elucidate the impact of CPFs on RIC. They should focus either on populations of carriers of specific gene mutations or on common susceptible variants using polygenic risk scores.

Introduction

Ionizing radiation (IR) plays an essential role in the diagnosis and follow-up of injuries, diseases, and the treatment of benign and malignant neoplasms (1). Medical sources of IR include conventional radiography, computed tomography (CT), nuclear medicine, fluoroscopy, and radiotherapy (RT).

Moderate to high doses of IR have been shown consistently to increase the risk of cancer in humans (2, 3), in particular in studies of cancer survivors where the radiation dose is related to an increased risk of second cancers in a number of different organs (4–8). One of the major concerns in radiation protection today, however, is characterizing and quantifying the effects of low doses (less than 100 mGy), as there is growing evidence that even low doses can increase cancer risk (3, 8–10), and identifying factors that may modify that risk, in particular age and genetic factors (3, 8, 11).

Medical applications of IR are a particular concern in radiation protection, particularly in children (8). In RT, though IR doses to the tumor target are very high (of the order of 50–60 Gy, to destroy cancer cells), distant organs receive low to moderate doses (100 mGy–500 Gy), since the dose decreases rapidly away from the target organ, and the long-term effects of these exposures on health, including second cancer risk, are very important to understand for the increasingly large populations of cancer survivors (5, 6, 8). Doses from diagnostic procedures are generally low, though repeated examinations, particularly from CT scanning, can lead to dose levels (hundreds of mGy) known to increase cancer risk. Because of the large numbers of persons undergoing diagnostic medical procedures every year, and the rapid development and implementation of new medical IR applications, medical diagnostic sources represent the largest source of general population IR exposure in high-income countries. It is therefore important to evaluate the potential impact of these exposures on risk of cancer in order to optimize practices and doses and reduce risks (6, 8).

Concerning factors that may modify the risk of radiation-induced cancer (RIC), it is well documented that exposure in childhood tends to confer a higher risk, compared with exposure later in life, especially in organs with high cell proliferation (6, 8). Genetic factors (8, 12), including mutations and variants in genes involved in detection or repair of DNA damage, in tumor-suppressor genes, and/or in proto-oncogenes may also play a role in RIC, conferring increased susceptibility (6, 8, 13). The link between cancer and radiation exposure (ultraviolet) in a population with mutations in DNA damage repair genes was first explored in the late 1960s among patients with xeroderma pigmentosum (*XP*) who developed skin cancer following sun exposure (6, 14). Persons with mutations in DNA damage repair genes, such as *BRCA1* or *2* mutations, ataxia telangiectasia (*AT*; homozygous for a recessive *AT* mutation), and Nijmegen breakage syndrome (*NBS*; homozygous for an *NBS* mutation), are at increased risk of tissue damage following high levels of IR as these genes alter DNA repair, and heterozygous *ATM* and *NBS* mutation carriers may be at increased cancer risk (6, 11, 15). An increased risk of secondary cancers has also been reported among children with heritable retinoblastoma (*RB*), neurofibromatosis, and Li–Fraumeni syndrome (*LFS*) following moderate to high doses of RT treatments (11).

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Children with increased susceptibility to RIC (genetic and/or related to immune deficiency) undergoing diagnostic or therapeutic radiation exposure are therefore of particular concern in radiation protection (6, 8). If such children can be identified, personalized screening, surveillance, management, and treatment can be offered to them to reduce their risk of RIC, including alternative diagnostic and treatment modalities (16, 17).

The objective of the current systematic review was to identify factors that may confer an increased susceptibility of RIC in subjects exposed during childhood, adolescence, and early adulthood (before the age of 25 years). Factors considered, termed cancer-predisposing factors (CPF) in this review, included conditions resulting from genetic disorders, immunodeficiency, mutation in DNA damage detection or repair genes, and family history of breast cancer.

Materials and Methods

The PRISMA-P 2015 checklist was used to formulate the systematic review protocol. The study was registered in PROSPERO (CRD4202014815; ref. 18).

Criteria for considering studies

An adaptation of the *Cochrane Handbook for Systematic Reviews* for observational studies was used as a study outline for the review (19). The Population, Exposure, Comparator, and Outcome and study design (PECO; Supplementary Table S1) framework was used to formulate the research question, assess eligibility, and synthesize each study (18–20).

The Population (P) of interest was children and young adults (<25 years) with a CPF. The list of conditions was compiled from a review by Journy and colleagues (21), Berrington de Gonzalez and colleagues (22), the BEIR VII report (6), and The Concise Handbook of Familial Cancer Susceptibility Syndromes (ref. 23; **Table 1**). The Exposure (E) was low–moderate doses of IR (<500 mGy) from medical, accidental, and environmental origins (including atomic bombings). Studies required an estimate of individual exposure or dose and an analysis of dose-/exposure-related response to allow the evaluation of the impact of the CPF on the risk of radiation-induced cancer. The Comparator (C) variable was excluded as it did not fit within the scope of the research aim. The Outcomes (O) of interest leukemia, breast, thyroid, and brain cancers and lymphoma. All but the latter are known to be associated with radiation exposure in childhood and adolescence (8). The evidence for lymphoma is less clear, though a number of large-scale recent studies have reported associations and changes in the classification of hematologic malignancies in recent decades have led to some leukemia subtypes being reclassified as lymphoma (21, 24–27).

If the exposure under study was RT for a primary cancer, secondary malignancies were only considered, if they occurred in tissues/organs far from the exposure field with doses below 500 mGy. Empirical quantitative studies of cohort and case–control study design were selected. Exclusions included: non-English publications, systematic reviews, and case studies. All publications up to December 31, 2020, were considered.

Source of information

Databases used were PubMed, Scopus, Web of Science, and EMBASE. A manual search in reference lists from relevant articles was also performed.

Search strategy and study selection

The PECO structure was used to formulate the search strategy with "Population AND Exposure AND Outcome" conditions or string factors. A combination of free-text words and MeSH (Medical Subject Headings) terms was used to search the title, abstract, and keywords of the publications. The whole commands used with the search strings are provided in Supplementary Table S2. The literature search was conducted on November 6, 2019, and repeated on February 11, 2020. An additional search was performed on May 2, 2020, and December 30, 2020, to integrate some additional search terms deemed necessary for the scope of this review.

Study eligibility criteria (Supplementary Table S1) were defined by R. Harbron and M. Canet and tested on a subset sample of 10 randomly selected publications. A consistency test was performed to test inter-reviewer agreement; a Cohen's kappa (K) coefficient > 0.8 was considered sufficient in order to move to the following stage of the systematic review process. Studies were reviewed in parallel by M. Canet, R. Harbron, and E. Cardis following two phases: phase I, screening of titles and abstracts retrieved from the literature search; phase II, screening of full-text articles identified in phase I and of publications identified in the reference lists of relevant papers. Results from each reviewer were compared. Seven studies required further assessment by all three reviewers to reach consensus on inclusion/exclusion.

Record management

Data management relied on the open access online software program CADIMA (28). Data collection was performed by M. Canet and reviewed by R. Harbron, E. Cardis, and I. Thierry-Chef. Publications gathered from each database were uploaded and screened for potential duplicates. Following phase II, details on selected studies were collected, including study population, study characteristics, exposure assessment, outcome measurement, and information contributing to the risk assessment.

Risk of bias assessment

An adaptation of the Cochrane Collaboration's risk of bias tool developed for observational studies was used to assess risk of bias for each individual study (29–32).

The following sources of bias were evaluated: recruitment, blinding, exposure assessment, confounding, outcome assessment, selective reporting, conflict of interest, and any other bias. For each source, the risk of bias was rated as "low," "probably low," "probably high," or "high." The bias assessment was individually performed by M. Canet, R. Harbron, and E. Cardis, with further discussions in case of discrepancies. Studies in which a coauthor contributed were reviewed by other authors. An overall judgment of the risk of bias was performed to aid in the synthesis of the results and confidence characterization (30). For each identified bias, we assessed the extent it influenced the results and validity of each study (32, 33). In the event an identified bias was considered to compromise study results, the overall risk of bias judgment was "the study presents one [or more, according to the number of biases] threat to validity."

Data synthesis and confidence characterization

Given the wide range of exposure measures and outcomes, a qualitative synthesis was carried out using the methods outlined in the Cochrane collaboration handbook and Popay and colleagues (19, 34). For each outcome, we reported the effect estimates from each study. We then used a standardized binary metric to estimate the direction of effect demonstrated across studies. Depending on the direction of effect IR exposure had on cancer risk estimates; either an ↑ suggested an increase

Table 1. List of CPFs considered for this review by cancer type.

	Leukemia	Lymphoma	Brain	Breast	Thyroid	Generic[a]	Studies
Genetic disorders							
Li–Fraumeni syndrome						Yes	Lindor et al. 2008; Journy et al. 2015, 2016; Berrington de Gonzalez et al. 2016
Fanconi anemia						Yes	BEIR VII report 2006; Lindor et al. 2008; Journy et al. 2015, 2016; Berrington de Gonzalez et al. 2016
Langerhans cell histocytosis	Yes						Berrington de Gonzalez et al. 2016
Kostmann granulocytopenia	Yes						Berrington de Gonzalez et al. 2016
Nevoid basal cell syndrome			Yes				BEIR VII report 2006; Lindor et al. 2008; Berrington de Gonzalez et al. 2016
Neurofibromatosis type 1						Yes	BEIR VII report 2006; Lindor et al. 2008; Journy et al. 2015, 2016; Berrington de Gonzalez et al. 2016
Neurofibromatosis type 2			Yes				BEIR VII report 2006; Journy et al. 2015, 2016; Lindor et al. 2008; Berrington de Gonzalez et al. 2016
Nijmegen breakage syndrome		Yes		Yes			BEIR VII report 2006; Lindor et al. 2008
Monosomy 7 (MDS)	Yes						Berrington de Gonzalez et al. 2016
Mismatch-repair deficiency				Yes	Yes		Lindor et al. 2008
Beckwith Wiedemann syndrome			Yes				Lindor et al. 2008
Congenital heart defects[b]						Yes	BEIR VII report 2006; Lindor et al. 2008
Noonan syndrome	Yes						Journy et al. 2015, 2016; Berrington de Gonzalez et al. 2016
Bloom syndrome	Yes	Yes		Yes			BEIR VII report 2006; Lindor et al. 2008; Journy et al. 2015, 2016; Berrington de Gonzalez et al. 2016
Ataxia telangiectasia	Yes	Yes		Yes			BEIR VII report 2006; Lindor et al. 2008; Journy et al. 2015, 2016; Berrington de Gonzalez et al. 2016
Shwachman–Diamond Syndrome	Yes						Berrington de Gonzalez et al. 2016
Tuberous sclerosis			Yes				BEIR VII report 2006; Berrington de Gonzalez et al. 2016
Von Hippel–Lindau			Yes				BEIR VII report 2006; Lindor et al. 2008; Berrington de Gonzalez et al. 2016
Multiple endocrine neoplasia 1 (MEN 1)					Yes		BEIR VII report 2006; Journy et al. 2015, 2016
Multiple endocrine neoplasia 2 (MEN 2)					Yes		BEIR VII report 2006; Journy et al. 2015, 2016
Familial adenomatous polyposis			Yes		Yes		BEIR VII report 2006; Journy et al. 2015, 2016
Turcot syndrome			Yes				Journy et al. 2015, 2016; Berrington de Gonzalez et al. 2016; Lindor et al. 2008
Down syndrome	Yes						Journy et al. 2015, 2016; Berrington de Gonzalez et al. 2016
Xeroderma pigmentosum	Yes		Yes	Yes			BEIR VII report 2006; Journy et al. 2015, 2016
Klinefelter syndrome		Yes		Yes			Journy et al. 2015, 2016; Berrington de Gonzalez et al. 2016
Other phacomatoses					Yes	Yes	Journy et al. 2015, 2016
Immunodeficiencies							
Primary immunodeficiency	Yes						Journy et al. 2015, 2016
Severe combined immune deficiency (SCID)		Yes					Journy et al. 2015, 2016; Berrington de Gonzalez et al. 2016
Common variable immune deficiency (CVID)		Yes					Journy et al. 2015, 2016; Berrington de Gonzalez et al. 2016
HIV/AIDS	Yes						Journy et al. 2015, 2016
Wiskott–Aldrich syndrome			Yes				Journy et al. 2015, 2016; Berrington de Gonzalez et al. 2016
Transplantation	Yes						Journy et al. 2015, 2016; Berrington de Gonzalez et al. 2016
Mutations							
BRCA 1/2 gene				Yes			BEIR VII report 2006; Lindor et al. 2008
A-T gene		Yes		Yes			BEIR VII report 2006; Lindor et al. 2008
Rb1 gene (retinoblastoma, retinocytoma)	Yes		Yes				BEIR VII report 2006; Lindor et al. 2008; Journy et al. 2015, 2016
TP53						Yes	BEIR VII report 2006; Lindor et al. 2008; Journy et al. 2015, 2016
CHEK2				Yes			BEIR VII report 2006; Lindor et al. 2008; Journy et al. 2015, 2016
XRCC1			Yes	Yes			BEIR VII report 2006

