# Recommendations for breast cancer surveillance for female survivors of childhood, adolescent, and young adult cancer given chest radiation: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group

*Renée L Mulder, Leontien C M Kremer, Melissa M Hudson, Smita Bhatia, Wendy Landier, Gill Levitt, Louis S Constine, W Hamish Wallace, Flora E van Leeuwen, Cécile M Ronckers, Tara O Henderson, Mary Dwyer, Roderick Skinner, Kevin C Oeffinger*

**Female survivors of childhood, adolescent, and young adult (CAYA) cancer who were given radiation to fields that include breast tissue (ie, chest radiation) have an increased risk of breast cancer. Clinical practice guidelines are essential to ensure that these individuals receive optimum care and to reduce the detrimental consequences of cancer treatment; however, surveillance recommendations vary among the existing long-term follow-up guidelines. We applied evidence-based methods to develop international, harmonised recommendations for breast cancer surveillance among female survivors of CAYA cancer who were given chest radiation before age 30 years. The recommendations were formulated by an international, multidisciplinary panel and are graded according to the strength of the underlying evidence.**

*Lancet Oncol* 2013; 14: e621–29

**Department of Paediatric Oncology, Emma Children's Hospital and Academic Medical Centre, Amsterdam, Netherlands** (R L Mulder PhD, L C M Kremer PhD); **Department of Epidemiology and Cancer Control and Department of Oncology, St Jude Children's Research Hospital, Memphis, TN, USA** (Prof M M Hudson MD); **Department of Population Sciences, City of Hope National Medical Center, Duarte, CA, USA** (Prof S Bhatia MD, W Landier PhD); **Department of Oncology/Haematology, Great Ormond Street Hospital for Children NHS Trust Foundation, London, UK** (G Levitt MD); **Department of Radiation Oncology and Department of Pediatrics, University of Rochester Medical Center, Rochester, NY, USA** (Prof L S Constine MD); **Department of Paediatric Oncology, Royal Hospital for Sick Children, Edinburgh, UK** (Prof W H Wallace MD); **Department of Epidemiology, Netherlands Cancer Institute, Amsterdam, Netherlands** (Prof F E van Leeuwen PhD); **Dutch Childhood Oncology Group–Late Effects after Childhood Cancer (DCOG–LATER), The Hague, Netherlands** (C M Ronckers PhD); **Department of Pediatrics, University of Chicago Pritzker School of Medicine, Chicago, IL, USA** (T O Henderson MD); **Department of Radiation Oncology and Cancer Imaging, Peter MacCallum Cancer Center, Melbourne, Australia** (M Dwyer MB); **Department of Paediatric and Adolescent Haematology and Oncology, Great North Children's Hospital, Royal Victoria Infirmary, Newcastle upon Tyne, UK** (R Skinner PhD); **and Department of Pediatrics and**

## Introduction

Advances in the treatment of childhood, adolescent, and young adult (CAYA) cancer over the past decades have greatly improved long-term survival, which now exceeds 80% for some cancer types.[1–3] As a result, survivors of CAYA cancer are a growing group, and many have a high risk of premature morbidity and mortality due to previous cancer treatment.[4,5] Of particular concern is the substantially elevated risk for breast cancer among female survivors who were given radiation to fields in or encompassing the chest area, thereby including breast tissue—ie, thorax, whole lung, mediastinal, axilla, mini-mantle, subtotal lymphoid, high abdominal, and total body irradiation. Among this group, the cumulative incidence of breast cancer by age 40–45 years ranges from 13% to 20%, with standardised incidence ratios ranging from 13·3 to 55·5 per 10 000 person-years and absolute excess risk ranging from 18·6 to 79·0 per 10 000 person-years.[6] The incidence of breast cancer after high-dose chest radiation in female survivors of CAYA cancer is similar to that in *BRCA* mutation carriers, in whom, by age 40 years, the cumulative incidence ranges from 10% to 19%.[7–10] In the general population, the cumulative incidence of breast cancer in women by age 45 years is only 1% to 2%.[6,11,12] Because of the high breast cancer risk in female survivors of CAYA cancer, these individuals might benefit from tailored long-term breast cancer surveillance.

