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Recommendations for Breast Cancer Surveillance for Female Childhood, Adolescent and Young Adult Cancer Survivors Treated with Chest Radiation: A Report from the International Late Effects of Childhood Cancer Guideline Harmonization Group

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Summary

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Female childhood, adolescent and young adult (CAYA) cancer survivors treated with radiation to fields that include breast tissue (chest radiation) have an increased risk of breast cancer. Clinical practice guidelines are essential to ensure that these survivors receive optimum care, and thereby reduce the detrimental consequences of cancer treatment. However, surveillance recommendations vary among the existing long-term follow-up guidelines. This guideline provides international harmonized breast cancer surveillance recommendations for female CAYA cancer survivors treated with chest radiation prior to age 30 years. We applied evidence-based methods to develop the international harmonized recommendations. The recommendations were formulated by an international multidisciplinary guideline panel and categorized according to a 4-level colour grading schema adapted from existing level of evidence criteria. The harmonized breast cancer surveillance recommendations are based on a transparent process and are intended to be scientifically rigorous, positively influence health outcomes, and facilitate care for CAYA cancer survivors.

Introduction

Advances in the treatment of childhood, adolescent and young adult (CAYA) cancer over the last decades have greatly improved long-term survival, which now exceeds 80% for some cancer types.¹⁻³ As a result, CAYA cancer survivors are a growing group of individuals, many of whom have a high risk of treatment-related morbidity and mortality.^{4,5} Of particular concern is the substantially elevated risk for breast cancer among female survivors treated with radiation to fields that includes breast tissue, i.e. thorax, whole lung, mediastinal, axilla, (mini-)mantle, (sub)total lymphoid, high abdominal, and total body irradiation (TBI) (hereafter referred to as chest radiation). Among this group, the cumulative breast cancer incidence by age 40-45 years ranges from 13% to 20%, with standardized incidence ratios ranging from 13.3 to 55.5 and absolute excess risk ranging from 18.6 to 79.0 per 10,000 person years.⁶ The incidence following high-dose chest radiation is similar to that in BRCA gene mutation carriers, where by age 40 years, the cumulative incidence ranges from 10% to 19%.⁷⁻¹⁰ This is substantially higher than that in young women in the general population, in whom the cumulative incidence by age 45 years is only 1% to 2%.^{6,11,12} Because of this high risk, it has been acknowledged that these survivors may benefit from tailored long-term breast cancer surveillance.

To ensure that CAYA cancer survivors receive optimum care, clinical practice guidelines are recommended.¹³⁻¹⁶ Survivors and providers need guidance to be appropriately aware of and proactive about cancer- and treatment-related health risks. To promote early detection of and intervention for complications that may potentially arise as a result of treatment for paediatric malignancies, clinical practice guidelines for the long-term follow-up of CAYA cancer survivors have been developed by groups in North America and Europe.¹⁷⁻²¹ These guidelines differ regarding the definition of patient risk groups, and surveillance modalities and frequencies. This raises uncertainty about which guideline to follow, potentially hindering the implementation, provision of and adherence to clinically effective care. Recognizing the need for collaboration, an international endeavour was initiated to harmonize guidelines for CAYA cancer survivors.²² The first aim of the International Late Effects of Childhood Cancer Guideline Harmonization Group was to harmonize

recommendations for breast cancer surveillance for female CAYA cancer survivors treated with chest radiation prior to age 30 years.

Methods

A detailed description of the international guideline harmonization methodology is provided elsewhere.²² The breast cancer surveillance recommendations were prepared by a core group consisting of eleven representatives from the North American Children's Oncology Group (COG),¹⁷ the Dutch Childhood Oncology Group (DCOG),¹⁸ the Scottish Intercollegiate Guidelines Network (SIGN)¹⁹ and the United Kingdom Children's Cancer and Leukaemia Group (UKCCLG),²⁰ and discussed in a working group of 31 experts from nine countries. The expert members represented all relevant disciplines, ranging from paediatric, radiation, and medical oncologists, and survivorship care providers to guideline methodologists and epidemiologists.