[a]Not specific to a particular cancer type.
[b]Selection based on increased exposure to medical IR and general increased cancer risk.

effect, ↓ decrease in effect, and ✗ when no evidence of an effect was reported in each paper. To determine our confidence in the results from each study we used the GRADE-CerQual approach (35). Briefly, the assessment of each individual study was based on four components: (i) methodological limitations, (ii) coherence, (iii) adequacy of data, and (iv) relevance of studies according to PECO inclusion criteria; and later contributed to the overall assessment of confidence.

Results

Search results

Our primary search yielded 16,315 articles. **Figure 1** shows the flow diagram for our selection of relevant studies. Following duplicate removal ($n = 6{,}308$), 10,005 articles were screened at title/abstract level, leaving 109 full texts for review. Ninety-four full-text articles were excluded (see Supplementary Table S3). Briefly, 30 articles were excluded based on the population criterion; 27 on the basis of study design; 12 did not fulfill our exposure criterion; 8 were excluded based on the population and outcome criterion; 5 for not fulfilling the exposure/outcome criterion; another 5 based on the population and exposure criteria; 3 articles were missing and 4 studies did not contain primary data or outcome. A total of 15 publications were finally included in this review, two of which described the same study (21, 36).

Study characteristics and risk of bias

Study characteristics are summarized in **Table 2**. There were eight cohorts and six case–control studies. Ten studies assessed the effects of diagnostic medical exposures: CT scanning in four and chest radiography in six. Three studies assessed therapeutic exposures and one accidental exposure. All studies considered exposures before age 25 years, five specifically below age 15. Nine studies included dose estimation and five assessed exposure based on the number of X-ray examinations only.

Synthesis of evidence/results

Eight studies assessed the effects of CPFs on the IR-related breast cancer risk; three studied leukemia risk, three brain tumor risk, two studies thyroid cancer, and one lymphoma. **Table 3** summarizes the results of the studies.

Strong heterogeneity was observed across studies regarding exposure measures and risk estimates. The risk of bias assessment is summarized in **Fig. 2** and Supplementary Table S4.

A summary of the evidence and evaluation of the possible modifying effects of CPFs is provided, by outcome, in **Table 4**.

Leukemia

Three studies considered leukemia risk (refs. 21, 22, 36, 37; **Table 2**): two cohorts of young CT patients in France (Journy and colleagues; refs. 21, 36) and the UK (Berrington de Gonzalez and colleagues; ref. 22) and one population-based case–control study in Finland (Nikkilä and colleagues; ref. 37). In all studies, historical records of CT examinations were obtained from the Radiological Information Systems of the participating hospitals to reconstruct CT exposure history of the patients. Red bone marrow (RBM) dose estimates were

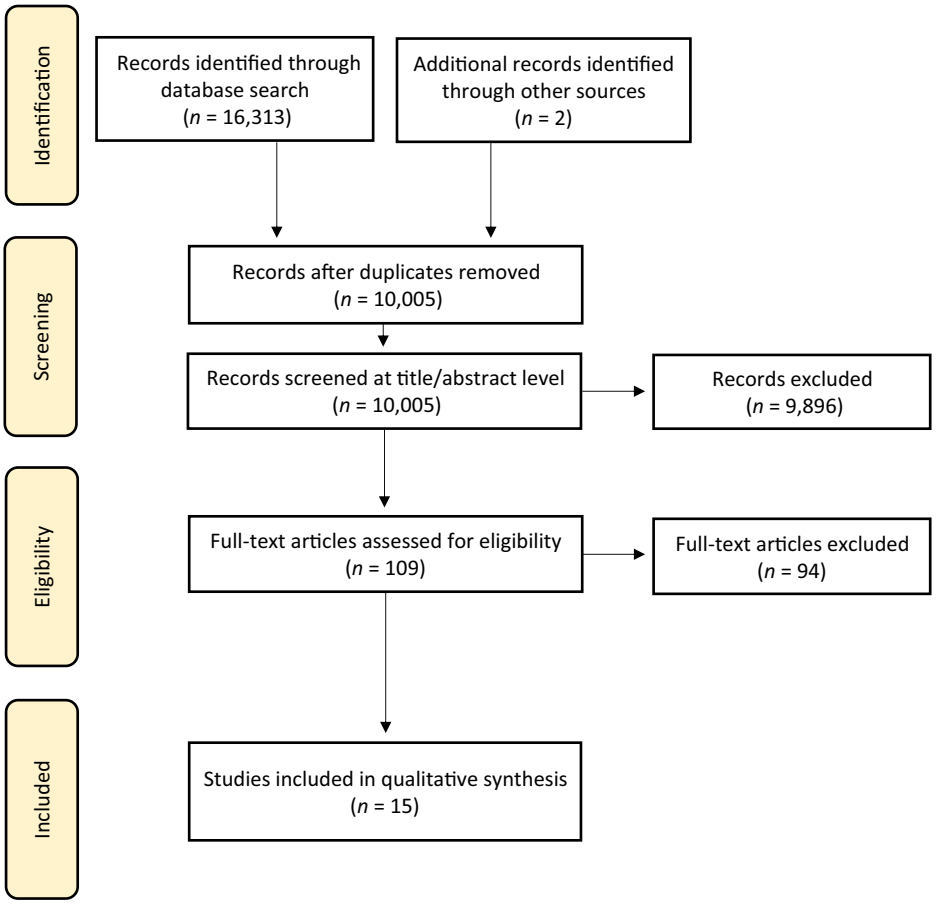

Figure 1.
Flow diagram displaying the results of the literature search and screening process.

Table 2. Characteristics of studies included.

	Methods					Radiation exposure		
Reference	**Study population and location**	**Study design**	**Sample size**	**Sex**	**CPFs**	**Type of exposure**	**Age at exposure**	**Dose distribution (mGy)**
Diagnostic exposure								
Andrieu et al. 2006	BRCA1 and BRCA2 mutation carriers *International* BRCA1/2 Carrier Cohort Study (IBCCS)—UK, NL, FR, AUSTRIA, SWE, SPAIN, DK, BELG, IT, GER, ICEL, HUNG, CA	Retrospective cohort	1,601 mutation carriers: Pseudo-incident subcohort: 969 BRCA 1 mutation: 726 BRCA 2 mutation: 243	Women only	BRCA1, BRCA2	Chest X-rays (excluding mammography)	<20 and ≥20	No estimation of dose Exposure metric is the number of X-rays. Never exposed 36% ≥1 period with 1–4 X-rays and none with ≥5 X-rays 33% ≥1 period with ≥5 X-rays* 31% *Breast dose unlikely to exceed 10–20 mGy.
Berrington de Gonzalez et al. 2016	Children and adolescents who underwent CT scanning. *Great Britain*	Retrospective Cohort	180,000	Women: 43.6% Men: 56.2%	Down, Noonan, Li–Fraumeni, Wiskott–Aldrich, Klinefelter, Shwachman–Diamond, Bloom, immunodeficiencies, nevoid basal cell, Turcot syndrome, Von Hippel–Lindau syndromes, Langerhans cell histiocytosis, Kostmann granulocytopenia, neurofibromatosis type 1 and type 2, ataxia telangiectasia, tuberous sclerosis, myelodysplasia monosomy, Fanconi anemia, solid organ, and bone marrow transplants	CT scans	<22 years	Dose range 2.32–51.13 RBM dose 0.25–330.18 Brain dose
Esther et al. 2007	Individuals part of the Breast Cancer Family Registry (Breast CFR) *Canada* (Ontario), *Australia* (Melbourne, Sydney)	Nested case–control study	2,254 cases: 402 with family history 1,704 without 3,431 controls (1,556 unaffected sisters and 1,875 unrelated population controls)	Women only	Family history of BC	Chest X-rays (excluding mammography)	<20 and ≥20	No estimation of dose Exposure metric is number of X-rays *≥10 X-rays for tuberculosis or pneumonia* Family history 4 ca, 14 cont without 17 ca, 14 cont *≥10 Other X-rays* Family history 16 ca, 114 cont without 60 ca, 114 cont

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Table 2. Characteristics of studies included. (Cont'd)