Clinical practice guidelines are needed to ensure that CAYA cancer survivors receive optimum care.[13–16] Survivors and health-care providers need guidance to be aware of and proactive about cancer-related and treatment-related health risks. To promote early detection and intervention for complications that might arise as a result of treatment for paediatric malignancies, clinical practice guidelines for 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 methods and frequencies. This raises uncertainty about which guidelines to follow, potentially hindering implementation, provision of, and adherence to clinically effective care. Recognising the need for collaboration, an international endeavour was initiated to harmonise guidelines for CAYA cancer survivors.[22] The first aim of the International Late Effects of Childhood Cancer Guideline Harmonization Group was to harmonise recommendations for breast cancer surveillance for female survivors of CAYA cancer given chest radiation before age 30 years.

## Concordance assessment and literature search

A detailed description of the international guideline harmonisation methods is provided elsewhere.[22] These 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 UK Children's Cancer and Leukaemia Group (UKCCLG).[20] The recommendations were discussed in a working group of 31 experts from nine countries who represented all relevant disciplines, including paediatric, radiation, and medical oncologists, survivorship care providers, guideline methodologists, and epidemiologists.

First, we evaluated concordance and discordance among the COG, DCOG, and UKCCLG guidelines for long-term follow-up of survivors of CAYA cancers.[17,18,20] Nationwide breast cancer screening guidelines, such as those from the US National Comprehensive Cancer Network and the National Breast Cancer Organization Netherlands, were the starting point of these existing long-term follow-up guidelines for CAYA cancer survivors. To achieve consensus, clinical questions

**Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York City, NY, USA** (Prof K C Oeffinger MD)

Correspondence to:
Dr Renée L Mulder, Department of Paediatric Oncology, Emma Children's Hospital/AMC, PO Box 22660, Rode luifel TKs0-227, 1100 DD Amsterdam, Netherlands
**r.l.mulder@amc.uva.nl**

were formulated to address discordance in existing breast cancer surveillance recommendations. Systematic electronic literature searches were done in August, 2011, to update a previous systematic review by Henderson and colleagues (1966–2008)[6] and the DCOG guideline (1945–2009).[18] Evidence summaries were formulated 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 between recommendations, we extracted and evaluated the evidence cited by the guidelines. The evidence summaries included studies published until August, 2011. Studies published after we began formulating the recommendations were not included in the evidence summaries; however our recommendations will be updated within 2 years. Guidance for screening women who have an inherently higher risk of breast cancer, such as those with a *BRCA* mutation, who are also survivors of CAYA cancer is beyond the scope of this Review.

## Levels of evidence and strength of recommendations

As agreed by the International Guideline Harmonization Group, levels of evidence and strength of recommendations were determined using an adapted version of the Grading of Recommendations Assessment Development and Evaluation (GRADE) criteria, and by applying the American Heart Association's classification of recommendations and level of evidence criteria.[23,24] The working group discussed the evidence and

| | North American Children's Oncology Group | Dutch Childhood Oncology Group | UK Children's Cancer and Leukaemia Group | Concordant or discordant |
|---|---|---|---|---|
| Who needs breast cancer surveillance? | | | | |
| At risk | | | | |
| Chest radiation | Yes | Yes | Yes | Concordant |
| Chest radiation plus alkylating agents* | Not specified | Not specified | Yes | Discordant |
| High risk | Not specified | 7–20 Gy chest radiation (excluding total body irradiation); 14–40 Gy abdominal radiation | Not specified | Discordant |
| Highest risk | ≥20 Gy chest radiation | ≥20 Gy chest radiation; ≥40 Gy abdominal radiation; total body irradiation | Not specified | Discordant |
| At what age should breast cancer surveillance be initiated? | 25 years | 25 years | 25 years | Concordant |
| At what frequency should breast cancer surveillance be done? | Every year | Every year | Every year | Concordant |
| At what age should breast cancer surveillance be stopped? | No age limit | 75 years | No age limit | Discordant |
| What surveillance method should be used? | | | | |
| Screening test | | | | |
| Clinical breast examination, mammography, and breast MRI | Yes | Yes | Yes | Concordant |
| Age at initiation | | | | |
| Clinical breast examination | Puberty | Age 25 years for highest risk; age 35 years for high risk | Age 25 years and at least 10 years after chest radiation | Discordant |
| Mammography | Age 25 years or 8 years after chest radiation | Age 30 years for highest risk; age 35 years for high risk | Age 30 years | Discordant |
| Breast MRI | Age 25 years or 8 years after chest radiation | Age 25 years for highest risk | Age 25 years | Concordant |
| Surveillance frequency | | | | |
| Clinical breast examination | Every year for puberty to age 25 years, then every 0·5 years after age 25 years | Every year | Regularly | Discordant |
| Mammography | Every year | Every year (age 30–60 years) then every 2 years (age 61–75 years) for highest risk; every year (age 35–60 years) then every 2 years (age 61–75 years) for high risk | Every year (age 30–50 years) then every 3 years (age >50 years) | Discordant |
| Breast MRI | Every year | Every year (age 25–60 years) | Every year (age 25–29 years, or age 25–50 years if dense breast tissue) | Partly concordant |