First, we evaluated the concordance and discordance among the available recommendations from the COG, DCOG and UKCCLG guidelines.^{17,18,20} Existing nationwide screening guidelines, like the breast cancer screening guidelines from the US National Comprehensive Cancer Network and the National Breast Cancer Organization Netherlands, served as a starting point for the breast cancer surveillance recommendations for the CAYA cancer survivor population. To achieve consensus, clinical questions were formulated relevant to discordant breast cancer surveillance recommendations. Systematic electronic literature searches were performed in August 2011, to update the previous systematic searches of Henderson et al. (1966-2008)⁶ and the DCOG guidelines (1945-2009).¹⁸ Evidence summaries were made to answer the relevant clinical questions. When evidence was lacking for CAYA cancer survivors, we carefully extrapolated evidence from other populations. In the case of concordance, we extracted and evaluated the evidence cited by the guidelines. We included studies in the evidence summaries published until September 2011. Studies published after we started with the formulation of the recommendations were not included in the evidence summaries. The recommendations will be updated within two years.

As agreed by the International Guideline Harmonization Group, levels of evidence and strength of recommendations were determined based upon an adapted version of the Grading of Recommendations Assessment Development and Evaluation (GRADE) criteria and the Applying classification of recommendations and level of evidence criteria of the American Heart Association.^{23,24} The working group discussed the evidence and formulated recommendations considering the quality of the evidence, the benefits versus harms of the surveillance intervention, and the need to maintain flexibility of application across different health care systems. The quality of the evidence was graded according to the following levels of evidence: A, high level of evidence (i.e. consistent evidence from well performed and high quality studies or systematic reviews with a low risk of bias, and direct, consistent and precise results); B, moderate to low level of evidence (i.e. evidence from studies or systematic reviews with few important limitations); and C, very low level of evidence (i.e. evidence from studies with serious flaws, only expert opinion or standards of care). Final recommendations were based on this scientific knowledge combined with other considerations such as clinical judgments, decisions about thresholds and costs. The

recommendations are categorized using the 4-color schema adapted from the American Heart Association.²³ Green is used for a strong recommendation (high quality evidence), using anchor terms such as ‘is recommended’, and with a low degree of uncertainty. Yellow (moderate quality evidence) and orange (weak quality evidence) are intermediate level recommendations, using terms such as ‘is reasonable’ and ‘may be reasonable’, respectively. Yellow and orange represent intermediate recommendations with a higher degree of uncertainty, meaning that other factors, such as the clinical scenario, family history, patient preferences, costs and relevant risk factors need to be considered in the decision-making process.²⁵ Red is used to recommend against a particular intervention, with harms outweighing benefits.

The international harmonized breast cancer surveillance recommendations were critically appraised by two independent external experts in the field and one patient representative.

Search strategy and selection criteria

We performed multiple searches in MEDLINE (through PubMed), and the Cochrane Central Library of Controlled Trials (CENTRAL) (to August 2011) to identify all available evidence with the search terms “childhood”, “adolescent”, “neoplasm”, “Hodgkin”, “survivor”, “breast”, “radiation”, “alkylating”, “mammogram”, “magnetic resonance imaging”, “clinical breast exam” from 1966 until August, 2011 (search strategies are provided in Appendix 1). In addition, references supporting the existing recommendations were critiqued, and experts in the field were contacted to determine if there was any additional evidence. Only papers published in English were reviewed. The final selection of studies was determined on the basis of relevance to the broad scope of this guideline.

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The funding sources had no involvement in the design and execution of the study; the drafting and editing of the manuscript; or the decision to submit for publication.

Results

In Table 1 the concordance and discordance among the breast cancer surveillance recommendations of the COG,¹⁷ DCOG¹⁸ and UKCCLG²⁰ is provided. There was concordance across guidelines for the following statements: female CAYA cancer survivors treated with chest radiation are at increased breast cancer risk; surveillance should be initiated at the age of 25 years or 8 years after radiation (whichever occurs last); surveillance should be performed annually; and clinical breast exam (CBE), mammography and breast magnetic resonance imaging (MRI) are diagnostic tests to be considered. For concordant areas, we extracted the evidence cited by the guidelines and determined the levels of the evidence.

There were also areas of discordance, as illustrated in Table 1, for which we formulated eight clinical questions that required more detailed investigation of the underlying evidence. We created evidence summaries covering the following discordances: breast cancer risk following 1-19 Gy chest radiation, TBI, and high abdominal field radiation; reduction of risk following alkylating agent chemotherapy; breast cancer risk in female CAYA cancer

survivors aged ≥ 50 years treated with chest radiation; diagnostic value of a MRI and/or mammography in CAYA cancer survivors, in women aged 25-35 years, and in younger versus older age groups; and diagnostic value of CBE in women aged ≥ 25 years. The evidence summaries for the discordant areas are presented in Appendix 2. The conclusions of the evidence and the final recommendations are summarized in Table 2 and Table 3, respectively. Below we describe the evidence and recommendations with the rationale.