Methods						Radiation exposure		
Reference	**Study population and location**	**Study design**	**Sample size**	**Sex**	**CPFs**	**Type of exposure**	**Age at exposure**	**Dose distribution (mGy)**
Esther et al. 2013	BRCA 1 / 2 mutation carriers *USA, Canada, Australia / New Zealand*	Nested case–control study	BRCA1 carriers: Cases: 167 Controls: 287 BRCA2 carriers: Cases: 104 Controls: 169	Women only	BRCA 1 and BRCA 2	Chest X-rays (excluding mammography)	<20 and ≥20	No estimation of dose Distribution by number of X-rays. *BRCA1 cases* 0 X-ray 125 ca, 246 cont 1–2 11 ca, 16 cont 3–5 8 ca, 6 cont ≥6 6 ca, 7 cont Unknown 11 ca, 9 cont B*RCA2 cases* 0 76 ca, 133 cont 1–2 7 ca, 15 cont 3–5 9 ca, 2 cont ≥6 3 ca, 3 cont Unknown 5 ca, 12 cont
Gronwald et al. 2008	Early-onset breast cancer patients. *Szczecin, Poland*	Case–case study.	Cases: 138 BC cases with BRCA 1 mutation Controls: 158 BC cases without	Women only	BRCA 1	Chest X-rays (excluding mammography)	<30 years	No estimation of dose Mean number of chest X-rays before age 20 0.6 ca 0.3 cont
Journy et al. 2015	Children who underwent CT scanning	Retrospective Cohort	67 274	Women: 43%	Familial adenomatous polyposis, retinocytoma, multiple endocrine neoplasia (MEN1, MEN2), Fanconi anemia, ataxia telangiectasia, xeroderma pigmentosum, Bloom syndrome, neurofibromatosis type 1 and type 2, other phakomatoses, Noonan syndrome, Bloom syndrome, Down syndrome, Klinefelter, HIV/AIDS, severe combined immunodeficiency, Wiskott–Aldrich syndrome, common variable immunodeficiency, transplantation	CT scans	<10 years	Mean cumulative dose (sd)
			CPC of interest (*n*): 5 Leukemia CPF 7 Lymphoma CPF 7 Brain tumor CPF	Men: 57%				8.9 (10.7) RBM dose 23.1 (31.8) Brain dose
Lecarpentier et al. 2011	Carriers of BRCA1 or BRCA2 mutation *France*	Retrospective Cohort	1,337 mutation carriers Subcohort: 990 BRCA1 mutation: 635 BRCA 2 mutation 355	Women only	BRCA 1, BRCA 2	Chest X-rays (excluding mammography)	<20 and ≥20	No estimation of dose Number of X-rays.: *n* (%). Never exposed: 10 (3) 1 period with 1–4 X-rays: 12 (3) Two periods with 1–4 X-rays: 276 (77) ≥1 period with 5+ X-rays: 62 (17)

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Table 2. Characteristics of studies included. (Cont'd)

	Methods					Radiation exposure		
Reference	Study population and location	Study design	Sample size	Sex	CPFs	Type of exposure	Age at exposure	Dose distribution (mGy)
Meulepas et al. 2019	Children and adolescents who underwent CT scanning *Netherlands*	Retrospective Cohort	168,394 CPC of interest (*n*): Tuberous sclerosis (TSC) 82	Women: 46.1% Men: 53.9%	Tuberous sclerosis	CT scans	<18 years	Mean cumulative dose (IQR) 9.5 (2.0–11.8) RBM dose 38.5 (1.5–49.4) Brain dose
Nikkilä et al. 2018	General population *Finland*	Registry-based case–control study	Cases: 1,093 Controls: 3,279 CPC of interest (*n*): Down syndrome: Cases: 40 (3.5%) Controls: 2 (0.1%)	Women: 48% Men: 52%	Down syndrome	CT scans	<15 years	RBM dose (IQ) 10.1 (4.79–13.6) ca 6.29 (5.69–7.14) cont
Pijpe et al. 2012	Carriers of BRCA1/2 mutations *France, UK, Netherlands* (overlap with Andrieu and Lecarpentier)	Retrospective cohort study	1,994 mutation carriers Subcohort: 1,122 BRCA 1 mutation: 685 BRCA 2 mutation: 437	Women only	BRCA 1, BRCA 2	Conventional radiography of chest or shoulders, fluoroscopy, mammography	<20 years 20–29 30–39	Cumulative breast dose <2 23% 2–6.5 25% 6.6–17.3 28% ≥17.3 24%
Therapeutic exposure								
Kleinerman et al. 2005	1-year retinoblastoma survivors treated with radiotherapy *New York and Boston, US*	Retrospective cohort	Cohort sample size: 1,601 RB patients (following exclusion) Hereditary: 963 Nonhereditary: 638	Women: 47.2% Men: 52.8%	Rb1	Radiotherapy for retinoblastoma	<8 years	Mean breast dose 400 mGy
Little et al. 2014	Retinoblastoma survivors *US (Kleinerman cohort) and UK*	Retrospective case–control, nested within cohort Controls matched on sex, RB heritable status, and birth date	31 cases (17 heritable RB) 77 controls (42 heritable RB)	Women: US: 97% UK: 100%	Rb 1	Radiotherapy for retinoblastoma	<15 years	Mean (range) breast bud dose 160–170 (0–1,300) mGy
Momani et al. 2004	Patients treated with radiation for benign head and neck disorders *US*	Cohort	Cohort sample size: 4,296 treated for benign disorders 251 sibling pairs	Women: 50% Men: 50%	Sibling concordance	Radiotherapy for treatment of benign disease	<16 years	Thyroid dose 581 ± 210 Concordant pairs 679 ± 440 Discordant pairs
Damiola et al. 2014	General population *Gomel, Belarus*	Retrospective case–control	83 cases 324 controls	Women: 61% Men: 40%	Polymorphisms in SNPs related to PTC, thyroid biology, or radiation-induced second primary tumors	1,31I fall-out from Chernobyl accident	<15 years	Median thyroid dose (range) 674 (14–4,921) ca 390 (2–6,003) cont

Table 3. Synthesis of evidence and results.

Reference	Age at outcome (years)	Outcome	Summary of results	Comments	Direction of effect
Diagnostic exposure					
Andrieu et al. 2016	>18	Breast cancer	Pseudo-incident cohort—compared with nonexposed	Adjusted for parity and oophorectomy (yes/no), stratified by country group.	↑
	Mean subcohort: 41		HR 1.76 (0.9–3.4) – ≥ 1 period 1–4 X-rays 50 cases		
			HR 2.69 (1.4–5.3) – ≥ 1 one period 5+ 76 cases	Adjusted for surveillance bias.	
			HR 5.21 (1.6–17.5)—Exp before age 20 only 12 cases		
			HR 1.91 (0.9 –4.1)—Exp after age 20 only 26 cases		
Berrington de Gonzalez et al. 2016	All	Brain tumors	ERR 0.023/mGy (0.010–0.049)—overall 135 cases	Adjusted for sex, attained age, age at exposure, SES.	✗
			ERR 0.027/mGy (0.010–0.065)—excluding brain tumor-related conditions 106 cases	Doses lagged by 2 years for leukemia and 5 years for brain tumors	
		Leukemia / MDS	ERR 0.036/mGy (0.005–0.118)—overall 74 cases		✗
			ERR 0.034/mGy (0.004–0.116)—excluding leukemia-related conditions /PF 67 cases		
Esther et al. 2007	18–69	Breast cancer	Cases with a family history of breast cancer vs. all controls	Adjusted for age (<35, 35–44, 45–54, ≥55), study center (Ontario, Australia), country of birth (same as study center: yes, no), education (high school graduate or less, some college or vocational school, university degree).	✗
			X-ray for TB or pneumonia		
			OR 2.27 (1.37–3.76): < 10 X-rays 21 cases, 80 controls		
			OR 2.75 (0.89–8.53): ≥ 10 X-rays 4 cases, 14 controls		
			OR 2.61 (1.51–4.51): age 1st exp < 20 18 cases, 64 controls		
			Other X-rays		
			OR 0.78 (0.60–1.01): < 10 X-rays 86 cases, 804 controls	Similar results when adjusting for personal history of benign breast disease, age at menarche, number of full-term pregnancies, age at first full-term pregnancy, menopausal status, oral contraception, hormonal therapy, alcohol consumption, and smoking.	
			OR 1.07 (0.62–1.85): ≥ 10 X-rays 16 cases, 114 controls		
			OR 1.21 (0.86–1.70): age 1st exp < 20 49 cases, 295 controls		
			Cases *without a family history* of breast cancer vs. all controls		
			X-ray for TB or pneumonia		
			OR 2.18 (1.57–3.02): < 10 X-rays 81 cases, 80 controls		
			OR 2.35 (1.13–4.89): ≥ 10 X-rays 17 cases, 14 controls		
			OR 2.51 (1.76–3.60): age 1st exp < 20 71 cases, 64 controls	Majority of cases had first exposure after 20 years of age.	
			Other X-rays		
			OR 0.72 (0.61–0.84): < 10 X-rays 294 cases, 804 controls		
			OR 1.21 (0.89–1.69): ≥ 10 X-rays 60 cases, 114 controls		
			OR 1.04 (0.83–1.30): age 1st exp< 20 143 cases, 295 controls		
Esther et al. 2013	<50	Breast cancer	**BRCA 1 mutation carriers**	Adjusted for reference age (<40 and 40–49 years), country/region, history of breast or ovarian cancer in first-degree relatives (yes, no), and number of full-term pregnancies). Subcohort: carriers diagnosed with breast cancer/censored within five years before questionnaire completion, follow-up counted only for this five-year period.	✗
			OR 1.0: No chest X-rays 125 cases, 246 controls		
			OR 0.84 (0.33–2.13): 1–2 chest X-rays 11 cases, 16 controls		
			OR 1.22 (0.35–4.21): 3–5 chest X-rays 8 cases, 6 controls		
			OR 1.20 (0.37–3.96): ≥ 6 chest X-rays 6 cases, 7 controls		
			OR 1.75 (0.57–5.35): unknown number 11 cases, 9 controls	Majority of cases had first exposure after 20 years of age.	
			OR 0.57 (0.22–1.48): age 1st exp < 20 years 10 cases, 22 controls		
			OR 1.69 (0.76–3.76): age 1st exp ≥ 20 years 21 cases, 14 controls		

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Table 3. Synthesis of evidence and results. (Cont'd)