*Exposure to alkylating agent chemotherapy might decrease risk of breast cancer.

***Table 1:*** **Concordance and discordance among breast cancer surveillance recommendations**

formulated recommendations for breast cancer surveillance in CAYA cancer survivors in view of 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: level A—high level of evidence (ie, consistent evidence from well performed and high-quality studies or systematic reviews with a low risk of bias, and direct, consistent, and precise results); level B—moderate to low level of evidence (ie, evidence from studies or systematic reviews with a few important limitations); and level C—very low level of evidence (ie, 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 judgment, decisions about harm–benefit thresholds, and costs. The recommendations are categorised as strong, moderate, or weak. A strong recommendation reflects high quality evidence, with a low degree of uncertainty. Moderate and weak recommendations reflect lower quality evidence and have a higher degree of uncertainty, therefore 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] The internationally harmonised recommendations were critically appraised by two independent external experts and one patient representative.

## Guideline concordance and discordance

Table 1 shows concordance and discordance among breast cancer surveillance recommendations by COG,[17] DCOG,[18] and UKCCLG.[20] There was concordance across guidelines for the following statements: female survivors of CAYA cancer who were given chest radiation have an increased risk for breast cancer; surveillance should be initiated at age 25 years or 8 years after radiation, whichever occurs last; surveillance should be done annually; and clinical breast examination, mammography, and breast MRI are the recommended diagnostic tests. For concordant areas, we extracted the evidence cited by the guidelines and determined the levels of the evidence.

For areas of discordance, we formulated eight clinical questions that required more detailed investigation of the underlying evidence, and created evidence summaries for the following areas: breast cancer risk after exposure to 1–19 Gy chest radiation, total body irradiation, and high abdominal field radiation; reduction of risk with alkylating agent chemotherapy; breast cancer risk in female survivors of CAYA cancer age 50 years or older who were given chest radiation; diagnostic value of MRI, mammography, or both, in female survivors of CAYA cancer aged 25–35 years, and in younger versus older age groups; and diagnostic value of clinical breast examination in women aged 25 years or younger. Evidence summaries for the discordant areas are presented in the appendix (p 2). Conclusions from our evidence summaries are shown in table 2, and the final recommendations are outlined in the panel 1.

See Online for appendix

## Who needs breast cancer surveillance?

Women given therapeutic radiation to fields that include breast tissue are at increased risk of breast cancer at a younger age than the general population. The risk is especially high for women given high-dose chest