Who needs breast cancer surveillance?

Evidence in CAYA cancer survivors—As described above, women treated with therapeutic radiation to fields that include breast tissue are at increased risk of breast cancer at a young age. The risk is especially high for women treated with high-dose chest radiation (≥ 20 Gy).⁶ However, for moderate-dose (10-19 Gy) and low-dose (1-9 Gy) chest radiation, the magnitude of breast cancer risk is less clear. There is evidence for a linear dose response relationship, but precise risk estimates following 1-9 and 10-19 Gy have not been published.²⁶⁻³⁰ For the purpose of this harmonization endeavour, Inskip et al. recalculated the breast cancer risk among 584 childhood cancer survivors included in their case-control study (personal communication, Peter Inskip, PhD, May 18, 2012).²⁷ The odds ratio (OR) for developing breast cancer in patients treated with 1.3-9.9 Gy (mean 4.4 Gy) compared to patients treated without chest radiation was 1.9 (95% CI 0.7-5.4). For patients treated with 10.0-19.9 Gy (mean 14.5 Gy) chest radiation the OR was 6.5 (95% CI 2.3-18.5) compared to patients treated without chest radiation. In this particular study, as in three other reports included in the evidence summaries,^{29,30} radiation dose was based on retrospective dose reconstruction and reflects absorbed dose at the site of the breast tumour, unlike some other studies that used prescribed radiation dose.

Another consideration is that no clear cut-off for a safe radiation dose could be defined. It is well known that women exposed to low-dose non-cancer treatment radiation (e.g. atomic bomb survivors, irradiation for enlarged thymus or haemangioma) have an excess risk of breast cancer.^{31,32} Indeed, the real issue is when the risk crosses the threshold where the benefits of surveillance outweigh the harms. Based upon the estimated risk-benefit ratio, as has been used by van Ravesteyn et al.³³, we recommend intensive surveillance for survivors with a relative risk of four-fold or more compared to survivors treated without chest radiation (strong recommendation). In survivors with a relative risk of two-fold or more we agreed that intensive surveillance may be recommended (weaker recommendation).^{33,34}

For TBI and high abdominal field radiation, the working group agreed that there most likely is an excess risk. However, evidence about the magnitude and latency are at present insufficiently clear to guide surveillance.^{28,35} Since the radiation fields involve the breasts and no safe dose could be defined, the decision should be based upon clinical judgment and after consideration of additional risk factors such as family history.

Irradiation to the ovaries at doses greater than 5 Gy lessens the carcinogenic effects of breast irradiation, most likely by reducing exposure of radiation-damaged breast cells to the stimulating effect of ovarian hormones.^{27,29,36} It is less clear whether alkylating agent chemotherapy, which may also affect ovarian function, substantially alters the breast cancer risk in this population. Although studies among cancer survivors treated with alkylating

agents at older ages (21–49 years) showed that there is a decreased risk of breast cancer,^{29,30,36,37} there is no evidence of a protective effect in childhood and adolescent cancer survivors.^{27,38,39} This could be explained by an age-related increased sensitivity of the ovarian follicles to alkylating agents in the older age group. Since irradiation to the ovaries and alkylating agent chemotherapy do not substantially modify the breast cancer risk among CAYA cancer survivors, the surveillance recommendations are not different based upon these exposures.

Recommendations—Based upon the evidence and consensus, we recommend breast cancer surveillance for female CAYA cancer survivors treated with chest radiation. The strength of the recommendation is based upon chest radiation dose categories as follows: green – high-dose (≥ 20 Gy); yellow – moderate-dose (10–19 Gy); and orange – low-dose (1–9 Gy). For the yellow and orange recommendations there is a higher degree of uncertainty. The medical decision should be based upon the clinical scenario, patient preferences and relevant risk factors, such as breast density, current age and family history.

At what age should breast cancer surveillance be initiated?