Reference	Age at outcome (years)	Outcome	Summary of results	Comments	Direction of effect
			OR 2.58 (0.42–15.8): unknown age 1st exp 5 cases, 2 controls **BRCA 2 mutation carriers** OR 1.0: No chest X-rays 76 cases, 133 controls OR 0.80 (0.28–2.28): 1–2 chest X-rays 7 cases, 15 controls OR 10.63 (1.93–58): 3–5 chest X-rays 9 cases, 2 controls OR 0.89 (0.15–5.49): ≥ 6 chest X-rays 3 cases, 3 controls OR 0.62 (0.18–2.17): unknown number 5 cases, 12 controls OR 1.55 (0.54–4.47): age 1st exp < 20 years 9 cases, 10 controls OR 1.06 (0.43–2.60): age 1st exp ≥ 20 years 11 cases, 17 controls OR 1.12 (0.24–5.26): unknown age 1st exp 4 cases, 5 controls		
Gronwald et al. 2008	<50	Breast cancer	Carriers (BRCA1) vs. noncarriers OR 1.8 (1.0–3.2): 1 chest X-ray < 20 years *numbers not specified* OR 5.7 (1.2–27): 4+chest X-rays < 20 years	Adjusted for birth year, age at diagnosis.	↑
Journy et al. 2015	Children <15	CNS Cancer	ERR 0.022/mGy (−0.016; 0.061): overall 22 cases ERR 0.028/mGy: excluding CNS PF 15 cases	Adjusted for sex, period of birth, attained age and time since entry in cohort, presence of any PF (yes/no) or presence of specific PF.	✗
		Leukemia	ERR 0.057/mGy (−0.079; 0.193): overall 17 cases ERR 0.187/mGy: excluding leukemia PF 12 cases	Lag period of 1–4 years was tested.	↓
		Lymphoma	ERR 0.018/mGy (−0.068; 0.104): overall 19 cases ERR 0.025/mGy: excluding lymphoma PF 12 cases		✗
Journy et al. 2016	Children <15	CNS tumor	HR 1.07/10 mGy (0.99–1.10): no PF 15 cases HR 0.80/10 mGy (0.45–1.06): with a PF 7 cases Interaction *P* value 0.22	Adjustment for sex and age at cohort entry.	✗
		Leukemia	HR 1.16/10 mGy (0.77–1.27): no PF 12 cases HR 0.57/10 mGy (0.06–1.32): with a PF 5 cases Interaction *P* value: 0.42		✗
Lecarpentier et al. 2011	>18 Mean: 44	Breast cancer	HR exposed vs. nonexposed 4.83 (1.83-12.8) one period with 1–4 X-rays 12 cases 6.22 (2.94-13.1) two periods with 1–4 X-rays 276 cases 2.80 (1.30–6.05) one period with 5+ X-rays 62 cases 4.16 (2.03–8.56): age at 1st exp. < 20 years 331 cases 6.45 (2.86–14.6): age at 1s^{t} exp. ≥ 20 years 34 cases	Adjusted for menopausal status (yes/no), parity, BMI, and gene. 90% cases had 1st exposure before age 20	✗
Meulepas et al. 2019	Children, adolescents, and adults NA	Brain tumors	Overall brain tumor risk ERR 0.0086 mGy (0.002–0.022) 84 cases Exclusion of TSC subjects did not change risk estimate (*not shown)* ERR 0.0079/mGy (0.002–0.021) 81 cases	Adjusted for age, sex, and calendar period, quartiles of income, and house value. Dose lagged by 5 years.	✗
Nikkilä et al. 2018	<15	Leukemia	Overall Leukemia risk (NCICT dosimetry) EOR 0.13/mGy (0.02-0.26) 15 cases, 10 controls exposed Down syndrome–radiation Interaction *P* value: 0.99 (risk estimate not shown: 5 cases of Down Syndrome)	Adjustments for large for gestational age, maternal smoking during pregnancy, parental education, and parental socioeconomic status. Dose lagged by 2 years.	✗

(Continued on the following page)

Table 3. Synthesis of evidence and results. (Cont'd)

Reference	Age at outcome (years)	Outcome	Summary of results	Comments	Direction of effect
Pijpe et al. 2012	>18 Mean: subcohort 41	Breast cancer	Exposed < 20 years HR 1.47 (0.89–2.42) <2 mGy 31 cases HR 1.09 (0.41–2.91) 2–6.5 mGy 6 cases HR 3.16 (1.19–8.36) 6.6 mGy+ 12 cases	Adjusted for age at entry in subcohort, parity, and menopause and clustered on family.	↑
Therapeutic exposure					
Kleinerman et al. 2005	Adults ≥ 40	Breast cancer	Hereditary RB survivors vs. general population SIR 3.3 (0.4–12): no radiation exposure 2 cases SIR 4.2 (1.8–8.2): moderate exposure 8 cases Overall SIRs: without taking radiation into account SIR 3.96 (1.9–7.3) hereditary RB SIR 2.84 (1.1–5.9) nonhereditary RB without taking radiation into account	Adjusted for age, sex, and calendar period.	✗
Little et al. 2014	Young adults and adults Range (mean): 25–56.1 (41.9)	Breast cancer	OR at 100 mGy 1.96 (1.06–inf) nonhereditary RB 8 cases and 0 controls 0.80 (0.58–1.04) hereditary RB 24 cases and 64 controls heterogeneity *p*- value 0.026	Adjusted for chemotherapy (US cohort) and bilateral blindness.	↓
Momani et al. 2004	Young adults and adults Mean (SD): 30.9 (10.1)	Thyroid cancer	No difference from expected 20: concordant pairs 63: discordant pairs		✗
Environmental exposure					
Damiola et al. 2014	Children, adolescents, and young adults <25 years	Papillary thyroid carcinoma	OR 0.34/mGy (0.16–0.73) ATM (D1853N) LRT interaction *P* value 0.45 OR 0.95/mGy (0.40–2.29) ATM P1526P (rs1800889) LRT interaction *P* value 0.02: ns when adjusted for multiple comparison OR 1.55/mGy (1.03–2.34) FOXE1 5′UTR (rs1867277) LRT interaction *P* value 0.53	Adjusted for age and sex through matching as well as iodine deficiency and supplementation.	✗

estimated for each CT scan from typical protocols, based on age, gender, examination type, and body part scanned (38–40) independently of disease status. Individual cumulative RBM doses were generally well below 100 mGy, ranging between 2 and 51 mGy. Doses from other medical procedures (e.g., conventional radiography, nuclear medicine, fluoroscopy) were not available. This is unlikely to lead to severe bias, however, as CT is likely to be, by far, the dominant radiation source overall.

Despite the large sample sizes of the studies, the number of leukemia cases among exposed individuals was relatively small: 17 and 74 cases, respectively, in the Journy and colleagues (21, 36) and Berrington de Gonzalez and colleagues (22) studies, and 15 cases in the Nikkilä and colleagues (37) study (**Table 3**).

Leukemia CPFs considered varied between studies (**Table 2**): only Down syndrome in the Nikkilä and colleagues study (37); a large number of genetic conditions and immunodeficiencies were considered in Journy and colleagues and Berrington de Gonzalez and colleagues studies (21, 22, 36). The number of exposed cases with leukemia CPFs was small in all studies: 7 and 5, respectively, in Journy and colleagues (21, 36), Berrington de Gonzalez and colleagues and Nikkilä and colleagues (37).

Studies by Journy and colleagues (21, 36) and Berrington de Gonzalez and colleagues (22) assessed the effect of leukemia CPFs on radiation risk estimates by comparing excess relative risk (ERR) estimates including and excluding subjects with these CPFs. Resulting estimates in Berrington de Gonzalez and colleagues (22) were nearly identical (**Table 3**). In Journy and colleagues (21), the ERR/mGy was higher (0.187 vs. 0.057) in subjects with no CPFs, although findings were based on small numbers of cases and confidence intervals overlapped. In a further analysis of this study (36), the Hazard Ratio among subjects without CPFs was also higher than among those with CPFs, but there was no evidence for heterogeneity of risk between the two groups. There was also no evidence for heterogeneity of risk between subjects with and without Down syndrome in the Nikkilä and colleagues study (ref. 37; risk estimates not shown).

All studies adjusted for the main confounding factors—age, sex, time period and, in by Nikkilä and colleagues (37) and Berrington de Gonzalez and colleagues (22), a measure of socioeconomic status (**Table 3**). Estimates of RIC in CT studies are subject to potential confounding by indication (meaning children who undergo CT scanning may be at higher risk of cancer due to some underlying condition) and reverse causation (whereby the CT scan was performed to investigate early symptoms of a later diagnosed cancer). Reverse causation is expected to be minimal for leukemia, as CT scanning is generally not used for the initial diagnosis. Reasons for scans could not generally be identified, and thus it is difficult to directly assess the effects of reverse causation. To minimize potential confounding by reverse causation, and to allow for a minimal latency period between exposure and leukemia diagnosis, all studies excluded cancers within 2 years after exposure and lagged doses by 2 years, as is typically done in radiation epidemiology studies (1). Confounding by indication is mainly suspected if subjects with a CPF are more likely than others to undergo CT scanning. As the objective of the analyses presented here is precisely to evaluate whether such predisposing factors might modify the association between radiation dose and cancer risk, confounding by indication is not a concern here.

Overall, we found no evidence that the risk of leukemia following exposure to low–moderate doses of IR differed between children with

Study	Bias categories								Overall evaluation
	Recruitment	*Blinding*	*Exposure*	*Confounding*	*Outcome*	*Other*	*Selective reporting*	*Conflict of interest*	
Andrieu et al. 2006									Possible differential recall bias but likely small. Possible participation bias
Berrington de Gonzalez et al. 2016									Possible indication and reverse causation bias but lagging of doses done to minimise this
Damiola et al. 2014									
Esther et al. 2007									Possible differential recall bias but likely small. Confounding: Parity not considered. Possible participation bias
Esther et al. 2013									Possible differential recall bias but likely small. Possible participation bias
Gronwald et al. 2008									Possible differential recall bias. Confounding: No adjustment for important risk factors for BC. Age adjustment unclear. Possible participation bias
Journy et al. 2015; Journy et al. 2016									Possible indication and reverse causation bias but lagging of doses done to minimise this
Kleinerman et al. 2005									Confounding: Parity not considered. New cases were identified through contact with the study subjects or their families. Completeness of case ascertainment not mentioned
Lecarpentier et al. 2011									Possible differential recall bias but likely small. Possible participation bias
Little et al. 2014									Confounding: Parity not considered. US study: New cases were identified through contact with the study subjects or their families. Completeness of case ascertainment not mentioned
Meulepas et al. 2019									Possible indication and reverse causation bias but lagging of doses done to minimise this
Momani et al. 2004									Confounding: Possible surveillance bias after thyroid cancer in first sibling. New cases identified from follow-up questionnaires. Completeness not mentioned
Nikkilä et al. 2018									Possible indication and reverse causation bias but lagging of doses done to minimise this
Pijpe et al. 2012									Possible differential recall bias but likely small. Possible participation bias

Legend				
Sources of risk of bias				
Low risk	Probably low risk	Probably high risk	High risk	Not applicable
Overall evaluation of paper				
The study presents no major threats to validity				
The study presents one major threat to validity (specified within the cell)				
The study presents more than one threat to validity, with high correlation between the bias domains				
The study presents more than one threat to validity				

Figure 2.
Results based on the evaluation of the major risk of bias categories considered for each study.

and without a leukemia CPF (**Table 4**). Given the small numbers of subjects in the studies, however, we cannot rule out the existence of an effect and conclude there is inadequate evidence of increased risk of radiation-induced leukemia among children with leukemia-related CPFs.

Lymphoma

One study investigated the risk of lymphoma, the Journy and colleagues cohort of pediatric CT patients in France (21). Characteristics of the study are shown in **Table 2**, and issues of follow-up, dosimetry, and potential biases are described above in the section on leukemia. Nineteen cases of lymphoma were identified (**Table 3**), seven with a lymphoma CPF. The ERR was slightly lower but statistically compatible with the ERR among subjects without a lymphoma CPF.

We, therefore, found no evidence that the risk of lymphoma following exposure to low-moderate doses of IR was different between children with and without a lymphoma CPF (**Table 4**). Again, given the small numbers of subjects in the studies, we cannot rule out the existence of an effect and conclude there is inadequate evidence of increased risk of radiation-induced lymphoma among children with a lymphoma-related CPF.