| | Evidence level* |
|---|---|
| **Who needs breast cancer surveillance among CAYA cancer survivors?** | |
| High risk after 20 Gy or higher 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[31] |
| High risk after high abdominal field radiation | Level C[28] |
| Decreased risk after alkylating agent chemotherapy† | Level B[27,29,30,32–35] |
| Decreased risk after 5 Gy or higher radiation to the ovaries† | Level B[27,29,32] |
| **At what age should breast cancer surveillance of CAYA cancer survivors be initiated?** | |
| Increased risk as early as 8 years after chest radiation or 25 years of age | Level A[6,32,34–37] |
| **At what frequency should breast cancer surveillance of CAYA cancer survivors be done?** | |
| Risk increases with increasing length of follow-up in survivors up to age 50 years | Level A[6,32,34–37] |
| **At what age should breast cancer surveillance of CAYA cancer survivors be stopped?** | |
| Course of breast cancer risk over time in survivors older than 50 years | No evidence |
| **What surveillance method should be used?** | |
| Diagnostic value of clinical breast examination, mammography, and breast MRI in CAYA cancer survivors | |
| Diagnostic value for breast cancer | No evidence |
| Mammography can detect breast cancer in survivors of Hodgkin's lymphoma given chest radiation‡ | Level B[38–43] |
| Diagnostic value of clinical breast examination in other populations | |
| Poor diagnostic value in women in the general population and in women with an inherited susceptibility to breast cancer | Level B[44–49] |
| Diagnostic value of clinical breast examination in women younger than 25 years | No evidence |
| Diagnostic value of mammography in other populations | |
| Good diagnostic value in women with an inherited susceptibility to breast cancer | Level A[50,51] |
| Diagnostic value of breast MRI in other populations | |
| Good diagnostic value in women with an inherited susceptibility to breast cancer | Level A[50,51] |
| Diagnostic value of breast MRI and mammography compared with either test alone in other populations | |
| Better diagnostic value with breast MRI and mammography than with either test alone in women with an inherited susceptibility to breast cancer | Level A[50,51] |
| Diagnostic value of breast MRI and mammography compared with breast MRI alone in women age 25–35 years | No evidence |
| Diagnostic value of mammography compared with breast MRI in women in a younger versus older age group in other populations | |
| Different diagnostic value for both mammography and breast MRI in a younger age group (<40 years or <50 years) than in an older age group (≥50 years) in women with an inherited susceptibility to breast cancer | Level B[52,53] |

CAYA=childhood, adolescent, and young adult. *Level A=high level of evidence; Level B=moderate or low level of evidence; Level C=very low level of evidence. †References 30 and 32 included women older than 30 years at diagnosis of Hodgkin's lymphoma. ‡Based on cohort studies; no diagnostic results such as sensitivity and specificity were given.

***Table 2*: Evidence underlying existing recommendations for breast cancer surveillance for female survivors of CAYA cancer**

***Panel 1*: Harmonised recommendations for breast cancer surveillance for female survivors of CAYA cancer given chest radiation before age 30 years***

**Who needs breast cancer surveillance?**

- Strong recommendation: providers and female survivors of CAYA cancer given chest radiation should be aware of breast cancer risk
- Strong recommendation: breast cancer surveillance is recommended for those given 20 Gy or higher chest radiation
- Moderate recommendation: breast cancer surveillance is reasonable for those given 10–19 Gy chest radiation, based on clinical judgment and additional risk factors
- Weak recommendation: breast cancer surveillance might be reasonable for those given 1–9 Gy chest radiation, based on clinical judgment and additional risk factors

**At what age should breast cancer surveillance be initiated?**

- Strong recommendation: initiation of breast cancer surveillance is recommended at age 25 years or at least 8 years after radiation (whichever occurs last) for those given 20 Gy or higher chest radiation
- Moderate recommendation: initiation of breast cancer surveillance is reasonable at age 25 years or at least 8 years after radiation (whichever occurs last) for those given 10–19 Gy chest radiation
- Weak recommendation: initiation of breast cancer surveillance might be reasonable at age 25 years or at least 8 years after radiation (whichever occurs last) for those given 1–9 Gy chest radiation

**At what frequency should breast cancer surveillance be done?**

- Strong recommendation: annual breast cancer surveillance is recommended for those given 20 Gy or higher chest radiation, for at least up to age 50 years
- Moderate recommendation: annual breast cancer surveillance is reasonable for those given 10–19 Gy chest radiation, for at least up to age 50 years
- Weak recommendation: annual breast cancer surveillance might be reasonable for those given 1–9 Gy chest radiation, for at least up to age 50 years

**At what age should breast cancer surveillance be stopped?**

- Moderate recommendation: annual breast cancer surveillance past age 50 years is reasonable, based on clinical judgment and pending availability of further data

**What surveillance method should be used?**

- Strong recommendation: mammography, breast MRI, or both is recommended. Evidence is insufficient to recommend the ideal imaging method
- Weak recommendation: clinical breast examination might be reasonable for CAYA cancer survivors returning for follow-up medical assessments in countries where access to breast cancer surveillance is through clinical referral

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

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 unclear. There is evidence for a linear dose-response relationship, but precise risk estimates for exposures of 1–9 Gy and 10–19 Gy have not been reported.[26–30] For the purpose of this harmonisation endeavour, Inskip and colleagues recalculated the breast cancer risk among 584 childhood cancer survivors included in their case-control study[27] (Inskip P, National Cancer Institute, Bethesda, MD, USA, personal communication). The odds ratio (OR) for developing breast cancer in patients given 1·3–9·9 Gy (mean 4·4 Gy) compared with patients who were not given chest radiation was 1·9 (95% CI 0·7–5·4, p>0·05). For patients given 10·0–19·9 Gy (mean 14·5 Gy) chest radiation, the OR was 6·5 (95% CI 2·3–18·5, p<0·05) compared with patients not given chest radiation. In this analysis, 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, whereas other studies used prescribed radiation dose.