Evidence in CAYA cancer survivors—Studies have shown that breast cancer risk in female CAYA cancer survivors is increased as early as eight years after radiation and that the cumulative breast cancer incidence increases from 25 years of age onwards.^{6,36,38–41}

Recommendations—Therefore, we recommend that breast cancer surveillance should be initiated at age 25 years or eight years after radiation, whichever occurs last. We agreed that for women treated with high-dose chest radiation (≥ 20 Gy) the benefits of surveillance initiation at age 25 years outweigh the harms. For women with low- to moderate-dose chest radiation (1–19 Gy) the decision should be an individual one, taking into account additional risk factors and patients' values.

At what frequency should breast cancer surveillance be performed?

Evidence in CAYA cancer survivors—There is evidence that the breast cancer risk in female CAYA cancer survivors treated with chest radiation increases with increasing length of follow-up.^{6,36,38–41} However, an appropriate surveillance interval is difficult to define. It is essential to detect breast cancer early, since women diagnosed in an early stage have a higher likelihood for a favourable outcome and a survival benefit.^{42–47} Notably, for women with node-positive breast cancer, therapy for the initial cancer may limit options for anthracycline-based adjuvant therapy for secondary breast cancer, which in turn may be associated with poorer outcomes.^{6,45}

Recommendations—The International Guideline Harmonization Group agreed that the frequency of surveillance is a balance between missing early stage breast cancer and the burden of regular visits to a clinic. We recommend annual specialized breast cancer surveillance for CAYA cancer survivors treated with chest radiation.

At what age should breast cancer surveillance be stopped?

Evidence in CAYA cancer survivors—With follow-up of women to age 50, it does not appear that the excess breast cancer risk significantly diminishes with age in CAYA cancer survivors treated with chest radiation. While larger studies with extended follow-up are needed to confirm this observation, the biological mechanisms of radiation-induced breast tissue apoptosis and carcinogenesis suggest that the cumulative incidence will continue to increase and that the excess risk will remain significantly elevated.

Recommendations—We decided that annual breast cancer surveillance in CAYA cancer survivors aged ≥ 50 years is reasonable based upon clinical judgment and pending availability of further data.

What surveillance modality should be used?

Evidence in CAYA cancer survivors—To date, there is little evidence describing the diagnostic value of different breast cancer surveillance modalities in female CAYA cancer survivors treated with chest radiation. Three prospective surveillance studies assessed screening mammography in 320 adult females who survived childhood or young adult Hodgkin lymphoma.⁴⁸⁻⁵⁰ The median age at study ranged from 35 to 41 years. The strengths and limitations of each of these studies were discussed by Henderson et al.⁶ Increased breast density was common across all three studies (60-6%). The false positive rate of the initial mammographic examination was 12.7%, of which the majority (8.4%) required only interval imaging (3.9% had a benign biopsy). Including incident and prevalent cases of breast cancer, 58% were detected by mammography and 42% were detected by palpation (patient and/or physician). Of the invasive breast cancer cases detected by mammography, all were T1 (<2 cm). There are no known published prospective studies evaluating the use of MRI in this population.

Evidence in other populations—There is evidence available in other high risk populations (i.e. BRCA carriers) and the general population.⁵¹ We considered the evidence published regarding three surveillance modalities – CBE, mammography and breast MRI. There is a lack of evidence about the effectiveness of CBE in reducing breast cancer mortality.^{52,53} Studies in the general population and in BRCA carriers have shown that CBE in addition to mammography has a low sensitivity and a high number of false positive results.⁵⁴⁻⁵⁹

Mammography is the only surveillance modality associated with a significant reduction of breast cancer mortality in women aged 40-75 years.^{51,52,60-63} It is most sensitive among older women with less dense breasts.⁶⁴ However, mammography has limitations in detecting early breast cancer in women with dense breast tissue. Nevertheless, as noted above, among young women with dense breast tissue mammography can detect breast cancer in survivors treated with chest radiation.^{46,48-50,65,66} The effectiveness, however, is unknown in this patient population. In addition, this modality is superior to MRI for the detection of ductal carcinoma-in-situ (DCIS).^{58,67} DCIS among younger women is associated with a much higher rate of recurrence and 10-year mortality compared to DCIS among older women.⁶⁸⁻⁷⁰

MRI is more effective than mammography in detecting breast cancer in young women with dense breast tissue, has higher sensitivity in detecting invasive breast cancer than mammography, and identifies cancer at earlier stages.^{64,71} There are no studies, including among female BRCA carriers, which have evaluated the effect of surveillance with MRI on mortality.