Brain and central nervous system (CNS) tumors

Three studies investigated the risk of brain and CNS tumors (refs. 21, 22, 41; **Table 2**). Studies by Journy and colleagues (21, 36) and Berrington de Gonzalez and colleagues (22) are described above (section "Leukemia") with brain doses estimated following the same strategy as RBM dose estimation. The third was a cohort of young CT patients in the Netherlands, Meulepas and colleagues (41)), focusing on tuberous sclerosis complex (TSC). In Berrington de Gonzalez and colleagues (22), 135 brain and CNS tumors were identified, 19 with a brain CPF. In Journy and colleagues, there were 15 cases, 7 with a brain CPF (21, 36),

Table 4. Synthesis of studies contributing to the outcome.

		Elements for assessing the certainty in the evidence		CERQual assessment of confidence in the evidence	
Summary of review finding	**Studies contributing to the review finding**	**Factors that decrease confidence**	**Factors that increase confidence**		**Explanation of CERQual assessment**
Leukemia					
No indication of a greater leukemia risk following low–moderate IR exposure, between individuals with a leukemia CPF and without.	No major methodological concerns: Berrington de Gonzalez et al. 2016, Nikkilä et al. 2018, Journy et al. 2015/2016	**Methods:** All studies are subject to reverse causation but lagging of doses done to minimize this in all studies, as well as revision of medical records in Berrington de Gonzalez et al. 2016. **Consistency:** One study (Journy et al.) found a reduction in HR when excluding subjects with a leukemia CPF; the confidence intervals are wide and numbers are very small so results are consistent with no effect of exclusion (Berrington de Gonzalez et al. 2016) and no heterogeneity (Nikkilä et al. 2018). **Relevance:** All studies were relevant to the PECO question. **Data adequacy:** Statistical power of concern in 1/3 studies (Journy et al. 2015/2016) due to small sample size and short follow-up. Based on the nature of the data, i.e., different CPF considered in different studies and small numbers, risks for individual CPFs cannot be studied. **Type of effect estimated:** Only one study provided an estimate of leukemia risk/dose level in children with leukemia CPFs (Journy et al. 2016).	**Magnitude of effect:** The 3 studies demonstrated little to no change in effect when excluding children with leukemia CPFs compared with overall cancer risk suggesting no major effect modification. **Dose response:** No evidence of a dose response in subjects with leukemia CPF (Journy et al. 2016). No effect modification (Nikkilä et al. 2018)	Inadequate	The numbers of subjects with Leukemia CPFs in all papers are small; hence, we cannot rule out the existence of an effect.
Lymphoma					
No indication of a greater lymphoma risk following low–moderate IR exposure, between individuals with a lymphoma CPF and without.	No major methodological concerns: Journy et al. 2015	**Methods:** The study is subject to possible confounding by indication and reverse causation but lagging of doses done to minimize this. **Consistency:** Not applicable considering only one study met criteria. **Relevance:** Study relevant to PECO criteria. **Data adequacy:** Statistical power of concern due to small sample size and short follow-up. **Type of effect estimated:** ERR/mGy for lymphoma overall and excluding subjects with lymphoma CPFs.	**Magnitude of effect:** ERR/mGy increased slightly when excluding subjects with lymphoma CPFs, suggesting possible slightly lower risk/mGy **Dose response:** Not reported for lymphoma CPFs	Inadequate	The number of subjects with lymphoma CPFs in the study is small; hence, we cannot conclude the existence or not of an effect.

(Continued on the following page)

Table 4. Synthesis of studies contributing to the outcome. (Cont'd)

		Elements for assessing the certainty in the evidence		CERQual assessment of confidence in the evidence	
Summary of review finding	**Studies contributing to the review finding**	**Factors that decrease confidence**	**Factors that increase confidence**		**Explanation of CERQual assessment**
Brain and CNS tumor					
No indication of a greater brain and CNS cancer risk following low–moderate IR exposure, between individuals with a brain and CNS tumors CPF vs. without.	No methodological concerns: Berrington de Gonzalez et al. 2016, Meulepas et al. 2019 Some methodological concerns: Journy et al. 2015/2016	**Methods:** 1/3 studies presented some methodological concerns: short follow-up time and small sample size (Journy et al. 2015/2016). **Consistency:** No evidence for heterogeneity (Meulepas et al. 2019), possibly slightly lower risk (Berrington de Gonzalez et al. 2016, Meulepas et al. 2019). **Relevance:** All studies were relevant to the PECO question **Data adequacy:** Statistical power of concern in 1/3 studies (Journy et al. 2015/2016) due to small sample size and short follow-up. Based on the nature of the data, i.e., various CPFs considered in different studies and small numbers, risks for individual CPFs cannot be studied. **Type of effect estimated:** Only one study provided an estimate for brain and CNS tumor risk/dose level in children with brain and CNS tumor CPFs (Journy et al. 2016)—the other two compared risk estimates overall with those obtained when excluding subjects with brain and CNS tumor CPFs (Berrington de Gonzalez et al. 2016; Meulepas et al. 2019)	**Magnitude of effect:** Studies showed little to no modification of radiation-related brain tumor risk **Dose response:** No evidence of a dose-response in subjects with brain and CNS tumors CPFs (Journy et al. 2016). No effect modification (Meulepas et al. 2019)	Inadequate	The numbers of subjects with brain and CNS tumors CPFs in all papers are small; hence, we cannot rule out the existence of an effect.
Breast cancer					
BRCA 1 and 2					
Most studies suggest a greater risk following very low IR doses among carriers of a BRCA 1 or 2 mutation	No major methodologic concerns: Andrieu et al. 2016, Esther et al. 2007, Esther et al. 2013, Lecarpentier et al. 2011, Pijpe et al. 2012, Little et al. 2014 Some methodological concerns: Esther et al. 2007, Gronwald et al. 2008	**Methods:** Information about X-rays was collected by questionnaire and is therefore subject to recall bias in all studies. Any effect is expected to be small however. Two studies (Esther et al. 2007, Gronwald et al. 2008) did not adjust for important breast cancer risk factors. **Consistency:** Results of the studies are not entirely consistent. **Relevance:** The studies of BRCA1/2: analyses by the number of X-rays not specific to children, except in Pijpe et al.	**Magnitude of effect:** Apart from the studies by Esther and collaborators, the studies of BRCA 1 or 2 mutation carriers show risk estimates for X-rays that are considerably larger than those expected in the general population at these levels of doses. **Dose response:** Risk appears to increase with the number of X-rays in Andrieu et al. 2016, Pijpe et al. 2012, and Gronwald et al. 2008.	Limited	Several studies suggest that carriers of mutations in BRCA 1 or 2 have a greater risk of breast cancer following low doses but the results are not consistent across studies and methodological limitations cannot be ruled out.

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Table 4. Synthesis of studies contributing to the outcome. (Cont'd)

Summary of review finding	Studies contributing to the review finding	Elements for assessing the certainty in the evidence: Factors that decrease confidence	Elements for assessing the certainty in the evidence: Factors that increase confidence	CERQual assessment of confidence in the evidence	Explanation of CERQual assessment
		Data adequacy: Statistical power of concern in Esther et al. 2013. Concerns regarding validation of exposures with medical records (Andrieu et al. 2016, Lecarpentier et al. 2011, Little et al. 2014). Age at exposures not precise in three studies (Andrieu et al. 2016, Lecarpentier et al. 2011, Gronwald et al. 2008). **Type of effect estimated:** HR or OR by number of X-rays in all studies except Pijpe et al. 2012, where HR was by the level of dose.			
Retinoblastoma					
Reduced risk among those with heritable RB	Some methodologic concern: Kleinerman et al. 2005, Little et al. 2014	**Methods:** Both studies did not collect information on important breast cancer risk factors in particular parity. Possible ascertainment bias in Kleinerman et al. 2005 and in the US part of Little et al. 2014. **Consistency:** One study of RB found significant heterogeneity, with no or even a reduced risk of breast cancer in relation to radiation (Little et al. 2014), whereas the other found no effect. **Relevance:** Kleinerman et al. 2005 did not show analyses by the level of radiation dose. **Data adequacy:** Low statistical power in Kleinerman et al. 2005 **Type of effect estimated:** OR at 100 mGy in Little et al.	**Magnitude of effect:** Heterogeneity of risk between those with heritable and nonheritable RB (Little et al. 2014) **Dose response:** No dose-related risk of BC among those with heritable RB	Inadequate	Reduced risk in Little et al. 2014, Kleinerman is not informative.
Thyroid cancer					
No apparent interaction between CPFs and radiation dose on risk of thyroid cancer	No methodological concerns: Damiola et al. 2014 Some methodologic concerns: Momani et al. 2004	**Methods:** Possible ascertainment and surveillance bias in Momani et al. 2004 **Consistency:** Both studies are consistent in showing no effect. **Relevance:** All studies considered to meet PECO criteria. **Data adequacy:** Overall data are considered good quality. Statistical power of concern in both studies (Momani et al. 2004, Damiola et al. 2014) is insufficient to be able to detect the subtle variations in susceptibility. **Type of effect estimated:** Only one study provided a measure of risk/dose level (Damiola et al. 2014).	**Magnitude of effect:** Not reported **Dose-response:** Not reported	Inadequate	Neither study shows an increased risk in those with CPFs but numbers of subjects limited.

(Continued on the following page)

Table 4. Synthesis of studies contributing to the outcome. (Cont'd)

Summary of review finding	Studies contributing to the review finding	Elements for assessing the certainty in the evidence		CERQual assessment of confidence in the evidence	Explanation of CERQual assessment
		Factors that decrease confidence	Factors that increase confidence		
Level	**Definition**				
Sufficient	A causal association between the exposure and the outcome has been established. That is, a positive association has been observed in the body of evidence on radiation dose and the outcome of interest in studies in which chance, bias, and confounding were ruled out with reasonable confidence.				
Limited	A causal interpretation of the positive association observed in the body of evidence on radiation exposure and the outcome of interest is credible, but chance, bias, or confounding could not be ruled out with reasonable confidence.				
Inadequate	The available studies are of insufficient quality, consistency, or statistical precision to permit a conclusion to be drawn about the presence or the absence of a causal association between exposure and outcome.				
Evidence of lack of effect	There are several high-quality studies covering the full range of levels of exposure of interest, which are mutually consistent in not showing a positive association between dose/exposure and the studied outcome at any observed level of dose.				

whereas there were 84 cases, with 3 cases of TSC in Meulepas and colleagues (41).

The approach for dose estimation in Meulepas and colleagues (41) was similar to that used in Journy and colleagues (21, 36) and Berrington de Gonzalez and colleagues (22). Brain doses from CT examinations tended to be greater than RBM doses ranging from 1.5 to 77 mGy, with the highest estimated dose in the UK (22) for a single individual being over 300 mGy. Analyses were adjusted for age, sex, calendar period and, in Berrington de Gonzalez and colleagues (22) and Meulepas and colleagues (41), a measure of SES. All studies excluded cases developing cancer within 5 years after exposure and lagged doses by 5 years to minimize potential confounding by reverse causation, a choice supported by results of an independent, population-based series of 695 brain tumor cases ages 10 to 24 years from 14 countries (42).