There is no clear cutoff for a safe radiation dose. It is well known that women exposed to low-dose, non-cancer-treatment radiation (eg, atomic bomb survivors or those who receive irradiation for enlarged thymus or haemangioma) have an increased risk of breast cancer.[54,55] In the context of breast cancer surveillance, it is important to consider the threshold at which the benefits outweigh the harms. Based on the estimated risk–benefit ratio used by van Ravesteyn and colleagues,[56] we strongly recommend intensive surveillance for CAYA cancer survivors who have a relative risk of breast cancer that is four or more times higher than the risk in survivors who were not given chest radiation. In survivors with a two or more times higher relative risk, intensive surveillance might be recommended, although the evidence is less robust.[56,57] Based on the evidence and consensus, we recommend breast cancer surveillance for female CAYA cancer survivors given chest radiation. The strength of the recommendation is based on chest radiation dose categories—eg, strong recommendation for those given a high dose (≥20 Gy), moderate recommendation for those given a moderate dose (10–19 Gy), and weak recommendation for those given a low dose (1–9 Gy). For the latter two recommendations, the medical decision should be based on the clinical scenario, patient preferences, and relevant risk factors, such as breast density, current age, and family history.

For patients who received total body irradiation and high abdominal field radiation, the working group agreed that there is probably an excess risk of breast cancer; however, evidence of the magnitude and latency of this risk are currently insufficient to guide surveillance.[28,31] Since the radiation fields involve the breasts and no safe dose has been defined, decisions regarding surveillance should be based on clinical judgment and 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, probably by reducing exposure of radiation-damaged breast cells to the stimulating effect of ovarian hormones.[27,29,32] It is less clear whether alkylating agent chemotherapy, which might also affect ovarian function, substantially changes the breast cancer risk in this population. Although studies among cancer survivors given alkylating agents at older ages (21–49 years) showed that there is a decreased risk of breast cancer,[29,30,32,33] there is no evidence of a protective effect in survivors of

childhood and adolescent cancer.[27,34,35] This discrepancy 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 on these exposures.

## At what age should breast cancer surveillance be initiated?

Studies have shown that breast cancer risk in female survivors of CAYA cancer is increased as early as 8 years after radiation, and that the cumulative breast cancer incidence increases from age 25 years onwards.[6,32,34–37] We recommend beginning breast cancer surveillance at age 25 years or 8 years after radiation, whichever occurs last. For women who were given high-dose chest radiation (≥20 Gy), the benefits of starting surveillance at age 25 years outweigh the harms. For women who received low-dose or 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 done?

There is evidence that breast cancer risk in female survivors of CAYA cancer who were given chest radiation increases with length of follow-up;[6,32,34–37] 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.[38,58–62] For women with node-positive breast cancer, the therapy given for the initial cancer might limit options for anthracycline-based adjuvant therapy for secondary breast cancer, which might be associated with poorer outcomes.[6,61] The frequency of surveillance should address a balance between missing early stage breast cancer and the burden of regular visits to a clinic. We recommend annual breast cancer surveillance for CAYA cancer survivors who were given chest radiation.

## At what age should breast cancer surveillance be stopped?

With follow-up of women to age 50 years, it does not seem that the increased breast cancer risk in CAYA cancer survivors who were given chest radiation diminishes with age. Although larger studies with extended follow-up are needed to substantiate this observation, the biological mechanisms of radiation-induced breast tissue apoptosis and carcinogenesis suggest that the cumulative incidence of breast cancer will continue to increase with age, and that the excess risk will remain substantially raised. We decided that annual breast cancer surveillance in CAYA cancer survivors older than 50 years is reasonable, based on clinical judgment and pending availability of further data.