The combination of MRI and mammography is superior to either test alone among women with a hereditary risk for breast cancer.^{64,71} There are, however, no studies evaluating the diagnostic value of a MRI and mammography compared to a MRI or mammography alone in women aged 25-35 years. Two studies comparing women in a younger age group with women in an older age group with an inherited susceptibility to breast cancer demonstrated the impact of age, finding an inferior diagnostic value in the younger age group for both MRI and mammography when used alone.^{72,73} It is unclear what percent of women with dense breast tissue, affecting about 60% of CAYA cancer survivors, will have largely fatty-replaced breast tissue in their post-menopausal years.⁶ Therefore, this group of patients will likely benefit from MRI surveillance in addition to mammography.

Harms of surveillance—Potential costs and harms associated with surveillance should be considered, including additional testing resulting from false positive tests, stress, anxiety, overdiagnosis, radiation exposure from mammography, and pain from the procedure.^{6,74} The estimated mean breast dose with contemporary standard two-view mammograms is about 3.85 to 4.5 mGy.⁷⁵⁻⁷⁷ Thus, in a woman treated with 20 Gy chest radiation, 15 additional surveillance mammograms from age 25 to 39 years would increase the total radiation exposure to 20.058 Gy or by about 0.3%. It would be unlikely for this small increase in radiation exposure administered at regular intervals many years after chest radiation to significantly increase breast cancer risk. Other than substantially increasing cost, the addition of MRI results in an increased rate of false-positive tests, leading to emotional stress, anxiety and costs of further testing and biopsies. Of note, the combination of MRI and mammography appears to be more cost-effective in surveillance of young women with a hereditary risk for breast cancer than mammography alone.^{6,78-81}

Recommendations—Based upon the currently available evidence and considerations, we recommend surveillance with mammography or MRI or a combination of mammography and MRI for CAYA cancer survivors treated with chest radiation. The evidence is insufficient to recommend the ideal imaging modality. There is a considerable degree of uncertainty about the balance between the benefits and harms of mammography and MRI in this patient population, i.e. early detection, mortality reduction and gained life-expectancy versus false-positives, false-negatives, radiation exposure, and costs. Especially for women treated with high-dose chest radiation (≥ 20 Gy) the benefits of surveillance with mammography and/or MRI outweigh the harms. For women treated with low- to moderate-dose chest radiation (1-19 Gy) the surveillance decision should be an individual one, taking into account patients' values regarding the benefits and harms, and costs. In addition, although there is a lack of evidence for the effectiveness of CBE, we recommend that CBE may be reasonable for female CAYA cancer survivors treated with chest radiation returning for follow-up medical evaluations in countries where breast cancer surveillance access is

through clinical referral. Special thought should be given to carry out surveillance investigations at time points which are convenient for the survivor, in order to minimize the burden of time.

Discussion

In this paper, we present the international harmonized breast cancer surveillance recommendations for female CAYA cancer survivors treated with chest radiation prior to age 30 years – the first aim of the International Late Effects of Childhood Cancer Guideline Harmonization Group. Based upon the evidence and consensus among the group, we formulated recommendations that are intended to be consistent and scientifically rigorous, to positively influence health outcomes, and to facilitate consistent follow-up care for female CAYA cancer survivors treated with chest radiation throughout the world.

There is extensive evidence to support the increased risk of breast cancer in female CAYA cancer survivors treated with chest radiation, especially in survivors treated in the higher dose range. An important finding was that few studies have evaluated diagnostic options in CAYA cancer survivors. There are no studies assessing a possible mortality reduction in this patient population. In addition, studies evaluating benefits, risks and costs of breast cancer surveillance in this population are lacking. Although there are gaps in evidence, we recommend yearly breast cancer surveillance by mammography or breast MRI or a combination of mammography and MRI in CAYA cancer survivors treated with high-dose chest radiation. For patients treated with low- to moderate-dose chest radiation there is a higher degree of uncertainty, indicating that shared decision making is preferred.

Our recommendations are mainly based on evidence from studies focused on women with an inherited susceptibility to breast cancer. Female CAYA cancer survivors have a risk of breast cancer approaching that of BRCA carriers. It is difficult to ignore the data from studies focused on women with an inherited susceptibility to breast cancer and it seems reasonable to extrapolate data from these studies to women treated with chest radiation, given the similar incidence rate and the increased likelihood of dense breast tissue.⁶ Importantly, though, the risk of radiation-induced breast cancer from mammography is likely different in women with a BRCA mutation and CAYA cancer survivors. Whereas the former group likely has a heightened sensitivity to radiation-induced DNA damage,⁸² the small additional radiation exposure from mammography is less likely to substantially change breast cancer risk in CAYA cancer survivors treated with large doses of therapeutic radiation.