All three studies assessed the effect of brain CPFs on RIC by comparing ERR/mGy in analyses including and excluding subjects with brain/CNS CPFs. Risk estimates changed minimally when subjects with brain CPFs were excluded (**Table 3**). In a further analysis of the Journy and colleagues study (36), the hazard ratio among subjects without CPFs was slightly higher than those with CPFs, but there was no evidence for heterogeneity of risk between the two groups.

Overall, we found no evidence that the risk of brain and CNS tumors following exposure at low-moderate doses of IR was different between children with and without CNS CPFs (**Table 4**). Again, given the small numbers of subjects in the studies, we cannot rule out the existence of an effect and conclude there is inadequate evidence of increased risk of radiation-induced brain and CNS tumors among young people with CPFs.

Breast cancer

Risk of breast cancer was investigated in five studies in relation to *BRCA1/2* mutations (43–48), to family history of breast cancer (48), and to heritable retinoblastoma (*Rb*; refs. 49, 50; **Table 2**).

BRCA 1 and 2 mutations

Most of the studies identified overlap partly (**Table 2**). The study by Andrieu and colleagues (43), based on the International BRCA1/2 Carrier Cohort Study (IBCCS), included 1,601 women with a mutation in one of the two genes recruited in Europe and Canada between 1997 and 2002. The study by Lecarpentier and colleagues (46) recruited 1,337 mutation carriers in France between 2000 and 2010, 319 of which were also included in the IBCCS. The cohort study by Pijpe and colleagues (44) included 1,994 mutation carriers, recruited as part of the GENE-RAD-RISK project between 2006 and 2009 in France (including 477 subjects from Lecarpentier and colleagues; ref. 46), the Netherlands, and the UK. There was also overlap between the cohorts in the Esther and colleagues (48) and Esther and colleagues (45) nested case–control studies. The former included 402 cases with a family history of breast cancer, whereas 271 *BRCA1/2* mutation carriers were considered in the latter (**Table 2**). Only the Polish case-case study of Gronwald and colleagues (47), is entirely independent. All studies of *BRCA1/2* mutation carriers were based on cohorts assembled from family cancer clinics, except Gronwald and colleagues (47), who recruited early onset of breast cancer cases from treatment centers across Poland and tested them for *BRCA 1* mutations. Recruitment from family clinics may induce a surveillance bias as disease status can affect the likelihood of case ascertainment, leading to an oversampling of affected women (Supplementary Table S3); however, analyses were corrected for such a bias through appropriate methods (51, 52).

Survival is another potential source of bias in studies of *BRCA 1* and *2* mutation carriers, where prevalent cases may have answered the questionnaire years after diagnosis of their diseases, whereas other cases died from breast cancer before questionnaire completion (Supplementary Table S3). The studies by Andrieu and colleagues (43), Pijpe and colleagues (44), and Esther and colleagues 2013 (45) presented analyses of subcohorts of "pseudo-incident" or relatively recent cases (diagnosed or censored within the five years before completion of the questionnaire) to minimize this potential bias.

A total of 126 exposed cases were identified in the "pseudo-incident" cohort of 969 carriers of *BRCA1/2* mutations in Andrieu et al, 365 in the subcohort of 990 women in Lecarpentier and colleagues and 49 in the subcohort of 1122 women in Pijpe and colleagues (**Table 3**). The number of exposed cases was not specified in Gronwald and colleagues (47). In the case–control study by Esther and colleagues (48), out of 402 cases with a family history of breast cancer, 25 reported at least one X-ray for TB or pneumonia and 305 at least one chest X-ray for other purposes. In the Esther and colleagues study (45), 36 out of 167 cases with a *BRCA1* mutation and 24 out of 104 cases with a *BRCA2* mutation reported at least one chest X-ray.

No individual dose reconstruction was conducted in most of the studies of *BRCA1/2* mutation carriers. Instead, breast cancer risk was evaluated as a function of the number of chest X-rays received (**Table 2**). No distinction was made between fluoroscopy and conventional X-rays, the former resulting in doses about 10 times higher,

on average, during the time period of relevance for exposures in these cohorts than the latter (44). Individual cumulative doses were estimated only in the study of Pijpe and colleagues (44), considering the types of examinations the subjects had undergone and nominal estimates of breast dose for fluoroscopy, radiography, mammography, and CT derived from a literature review and expert judgment—the average dose was low (14 mGy), of the order of several years of annual natural background radiation. Information on diagnostic procedures, collected through a questionnaire in studies of *BRCA 1/2* mutation carriers, is subject to recall bias (Supplementary Table S3). The extent of this bias is likely to be small, however, in populations of women who are at high breast cancer risk due to the mutations they carry.

All studies of *BRCA 1/2* mutation carriers adjusted for the main breast cancer risk factors, except Esther and colleagues (48), which did not adjust for parity, and Gronwald and colleagues (47), where adjustment variables are not clear.

The Andrieu and colleagues study (43) reported hazard ratios (HR) that increased with an increasing number of X-rays, with the highest risk estimate among subjects who only reported exposures before age 20 (**Table 3**). This pattern of risk, similar to that seen in other populations exposed to radiation at considerably higher levels, suggests that women with *BRCA1* or *2* mutations might be at higher risk of radiation-induced breast cancer than the general population. A similar pattern was seen in Gronwald and colleagues (47), where risk in carriers compared with noncarriers increased with the number of X-rays. The Pijpe and colleagues study (44), with individual dose estimates, also suggests an increased risk at very low doses, much lower than those at which similar increases have been observed in the general population. In Lecarpentier and colleagues (46), though elevated HRs were observed in all categories of numbers of X-rays, no trend with the number of X-rays was found, and the HR was somewhat higher (but statistically compatible) in subjects who reported a later age at first exposure.

Esther and colleagues (48), however, provide no evidence of differential risk between those with and without a family history of beast cancer, whereas Esther and colleagues (45), based on small numbers of exposed cases found no trend in OR by number of X-rays and no greater risk in those youngest at exposure.

The differences in results between the studies are difficult to interpret. Although the studies by Andrieu and colleagues (43), Gronwald and colleagues (47), Pijpe and colleagues (44), and Lecarpentier and colleagues (46) all found increased risks of breast cancer following extremely low doses (typically equivalent to a few days of natural background radiation), the two case–control studies by Esther and collaborators (45, 48) did not. The number of cases studied by Esther and colleagues (45) was low, however, and the proportion of subjects reporting chest X-rays is substantially lower than in the other studies. Further, although analyses of risk by age at first exposure (below 20 years and 20 and above) were conducted in all *BRCA1/2* mutation carrier studies, the analyses by the number of X-rays are not stratified by age at exposure, and hence direct estimation of the effect of *BRCA 1/2* mutations on breast cancer risk from exposure to radiation below the age of 20 is possible only in one study, that of Pijpe and colleagues (44). Differences in the distribution of X-rays at different ages may therefore confound a possible association.

Overall, therefore, we found limited evidence that carriers with a *BRCA1/2* mutation might modify breast cancer risk following exposure before the age of 20 (**Table 4**). Most studies suggest an increased risk but the results are not consistent across studies and methodological limitations cannot be ruled out.

Retinoblastoma

Kleinerman and colleagues (49) studied breast cancer risk in a cohort of women who had survived retinoblastoma from two US hospitals. Little and colleagues (50) conducted a case–control study of breast cancer, nested within the Kleinerman cohort (49) and within a separate UK cohort of childhood retinoblastoma survivors (**Table 2**).

In Kleinerman and colleagues (49), information was available only on whether subjects underwent radiotherapy or not, with no indication of the dose. In their case–control study, however, Little and colleagues (50) estimated individual doses for each subject, based on RT treatment details from records and detailed modeling of scatter radiation to the breast tissue based on doses to the eye.

In Kleinerman and colleagues (49), breast cancer cases were ascertained through contact with the study subjects or their families; hence, it is possible that some cases were missed (Supplementary Table S3). Diagnoses were validated with hospital records. As the US subjects in Little and colleagues (50) come from the Kleinerman and colleagues (49) study, the same limitation applies; the UK cases, however, were identified through linkage with the national population-based cancer registry. A further limitation of both studies is the lack of adjustment for important breast cancer risk factors, in particular parity (Supplementary Table S3).

Kleinerman and colleagues (49) found a similar SIR for breast cancer among those who were exposed to radiation and those who were not, but results are based on very small numbers of exposed cases (**Table 3**). Little and colleagues (50) found heterogeneity in risk between those with hereditary and nonhereditary retinoblastoma, with a lower OR among those with hereditary retinoblastoma. There was evidence of a dose–response relationship only among those whose retinoblastoma was not hereditary.

Overall, we found "inadequate" evidence supporting a reduced risk of radiation-induced breast cancer among individuals with hereditary retinoblastoma, based only on one study (50).

Thyroid cancer

Two studies investigated the risk of thyroid cancer (refs. 53, 54; **Table 2**). The first study, by Damiola and colleagues (53), studied polymorphic associated thyroid carcinoma (TC) risk following the Chernobyl nuclear accident in a population-based case–control study, of 83 cases and 324 controls from Belarus exposed in childhood. The second study, by Momani and colleagues (54), investigated familial concordance in relation to thyroid cancer risk in 251 exposed sibling pairs, with 83 thyroid cancer cases, from a cohort of 4,296 children treated for benign (head/neck) disorders in the USA.

In Damiola and colleagues (53), individual doses were estimated for each study subject (55) taking into account information obtained by questionnaire on the whereabouts and dietary habits of the study subjects and information on environmental contamination available for each settlement where they resided. The main contribution to thyroid dose was from ^{131}I, predominantly from milk intake. In Momani and colleagues (54), individual doses were estimated from RT records and modeling (56).

Case ascertainment is expected to be reasonably complete in Damiola and colleagues (53), where cancer cases were found in all appropriate medical and surgical departments in the study regions. In Momani and colleagues (54), however, cases were ascertained by questionnaires addressed to cohort members. There is, therefore, potential for ascertainment bias, as well as surveillance bias as most

members of the cohort were under surveillance for follow-up of their head/neck disorder.

Damiola and colleagues (53) found associations between papillary TC and a number of single-nucleotide polymorphism (SNP) and genes, as well as between papillary TC and radiation dose. Overall, however, the genetic polymorphisms studied and radiation dose appeared to act independently on the risk of TC, though the numbers of subjects in each analysis were small (**Table 3**). In Momani and colleagues (54), familial influence on TC risk was assessed by evaluating whether the distribution of tumors within family pairs could be accounted by known risk factors, considering years at risk, sex, age at exposure, and radiation dose. The distribution of concordant and discordant pairs was as expected (**Table 3**), suggesting no familial influence on the risk of radiation-induced thyroid cancer.

Overall, we found "inadequate evidence" that the risk of radiation-induced thyroid cancer following exposure to IR at low–moderate doses was different between children with and without a thyroid CPF. Neither study found an increased risk among those with CPFs but the numbers of subjects in the analyses limit the statistical power of the studies.