## What surveillance method should be used?

### Evidence in CAYA cancer survivors

So far, there is little evidence describing the diagnostic value of different breast cancer surveillance methods in female survivors of CAYA cancer who were given chest radiation. Three prospective surveillance studies assessed screening mammography in 320 adult women (median age ranged from 35 to 41 years) who survived childhood or young adult Hodgkin's lymphoma.[39–41] The strengths and limitations of each of these studies were discussed by Henderson and colleagues.[6] Increased breast density was common across all three studies (239 baseline mammography examinations were done and 60·6% showed increased breast density). The false positive rate for initial mammographic examination was 12·3%, of which 8·4% required 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 (by the patient or physician). Of the invasive breast cancer cases detected by mammography, all were T1 (<2 cm). To our knowledge, no prospective studies have assessed the use of MRI screening in this population.

### Evidence in other populations

The diagnostic value of breast cancer screening methods has been assessed in other high-risk populations (ie, *BRCA* mutation carriers) and the general population.[63] We reviewed evidence regarding three surveillance methods—clinical breast examination, mammography, and breast MRI. There is not enough evidence to draw a conclusion on the effectiveness of clinical breast examination in reducing breast cancer mortality.[64,65] Studies in the general population and in *BRCA* mutation carriers have shown that clinical breast examination in addition to mammography has a low sensitivity and a high number of false positive results.[44–49]

Mammography is the only surveillance method associated with a significant reduction in breast cancer mortality in women age 40–75 years.[63,64,66–69] It is most sensitive for screening older women with low-density breast tissue,[50] and has limitations in detecting early breast cancer in women with dense breast tissue. Mammography can detect breast cancer in young women with dense tissue who are survivors of CAYA cancer and were given chest radiation,[38–43] but the effectiveness in this population is unknown. Additionally, mammography is better than MRI for detecting ductal carcinoma in situ (DCIS).[48,70] DCIS among younger women is associated with a much higher rate of recurrence and 10-year mortality than DCIS among older women.[71–73]

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, and identifies cancer at earlier stages.[50,51] There are no studies, including among female *BRCA* mutation carriers, that have assessed the effect of MRI surveillance

on mortality. The combination of MRI and mammography is better than using either test singly among women with a hereditary risk for breast cancer.[50,51] However, no studies have assessed the diagnostic value of MRI and mammography compared with MRI or mammography alone in women age 25–35 years. Two studies comparing women in a younger age group with women in an older age group, both with an inherited susceptibility to breast cancer, noted lower diagnostic value in the younger age group (compared with the older age group) for both MRI and mammography when used alone.[52,53] It is unclear what proportion 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 probably 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 standard two-view mammograms is about 3·9–4·5 mGy.[75–77] Thus, in a woman who receives 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 is unlikely that this small increase in radiation exposure, administered at regular intervals many years after chest radiation, would substantially increase breast cancer risk. In addition to increasing the cost of surveillance, 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. However, in young women with a hereditable risk of breast cancer, the combination of MRI and mammography seems to be more cost effective than mammography alone.[6,78–81]

At this moment, evidence is insufficient to recommend the ideal imaging modality in female survivors of CAYA cancer given chest radiation; therefore, we recommend surveillance with mammography, breast MRI, or a combination. There is substantial uncertainty about the balance between the benefits and harms of mammography and breast MRI in this patient population—ie, early detection, mortality reduction, and gained life expectancy versus false-positives, false-negatives, radiation exposure, and costs. Particularly for women who were given high-dose chest radiation (≥20 Gy), the benefits of surveillance with mammography, breast MRI, or both outweigh the harms. For women who were given low-dose or moderate-dose chest radiation (1–19 Gy), the decision should be an individual one, taking into account patients' values regarding the benefits, harms, and costs. Consideration should be given to carrying out surveillance investigations at time points that are convenient for the patient, to minimise the burden of time.

## Conclusion

In this report, we presented international, harmonised, breast cancer surveillance recommendations for female survivors of CAYA cancer who were given chest radiation before age 30 years. Based on the evidence and consensus among the group, we formulated recommendations that are intended to be consistent and scientifically rigorous, to positively affect health outcomes, and to facilitate consistent follow-up care globally for female survivors of CAYA cancer given chest radiation.