The clinical effectiveness of any surveillance modality depends on its ability to reduce breast cancer mortality rather than merely increasing the lead time, i.e. the time interval by which the diagnosis of breast cancer is advanced by surveillance. It is challenging to review the evidence on the effectiveness of mammography and MRI due to the lack of randomized controlled trials in CAYA cancer survivors. A randomized controlled trial that examines surveillance versus no surveillance in CAYA cancer survivors – traditionally the highest level of evidence – is not feasible due to inability to achieve appropriate power given the small patient numbers, and to achieve ethical approval by human subject protection

committees. High-quality prospective and retrospective studies are of major importance to assess surveillance outcomes in females treated with chest radiation.⁶

Elaborating on the latter, an important result of the harmonization process is the demonstration of a research agenda, based upon the clinical issues for which no or insufficient supporting evidence exist. According to our findings, future studies should focus on the effects of moderate-dose chest radiation (10-19 Gy) and the possible joint effects of radiation dose and radiation volume to the breasts in CAYA cancer survivors, preferably in a prospective setting comparing the exposed group with a non-exposed group. In addition to radiation dose, radiation volume appears to be of major importance in predicting the breast cancer risk.³⁶ At this moment, however, limitations in published data precluded our ability to formulate recommendations based on radiation volume and field. Although it was found that family history was independently associated with breast cancer risk in childhood cancer survivors treated with chest radiation in one study,³⁹ it is unclear what the relative contribution is concurrent with other risk factors, such as chest radiation dose and field, ovarian toxic therapy, and other traditional risk factors. Breast cancer risk prediction models should be developed to inform us on this question. Furthermore, it is still unclear what the magnitude of breast cancer risk will be in this population as they age into their fifth and sixth decades of life. Since the study cohorts are still relatively young, extended follow-up studies of CAYA cancer survivors are necessary to provide more data on this issue. Finally, new prospective studies should give insight into the benefits versus harms of surveillance modalities in CAYA cancer survivors, including cost-effectiveness analyses. The implementation of the harmonized recommendations will be an ongoing process. Countries, with or without existing long-term follow-up guidelines for CAYA cancer survivors, can use the current harmonised guidelines as a basis for an evidence-based national policy. As the international guideline harmonization endeavour proceeds, we will be proactive in educating professionals, health policy makers and patients. In addition, we will focus on the development of interactive clinical decision-support systems and quality indicators to evaluate guideline adherence to strong recommendations based on high quality evidence.

Strengths of our process are the evidence-based approach, the transparency in deriving and rating the strength of recommendations, and the multidisciplinary working group involved in the harmonization process. Since there is an ongoing interactive relationship between those who appraise the evidence and those who formulate recommendations, we increase the validity and trustworthiness of our guideline development process. A limitation of our recommendations may be the gaps in evidence concerning the effectiveness of specialized surveillance in CAYA cancer survivors. Therefore, the surveillance modality recommendations were based on evidence carefully extrapolated from other high risk populations and clinical experience.

In conclusion, we described the state of evidence and international harmonized recommendations for breast cancer surveillance for female CAYA cancer survivors treated with chest radiation prior to age 30 years. We recommend annual risk-based breast cancer surveillance with mammography or breast MRI or a combination of mammography and MRI. With the successful harmonization of the breast cancer surveillance recommendations, we have demonstrated that our evidence-based methods for worldwide guideline

development are feasible. International collaboration has major advantages in terms of reducing duplication of effort, optimizing the use of expertise and identifying gaps in knowledge. With the initiation of this international guideline harmonization endeavor we have taken the first step in optimizing collaboration in guideline development with the ultimate goal to optimize the quality of care for CAYA cancer survivors and thereby improving their quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Concordances and discordances among breast cancer surveillance recommendations