Discussion

The current systematic review aimed to identify cancer-predisposing factors that may modify the risk of radiation-induced cancer following exposure to low–moderate doses of ionizing radiation in populations below 25 years of age. To our knowledge, this is the first systematic review on the topic. Based on the scientific literature reviewed, we concluded that there was inadequate evidence that such factors increase or decrease the risk of radiation-induced leukemia, lymphoma, brain/CNS tumors, and thyroid cancers. However, for breast cancer, we found limited evidence that *BRCA1/2* mutation might increase the risk following very low doses of radiation, and this needs to be further explored.

Most of the studies reviewed—even the large-scale cohort studies of pediatric CT patients—identified very small numbers of exposed subjects with CPFs, resulting in low statistical power, as seen also in a recent systematic review of genetic susceptibility to radiation-induced thyroid cancer (57). The low prevalence of CPFs in these studies is not surprising considering the rarity of these conditions in the general population as well as, for some CPFs, the short life expectancy of the carriers (8, 23, 58). The CPF with highest prevalence in these studies was organ transplantation (about 1% in the Journy and colleagues study; ref. 21), a known risk factor for lymphoma (59). Prevalence was lower for other CPFs, 0.3% for Down syndrome and 0.05% for TSC in Journy and colleagues (21) and Meulepas and colleagues (41), respectively, and much less than 1/1,000 or 1/10,000 for most of the others (22). Because of this, analyses by Journy and colleagues (21, 36) and Berrington de Gonzalez and colleagues (22) have considered all CPFs as a group, when in fact any susceptibility conferred is likely to vary between types, and even these analyses were underpowered as shown above.

The only studies with some statistical power to evaluate a possible effect were studies of cohorts of women selected on the basis of CPF status—namely, women with a *BRCA1* or *2* mutation or with hereditary RB—and hence all, or the majority of study participants, had a CPF. Several of these studies suggest that risk among *BRCA1/2* carriers at very low doses (of the level of one-year dose from natural background radiation) is much higher than in the general population, increases with the number of chest X-rays and may be highest for exposures at younger ages. Results are not entirely consistent across studies; hence, they provide only limited evidence of an effect of CPF on risk of RIC. The studies reviewed are subject to some limitations that need to be better addressed in the future. Apart from Pijpe and colleagues, studies (43, 46, 47) only considered chest X-ray exposures; whereas in these studies, X-rays (both fluoroscopy and conventional) were likely to be the main source of dose, missing doses from other procedures may potentially bias risk estimates. Moreover, Pijpe and colleagues (44) was the only study providing individual radiation dose estimates to the breast. Information about exact age at exposure was generally missing, with information collected only about X-ray procedures in different age ranges. Though a number of other specific gene mutations were included in our systematic review, only studies of *RB* and *BRCA1/2* mutations were found.

The effect of mutations in a number of specific genes—including *BRCA1*, *BRCA2*, *ATM*, *TP53*, *CHEK2*—on risk of radiation-induced breast cancer has only been examined systematically in one study, the large multinational WECARE study of contralateral breast cancer following moderate–high doses of RT in adults (60, 61). WECARE provided no clear indication that carriers of *BRCA1/2* mutations were more susceptible to RIC than noncarriers (60), though *ATM* mutations appeared to increase the risk of contralateral breast cancer after RT (62).

Although the role of specific mutations as modifiers of radiation-induced breast cancer risk in cancer survivors is unclear due to the rarity of these mutations, recent genetic associations studies in adult women who received low doses of radiation in occupational settings suggest that common susceptibility variants may play an important role in modulating RIC (63–69). Indeed, a genome-wide association study identified specific variants that appear to confer a higher risk of radiation-induced breast cancer among childhood cancer survivors (70). Polygenic risk scores (PRS), aggregating associations with many variants, are increasingly being used in gene–environment interaction to identify risks that may not be detectable for individual variants (71). This method was also used in the WECARE study, in which a PRS comprising variants in DNA repair pathways was associated with an increased risk of subsequent radiation-associated contralateral breast cancer (72). Similarly, the use of a PRS among Hodgkin lymphoma patients confirms the existence of genetic susceptibility to radiation-induced breast cancer (73). These results have important implications for the radiation protection of patients.

To adequately address whether CPFs may modify the risk of RICs in young people, further studies with sufficient power are necessary. Given the rarity of CPFs in the general population, informative studies should be based either on (i) cohorts of persons who are carriers of mutations of interest—e.g., *BRCA1/2*, *AT* heterozygotes—in which detailed information regarding radiation exposure can be obtained and doses estimated either at the level of the cohort or in a nested case–control study; or (ii) general population/patient studies with adequate individual dosimetry, focusing on common variants using PRS.

Children with genetic conditions that confer an increased susceptibility to RIC are of particular concern in medical radiation protection (8, 11). If such children can be identified, personalized screening, surveillance, management, and treatment can be offered to reduce their risk of RIC. The studies identified in this systematic review are too limited—mainly because of low statistical power—to address this issue, with the exception of studies of women with *BRCA1/2* mutations that provided limited evidence of an increased risk of RIC. Further studies with more appropriate study designs are

needed to better identify cancer-predisposing conditions/variants that may increase the risk of RIC.

Authors' Disclosures

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Note

Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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References

1. International Agency for Research on Cancer, Weltgesundheitsorganisation, editors. IARC monographs on the evaluation of carcinogenic risks to humans, volume 100 D, radiation: this publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 02 - 09 June 2009. Lyon: IARC; 2012. p. 341.
2. Pearce N, Blair A, Vineis P, Ahrens W, Andersen A, Anto JM, et al. IARC monographs: 40 years of evaluating carcinogenic hazards to humans. Environ Health Perspect 2015;123:507–14.
3. Hauptmann M, Daniels RD, Cardis E, Cullings HM, Kendall G, Laurier D, et al. Epidemiological studies of low-dose ionizing radiation and cancer: summary bias assessment and meta-analysis. JNCI Monogr 2020;2020:188–200.
4. Kleinerman RA. Cancer risks following diagnostic and therapeutic radiation exposure in children. Pediatr Radiol 2006;36:121–5.
5. Dracham CB, Shankar A, Madan R. Radiation induced secondary malignancies: a review article. Radiat Oncol J 2018;36:85–94.
6. Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, Board on Radiation Effects Research, Division on Earth and Life Studies, National Research Council. Health risks from exposure to low levels of ionizing radiation: BEIR VII Phase 2 [Internet]. National Academies Press; 2006. p. 1. (Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2). [cited 2020 Feb 17]. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85032843101&doi=10.17226%2f11340&partnerID=40&md5=1de4e596edeee67087e3c219b572bf71.
7. Scholz-Kreisel P, Kaatsch P, Spix C, Schmidberger H, Marron M, Grabow D, et al. Second malignancies following childhood cancer treatment in Germany from 1980 to 2014. Dtsch Ärztebl Int 2018;115:385–92.
8. UNSCEAR. Sources, effects and risks of ionizing radiation, UNSCEAR 2013 report, Volume II: Scientific Annex B. Geneva: United Nations; 2014.
9. Bouffler SD, Auvinen A, Baiocco G, Candéias S, Cardis E, Galderisi U, et al. MELODI strategic research agenda 2021. The MELODI platform; 2021. [cited 2022 Feb 9]. Available from: https://melodi-online.eu/wp-content/uploads/2021/10/MELODI-SRA-2021-FINAL-post-consultation.pdf.
10. UNSCEAR. Sources, effects and risks of ionizing radiation. UNSCEAR 2013 report to the General Assembly with scientific annexes. Vol. II, scientific annex B. Vol. II, scientific annex B. [Internet]. 2013 [cited 2021 Jul 13]. Available from: http://search.ebscohost.com/login.aspx?direct=true&scope=site&db=e000xna&AN=857633.
11. Kleinerman RA. Radiation sensitive genetically susceptible pediatric sub-populations. Pediatr Radiol 2009;39:S27–31.
12. McKusick VA. Mendelian inheritance in man and its online version, OMIM. Am J Hum Genet 2007;80:588–604.
13. Bourguignon MH, Gisone PA, Perez MR, Michelin S, Dubner D, Giorgio MD, et al. Genetic and epigenetic features in radiation sensitivity: Part II: implications for clinical practice and radiation protection. Eur J Nucl Med Mol Imaging 2005;32:351–68.
14. Cleaver JE. Defective repair replication of DNA in xeroderma pigmentosum. Nature 1968;218:652–6.
15. Bourguignon MH, Gisone PA, Perez MR, Michelin S, Dubner D, Giorgio MD, et al. Genetic and epigenetic features in radiation sensitivity: Part I: cell signalling in radiation response. Eur J Nucl Med Mol Imaging 2005;32:229–46.
16. Reid JR, States LJ. Ionizing radiation use and cancer predisposition syndromes in children. J Am Coll Radiol 2018;15:1238–9.
17. Walsh MF, Chang VY, Kohlmann WK, Scott HS, Cunniff C, Bourdeaut F, et al. Recommendations for childhood cancer screening and surveillance in DNA repair disorders. Clin Cancer Res 2017;23:e23–31.
18. Moher D. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Ann Intern Med 2009;151:264.
19. Cochrane handbook for systematic reviews of interventions. [cited 2019 Nov 26]. Available from: https://handbook-5-1.cochrane.org/.
20. Morgan RL, Whaley P, Thayer KA, Schünemann HJ. Identifying the PECO: a framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. Environ Int 2018;121:1027–31.
21. Journy N, Rehel JL, Ducou Le Pointe H, Lee C, Brisse H, Chateil JF, et al. Are the studies on cancer risk from CT scans biased by indication? Elements of answer from a large-scale cohort study in France. Br J Cancer 2015;112:185–93.
22. Berrington de Gonzalez A, Salotti JA, McHugh K, Little MP, Harbron RW, Lee C, et al. Relationship between paediatric CT scans and subsequent risk of leukaemia and brain tumours: assessment of the impact of underlying conditions. Br J Cancer 2016;114:388–94.
23. Lindor NM, McMaster ML, Lindor CJ, Greene MH. Concise handbook of familial cancer susceptibility syndromes, second edition. JNCI Monogr 2008;2008:3–93.
24. Schmitz-Feuerhake I, Frentzel-Beyme R, Wolff R. Non-Hodgkin lymphomas and ionizing radiation: case report and review of the literature. Ann Hematol 2022;101:243–50.
25. Hunter N, Haylock R. Radiation risks of lymphoma and multiple myeloma incidence in the updated NRRW-3 cohort in the UK: 1955–2011. J Radiol Prot 2022;42:011517.
26. Pasqual E, Turner MC, Gracia-Lavedan E, Casabonne D, Benavente Y, Chef IT, et al. Association of ionizing radiation dose from common medical diagnostic procedures and lymphoma risk in the Epilymph case-control study. PLoS One 2020;15:e0235658.
27. Harbron RW, Pasqual E. Ionising radiation as a risk factor for lymphoma: a review. J Radiol Prot 2020;40:R151–85.
28. Kohl C, McIntosh EJ, Unger S, Haddaway NR, Kecke S, Schiemann J, et al. Online tools supporting the conduct and reporting of systematic reviews and systematic maps: a case study on CADIMA and review of existing tools. Environ Evid 2018;7:8.
29. Lundh A, Gøtzsche PC. Recommendations by Cochrane Review Groups for assessment of the risk of bias in studies. BMC Med Res Methodol 2008;8:22.
30. Morgan RL, Thayer KA, Santesso N, Holloway AC, Blain R, Eftim SE, et al. A risk of bias instrument for non-randomized studies of exposures: a users' guide to its application in the context of GRADE. Environ Int 2019;122:168–84.
31. Table 8.5.d: Criteria for judging risk of bias. [cited 2019 Sep 8]. Available from: https://handbook-5-1.cochrane.org/chapter_8/table_8_5_d_criteria_for_judging_risk_of_bias_in_the_risk_of.htm.
32. Johnson PI, Sutton P, Atchley DS, Koustas E, Lam J, Sen S, et al. The navigation guide—evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. Environ Health Perspect. 2014;122:1028–39.
33. Savitz DA, Wellenius GA, Trikalinos TA. The problem with mechanistic risk of bias assessments in evidence synthesis of observational studies and a practical alternative: assessing the impact of specific sources of potential bias. Am J Epidemiol 2019;188:1581–5.
34. Popay J, Roberts H, Sowden A, Petticrew M, Arai L, Rodgers M, et al. Guidance on the conduct of narrative synthesis in systematic reviews. [cited 2019 Sep 26]. Available from: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.178.3100&rep=rep1&type=pdf.