There is extensive evidence showing an increased risk of breast cancer in female survivors of CAYA cancer given chest radiation, particularly those who received high doses. However, few studies have assessed diagnostic options in CAYA cancer survivors, and no studies have investigated a possible mortality reduction with surveillance. Studies evaluating benefits, risks, and costs of breast cancer surveillance in this population are also lacking. Although there are gaps in evidence, we recommend yearly breast cancer surveillance by mammography, breast MRI, or both in CAYA cancer survivors given high-dose chest radiation. For patients given low-dose to moderate-dose chest radiation, there is a higher degree of uncertainty about the benefits versus harms of screening, therefore shared decision making is preferred.

Our recommendations are mainly based on evidence from studies of women with an inherited susceptibility to breast cancer. Female CAYA cancer survivors have a risk of breast cancer approaching that of *BRCA* mutation carriers, and it seems reasonable to extrapolate data from studies of women with an inherited susceptibility to women given chest radiation, in view of the similar incidence rate and the increased likelihood of dense breast tissue.[6] However, the risk of radiation-induced breast cancer from mammography is probably different in women with a BRCA mutation versus in CAYA cancer survivors. Whereas the former group probably 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 who were given large doses of therapeutic radiation.

The clinical effectiveness of any breast cancer surveillance method depends on its ability to reduce mortality rather than merely increase the lead time—ie, the time interval by which surveillance advances the diagnosis. It is challenging to review evidence on the effectiveness of mammography and MRI in CAYA cancer survivors because of a lack of randomised controlled trials. Such a trial investigating surveillance versus no surveillance in CAYA cancer survivors is not feasible, because of small patient numbers and low statistical power, and inability to obtain ethical approval. High-

quality prospective and retrospective studies are needed to assess surveillance outcomes in women who were given chest radiation.[6]

As part of the harmonisation process, we outlined a research agenda based on the clinical issues for which insufficient supporting evidence exists. 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 an exposed group with a non-exposed group. In addition to radiation dose, radiation volume seems to be crucial for predicting breast cancer risk;[32] however, limitations in published data precluded our ability to formulate recommendations based on radiation volume and field. Family history was independently associated with breast cancer risk in a study of survivors of childhood cancer given chest radiation,[35] but the relative contribution of family history, concurrent with other risk factors such as chest radiation dose and field, ovarian toxic therapy, and other traditional risk factors, is unclear. Breast cancer risk-prediction models should be developed to help inform on this question. Furthermore, it remains unclear what the magnitude of breast cancer risk will be as female survivors of CAYA cancer given chest radiation age into their 50s and 60s. Since study cohorts are still relatively young, extended follow-up studies of CAYA cancer survivors are necessary to provide more data. Finally, new prospective studies should give insight into the benefits versus harms of surveillance methods in CAYA cancer survivors, including cost-effectiveness analyses.

Implementation of the harmonised recommendations presented here will be an ongoing process. Countries with or without existing long-term follow-up guidelines for CAYA cancer survivors can use the harmonised guidelines as a basis for national policy. As the international guideline harmonisation endeavour proceeds, we aim to educate professionals, health policy makers, and patients on recommended follow-up care, being aware of secondary breast cancer in this patient population, and that surveillance is recommended. Additionally, we will focus on the development of interactive clinical decision-support systems and quality indicators to evaluate guideline adherence to strong recommendations that are 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 harmonisation 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 might be the gaps in evidence concerning the effectiveness of specialised surveillance in CAYA cancer survivors. Therefore, recommendations regarding surveillance method were based on evidence carefully extrapolated from other high-risk populations, and clinical experience.

### Search strategy and selection criteria

We searched Medline (through PubMed), and the Cochrane Central Library of Controlled Trials from January, 1966, to August, 2011, using the search terms "childhood", "adolescent", "neoplasm", "Hodgkin", "survivor", "breast", "radiation", "alkylating", "mammogram", "magnetic resonance imaging", and "clinical breast exam" (detailed search strategies are provided in the appendix [p 1]). Additionally, references supporting the existing recommendations were critiqued, and experts in the field were contacted to determine if there was any additional evidence. Only reports published in English were reviewed. The final selection of studies was based on relevance to the broad scope of this guideline.