	North American Children's Oncology Group	Dutch Childhood Oncology Group	UK Children's Cancer and Leukaemia Group	Concordant/ discordant
Who needs breast cancer surveillance?				
At risk				
Chest radiation	Yes	Yes	Yes	Concordant
± Alkylating agents	Not specified	Not specified	Yes	Discordant
High risk	Not specified	7-20 Gy chest radiation (excl. TBI) 14-40 Gy abdominal radiation	Not specified	Discordant
Highest risk	20 Gy chest radiation	20 Gy chest radiation 40 Gy abdominal radiation TBI	Not specified	Discordant
At what age should breast cancer surveillance be initiated?				
	25 yr	25 yr	25 yr	Concordant
At what frequency should breast cancer surveillance be performed?				
	Every 1 yr	Every 1 yr	Every 1 yr	Concordant
At what age should breast cancer surveillance be stopped?				
	No age limit	75 yr	No age limit	Discordant
What surveillance modality should be used?				
Screening test				
Clinical breast exam	Yes	Yes	Yes	Concordant
Mammography	Yes	Yes	Yes	Concordant
Breast MRI	Yes	Yes	Yes	Concordant
Age at initiation				
Clinical breast exam	Puberty	25 yr (highest risk) 35 yr (high risk)	25 yr and >10 yr after chest radiation	Discordant
Mammography	25 yr or 8 yr after chest radiation	30 yr (highest risk) 35 yr (high risk)	30 yr	Discordant
Breast MRI	25 yr or 8 yr after chest radiation	25 yr (highest risk)	25 yr	Concordant
Surveillance frequency				
Clinical breast exam	Every 0.5 yr (age >25 yr) Every 1 yr (puberty to age 25 yr)	Every 1 yr	Regularly	Discordant
Mammography	Every 1 yr	Every 1 yr (age 30-60 yr) Every 2 yr (age 60-75 yr) (highest risk) Every 1 yr (age 35-60 yr) Every 2 yr (age 60-75 yr)(high risk)	Every 1 yr (age 30-50 yr) Every 3 yr (age >50 yr)	Discordant
Breast MRI	Every 1 yr	Every 1 yr (age 25-60 yr)	Every 1 yr (age 25-29 yr and 30-50 yr if dense breast tissue)	Partly concordant

TBI = total body irradiation.

Table 2
Conclusions of evidence for breast cancer surveillance for female childhood, adolescent and young adult cancer survivors

Who needs breast cancer surveillance?	
Breast cancer risk in childhood, adolescent and young adult cancer survivors	
○ High risk after >20 Gy chest radiation	Level A ⁶
• High risk after 10-19 Gy chest radiation *	Level B ²⁶⁻³⁰
• High risk after 1-9 Gy chest radiation *	Level C ²⁶⁻³⁰
• High risk after total body irradiation *	Level C ³⁵
• High risk after high abdominal field radiation	Level C ²⁸
• Decreased risk after alkylating agent chemotherapy *	Level B ^{27,29,30,36-39}
○ Decreased risk after 5 Gy radiation to the ovaries *	Level B ^{27,29,36}
At what age should breast cancer surveillance be initiated?	
Breast cancer risk in childhood, adolescent and young adult cancer survivors	
○ Increased risk as early as 8 years after chest radiation or 25 years of age	Level A ^{6,36,38-41}
At what frequency should breast cancer surveillance be performed?	
Breast cancer risk in childhood, adolescent and young adult cancer survivors	
○ Risk increases with increasing length of follow-up in survivors up to age 50 years	Level A ^{6,36,38-41}
At what age should breast cancer surveillance be stopped?	
Breast cancer risk in childhood, adolescent and young adult cancer survivors	
• Course of breast cancer risk over time in survivors aged >50 years	No evidence
What surveillance modality should be used?	
Diagnostic value clinical breast exam, mammography and breast MRI in childhood, adolescent and young adult cancer survivors	
• Diagnostic value for breast cancer	No evidence
• Mammography can detect breast cancer in Hodgkin lymphoma survivors treated with chest radiation	Level B ^{46,48-50,65,66}
Diagnostic value clinical breast exam in other populations	
○ Poor diagnostic value for breast cancer in women in the general population and in women with an inherited susceptibility to breast cancer	Level B ⁵⁴⁻⁵⁹
Diagnostic value clinical breast exam in women aged <25 years in other populations	
• Diagnostic value for breast cancer	No evidence
Diagnostic value mammography in other populations	

○ Good diagnostic value for breast cancer in women with an inherited susceptibility to breast cancer

Level A^{64,71}

Diagnostic value breast MRI in *other populations*

○ Good diagnostic value for breast cancer in women with an inherited susceptibility to breast cancer

Level A^{64, 11}

Diagnostic value breast MRI and mammography compared to either test alone in *other populations*