35. Lewin S, Bohren M, Rashidian A, Munthe-Kaas H, Glenton C, Colvin CJ, et al. Applying GRADE-CERQual to qualitative evidence synthesis findings—paper 2: how to make an overall CERQual assessment of confidence and create a summary of qualitative findings table. Implement Sci 2018;13:10.
36. Journy N, Roué T, Cardis E, Pointe HDL, Brisse H, Chateil JF, et al. Childhood CT scans and cancer risk: impact of predisposing factors for cancer on the risk estimates. J Radiol Prot 2016;36:N1-7.
37. Nikkilä A, Raitanen J, Lohi O, Auvinen A. Radiation exposure from computerized tomography and risk of childhood leukemia: Finnish register-based case-control study of childhood leukemia (FRECCLE). Haematologica 2018;103:1873–80.
38. Lee C, Kim KP, Bolch WE, Moroz BE, Folio L. NCICT: a computational solution to estimate organ doses for pediatric and adult patients undergoing CT scans. J Radiol Prot 2015;35:891–909.
39. Lee C, Kim KP, Long DJ, Bolch WE. Organ doses for reference pediatric and adolescent patients undergoing computed tomography estimated by Monte Carlo simulation: pediatric organ dose for computed tomography. Med Phys 2012;39:2129–46.
40. Kim KP, Berrington de Gonzalez A, Pearce MS, Salotti JA, Parker L, McHugh K, et al. Development of a database of organ doses for paediatric and young adult CT scans in the United Kingdom. Radiat Prot Dosimetry 2012;150:415–26.
41. Meulepas JM, Ronckers CM, Smets AMJB, Nievelstein RAJ, Gradowska P, Lee C, et al. Radiation exposure from pediatric CT scans and subsequent cancer risk in the Netherlands. JNCI J Natl Cancer Inst 2018;111:256–63.
42. Zumel-Marne A, Kundi M, Castaño-Vinyals G, Alguacil J, Petridou ET, Georgakis MK, et al. Clinical presentation of young people (10–24 years old) with brain tumors: results from the international MOBI-Kids study. J Neurooncol 2020;147:427–40.
43. Andrieu N, Easton DF, Chang-Claude J, Rookus MA, Brohet R, Cardis E, et al. 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 2006;24:3361–6.
44. Pijpe A, Andrieu N, Easton DF, Kesminiene A, Cardis E, Noguès C, et al. Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations: retrospective cohort study (GENE-RAD-RISK). BMJ Online 2012;345:e5660.
45. John EM, McGuire V, Thomas D, Haile R, Ozcelik H, Milne RL, et al. Diagnostic chest x-rays and breast cancer risk before age 50 years for BRCA1 and BRCA2 mutation carriers. Cancer Epidemiol Biomarkers Prev 2013;22:1547–56.
46. Lecarpentier J, Noguès C, Mouret-Fourme E, Stoppa-Lyonnet D, Lasset C, Caron O, et al. Variation in breast cancer risk with mutation position, smoking, alcohol, and chest X-ray history, in the French National BRCA1/2 carrier cohort (GENEPSO). Breast Cancer Res Treat 2011;130:927–38.
47. Gronwald J, Pijpe A, Byrski T, Huzarski T, Stawicka M, Cybulski C, et al. Early radiation exposures and BRCA1-associated breast cancer in young women from Poland. Breast Cancer Res Treat 2008;112:581–4.
48. John EM, Phipps AI, Knight JA, Milne RL, Dite GS, Hopper JL, et al. Medical radiation exposure and breast cancer risk: findings from the breast cancer family registry. Int J Cancer 2007;121:386–94.
49. Kleinerman RA, Tucker MA, Tarone RE, Abramson DH, Seddon JM, Stovall M, et al. Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: an extended follow-up. J Clin Oncol 2005;23:2272–9.
50. Little MP, Schaeffer ML, Reulen RC, Abramson DH, Stovall M, Weathers R, et al. Breast cancer risk after radiotherapy for heritable and non-heritable retinoblastoma: a US–UK study. Br J Cancer 2014;110:2623–32.
51. Antoniou AC, Goldgar DE, Andrieu N, Chang-Claude J, Brohet R, Rookus MA, et al. A weighted cohort approach for analysing factors modifying disease risks in carriers of high-risk susceptibility genes. Genet Epidemiol 2005;29:1–11.
52. Whittemore AS, Halpern J. Multi-stage sampling in genetic epidemiology. Stat Med 1997;16:153–67.
53. Damiola F, Byrnes G, Moissonnier M, Pertesi M, Deltour I, Fillon A, et al. Contribution of ATM and FOXE1 (TTF2) to risk of papillary thyroid carcinoma in Belarusian children exposed to radiation. Int J Cancer 2014;134:1659–68.
54. Momani MS, Shore-Freedman E, Collins BJ, Lubin J, Ron E, Schneider AB. Familial concordance of thyroid and other head and neck tumors in an irradiated cohort: analysis of contributing factors. J Clin Endocrinol Metab 2004;89:2185–91.
55. Drozdovitch V, Maceika E, Khrouch V, Zvonova I, Vlasov O, Bouville A, et al. Uncertainties in individual doses in a case–control study of thyroid cancer after the Chernobyl accident. Radiat Prot Dosimetry 2007;127:540–3.
56. Schneider AB, Ron E, Lubin J, Stovall M, Gierlowski TC. Dose-response relationships for radiation-induced thyroid cancer and thyroid nodules: evidence for the prolonged effects of radiation on the thyroid. J Clin Endocrinol Metab 1993;77:362–9.
57. Zidane M, Cazier JB, Chevillard S, Ory C, Schlumberger M, Dupuy C, et al. Genetic susceptibility to radiation-related differentiated thyroid cancers: a systematic review of literature. Endocr Relat Cancer 2019;26:R583–96.
58. Hernán MA, Clayton D, Keiding N. The Simpson's paradox unraveled. Int J Epidemiol 2011;40:780–5.
59. Clarke CA, Morton LM, Lynch C, Pfeiffer RM, Hall EC, Gibson TM, et al. Risk of lymphoma subtypes after solid organ transplantation in the United States. Br J Cancer 2013;109:280–8.
60. Bernstein JL, Thomas DC, Shore RE, Robson M, Boice JD, Stovall M, et al. Contralateral breast cancer after radiotherapy among BRCA1 and BRCA2 mutation carriers: a WECARE study report. Eur J Cancer 2013;49:2979–85.
61. Stovall M, Smith SA, Langholz BM, Boice JD, Shore RE, Andersson M, et al. Dose to the contralateral breast from radiation therapy and risk of second primary breast cancer in the WECARE study. Int J Radiat Oncol Biol Phys 2008;72:1021–30.
62. Bernstein JL, Haile RW, Stovall M, Boice JD, Shore RE, Langholz B, et al. Radiation exposure, the ATM gene, and contralateral breast cancer in the Women's Environmental Cancer and Radiation Epidemiology Study. J Natl Cancer Inst 2010;102:475–83.
63. Bhatti P, Doody MM, Alexander BH, Yuenger J, Simon SL, Weinstock RM, et al. Breast cancer risk polymorphisms and interaction with ionizing radiation among U.S. radiologic technologists. Cancer Epidemiol Biomark Prev 2008;17:2007–11.
64. Bhatti P, Doody MM, Rajaraman P, Alexander BH, Yeager M, Hutchinson A, et al. Novel breast cancer risk alleles and interaction with ionizing radiation among U.S. radiologic technologists. Radiat Res 2010;173:214–24.
65. Bhatti P, Struewing JP, Alexander BH, Hauptmann M, Bowen L, Mateus-Pereira LH, et al. Polymorphisms in DNA repair genes, ionizing radiation exposure and risk of breast cancer in U.S. radiologic technologists. Int J Cancer 2008;122:177–82.
66. Rajaraman P, Bhatti P, Doody MM, Simon SL, Weinstock RM, Linet MS, et al. Nucleotide excision repair polymorphisms may modify ionizing radiation-related breast cancer risk in US radiologic technologists. Int J Cancer J Int Cancer 2008;123:2713–6.
67. Schonfeld SJ, Bhatti P, Brown EE, Linet MS, Simon SL, Weinstock RM, et al. Polymorphisms in oxidative stress and inflammation pathway genes, low-dose ionizing radiation, and the risk of breast cancer among US radiologic technologists. Cancer Causes Control 2010;21:1857–66.
68. Sigurdson AJ, Bhatti P, CS chen, Rajaraman P, Doody MM, Bowen L, et al. Polymorphisms in estrogen biosynthesis and metabolism-related genes, ionizing radiation exposure, and risk of breast cancer among U.S. radiologic technologists. Breast Cancer Res Treat 2009;118:177–84.
69. Sigurdson AJ, Bhatti P, Doody MM, Hauptmann M, Bowen L, Simon SL, et al. Polymorphisms in apoptosis- and proliferation-related genes, ionizing radiation exposure, and risk of breast cancer among U.S. radiologic technologists. Cancer Epidemiol Prev Biomark 2007;16:2000–7.
70. Morton LM, Sampson JN, Armstrong GT, Chen TH, Hudson MM, Karlins E, et al. Genome-wide association study to identify susceptibility loci that modify radiation-related risk for breast cancer after childhood cancer. J Natl Cancer Inst 2017;109:djx058.
71. Thomas D. Gene–environment-wide association studies: emerging approaches. Nat Rev Genet 2010;11:259–72.
72. Watt GP, Reiner AS, Smith SA, Stram DO, Capanu M, Malone KE, et al. Association of a pathway-specific genetic risk score with risk of radiation-associated contralateral breast cancer. JAMA Netw Open 2019;2:e1912259.
73. Opstal-Van Winden AWJ, De Haan HG, Hauptmann M, Schmidt MK, Broeks A, Russell NS, et al. Genetic susceptibility to radiation-induced breast cancer after Hodgkin lymphoma. Blood 2019;133:1130–9.