○ Better diagnostic value for breast cancer of a breast MRI and mammography than either test alone in women with an inherited susceptibility to breast cancer

Level A^{64,71}

Diagnostic value breast MRI and mammography compared to breast MRI alone in women aged 25-35 years in *other populations*

• Diagnostic value for breast cancer of a breast MRI and mammography compared to breast MRI alone in women aged 25-35 years

No evidence

Diagnostic value mammography compared to breast MRI in women in a young age group compared to another age group in *other populations*

• Different diagnostic value for breast cancer in the younger age group (<40 year or <50 year) than in the older age group (50 year) for both mammography and breast MRI in women with an inherited susceptibility to breast cancer

Level B^{72,73}

Level A = high level of evidence; Level B = moderate/low level of evidence; Level C = very low level of evidence.

○Evidence extracted from the existing guidelines: COG,¹⁷ DCOG¹⁸ (including the National Breast Cancer Organization Netherlands (NABON) guideline),³⁴ and UKCCLG.²⁰ •Evidence as presented in the evidence summaries (Appendix 2).

* Reference numbers 30 and 36 also included women aged >30 years at Hodgkin lymphoma diagnosis.

Table 3
Harmonized recommendations for breast cancer surveillance for female childhood, adolescent and young adult cancer survivors treated with chest radiation prior to age 30 years*

Who needs breast cancer surveillance?
Providers and female childhood, adolescent and young adult cancer survivors treated with chest radiation should be aware of breast cancer risk.
Breast cancer surveillance <i>is recommended</i> for female childhood, adolescent and young adult cancer survivors treated with ≥20 Gy chest radiation.
Breast cancer surveillance <i>is reasonable</i> for female childhood, adolescent and young adult cancer survivors treated with 10-19 Gy chest radiation based on clinical judgment and considering additional risk factors.
Breast cancer surveillance <i>may be reasonable</i> for female childhood, adolescent and young adult cancer survivors treated with 1-9 Gy chest radiation based on clinical judgment and considering additional risk factors.
At what age should breast cancer surveillance be initiated?
Initiation of breast cancer surveillance <i>is recommended</i> at age 25 years or ≥8 years from radiation (whichever occurs last) for female childhood, adolescent and young adult cancer survivors treated with ≥20 Gy chest radiation.
Initiation of breast cancer surveillance <i>is reasonable</i> at age 25 years or ≥8 years from radiation (whichever occurs last) for female childhood, adolescent and young adult cancer survivors treated with 10-19 Gy chest radiation.
Initiation of breast cancer surveillance <i>may be reasonable</i> at age 25 years or ≥8 years from radiation (whichever occurs last) for female childhood, adolescent and young adult cancer survivors treated with 1-9 Gy chest radiation.
At what frequency should breast cancer surveillance be performed?
Annual breast cancer surveillance <i>is recommended</i> for female childhood, adolescent and young adult cancer survivors treated with ≥20 Gy chest radiation for at least up to 50 years of age.
Annual breast cancer surveillance <i>is reasonable</i> for female childhood, adolescent and young adult cancer survivors treated with 10-19 Gy chest radiation for at least up to 50 years of age.
Annual breast cancer surveillance <i>may be reasonable</i> for female childhood, adolescent and young adult cancer survivors treated with 1-9 Gy chest radiation for at least up to 50 years of age.
At what age should breast cancer surveillance be stopped?
Annual breast cancer surveillance in female childhood, adolescent and young adult cancer survivors older than age 50 <i>is reasonable</i> based upon clinical judgment and pending availability of further data.
What surveillance modality should be used?
Mammography or breast MRI or a combination of mammography and breast MRI <i>is recommended</i> for female childhood, adolescent and young adult cancer survivors treated with chest radiation. The evidence is insufficient to recommend the ideal imaging modality.
Clinical breast exam <i>may be reasonable</i> for female childhood, adolescent and young adult cancer survivors treated with chest radiation returning for follow-up medical evaluations in countries where breast cancer surveillance access is through clinical referral.

* Green, class I = strong recommendations to do; yellow, class IIa = moderate recommendation to do; orange, class IIb = weak recommendation to do.

Note: Breast cancer surveillance recommendations for female childhood, adolescent and young adult cancer survivors with a genetic predisposition to breast cancer are outside the scope of this paper. For that purpose, we refer to the country-specific recommendations.