In conclusion, we described the state of evidence and provided international harmonised recommendations for breast cancer surveillance for female survivors of CAYA cancer given chest radiation before age 30 years. We recommend annual risk-based breast cancer surveillance with mammography, breast MRI, or both. With the successful harmonisation of the breast cancer surveillance recommendations, we have shown that our evidence-based methods for worldwide guideline development are feasible. International collaboration has key advantages in terms of reducing duplication of effort, optimising the use of expertise, and identifying gaps in knowledge. With the initiation of this international guideline harmonisation endeavour, we have taken the first step in collaborative guideline development with the ultimate goal to optimise quality of care and improve quality of life for CAYA cancer survivors.

#### Contributors

RLM, LCMK, MMH, SB, WL, GL, LSC, WHW, RS, and KCO contributed to the conception and design of the study. RLM, LCMK, and KCO contributed to the search strategy and data extraction. RLM, LCMK, MMH, SB, WL, GL, LSC, WHW, FEvL, CMR, TOH, MD, RS, and KCO contributed to the interpretation of data and formulation of the recommendations. RLM, LCMK, MMH, and KCO drafted the manuscript, and SB, WL, GL, LSC, WHW, FEvL, CMR, TOH, MD, and RS critically revised the manuscript. All authors approved the final version.

#### Conflicts of interest

We declare that we have no conflicts of interest.

#### Acknowledgments

RLM is supported by the Dutch Cancer Society (UVA 2011-4938). KCO receives support from the National Institutes of Health (K05CA160724). MMH receives support from the American Lebanese Syrian Associated Charities (ALSAC). LCMK receives support from Kinderen Kankervrij (KiKa). GL and RS receive support from the 7th Framework Programme of the EU, PanCareSurfUp (257505). We thank the following experts of the International Late Effects of Childhood Cancer

Guideline Harmonization Group and members of the PanCareSurfUp Consortium for their participation in the international guideline harmonisation process: Saro Armenian, Huib Caron, Richard Cohn, Riccardo Haupt, Lars Hjorth, David Hodgson, Yasushi Ishida, Hiroyuki Ishiguro, Shunichi Kato, Miho Maeda, Paul Nathan, Liedeke Postma, Sadhna Shankar, Michael Sullivan, Wim Tissing, Elvira van Dalen, Marry van den Heuvel-Eibrink, Helena van der Pal, Eline van Dulmen-den Broeder, and Susumu Yokoya. We thank Peter Inskip for his input and contribution, and Robert Smith, Harry de Koning, and Alexandra Brownsdon for critically appraising the recommendations and manuscript as external reviewers.

**References**

1 Curry HL, Parkes SE, Powell JE, Mann JR. Caring for survivors of childhood cancers: the size of the problem. *Eur J Cancer* 2006; **42:** 501–08.

2 Gatta G, Zigon G, Capocaccia R, et al. Survival of European children and young adults with cancer diagnosed 1995–2002. *Eur J Cancer* 2009; **45:** 992–1005.

3 Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975–2008. Bethesda, MD, USA: National Cancer Institute, 2011. http://seer.cancer.gov/csr/1975_2010 (accessed April 16, 2012).

4 Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 2006; **355:** 1572–82.

5 Geenen MM, Cardous-Ubbink MC, Kremer LC, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA* 2007; **297:** 2705–15.

6 Henderson TO, Amsterdam A, Bhatia S, et al. Systematic review: surveillance for breast cancer in women treated with chest radiation for childhood, adolescent, or young adult cancer. *Ann Intern Med* 2010; **152:** 444–55.

7 Begg CB, Haile RW, Borg A, et al. Variation of breast cancer risk among BRCA1/2 carriers. *JAMA* 2008; **299:** 194–201.

8 Easton DF, Ford D, Bishop DT. Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. *Am J Hum Genet* 1995; **56:** 265–71.

9 Easton DF, Steele L, Fields P, et al. Cancer risks in two large breast cancer families linked to BRCA2 on chromosome 13q12–13. *Am J Hum Genet* 1997; **61:** 120–28.

10 Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am J Hum Genet* 1998; **62:** 676–89.

11 Fay MP, Pfeiffer R, Cronin KA, Le C, Feuer EJ. Age-conditional probabilities of developing cancer. *Stat Med* 2003; **22:** 1837–48.

12 Fay MP. Estimating age conditional probability of developing disease from surveillance data. *Popul Health Metr* 2004; **2:** 6.

13 Bero LA, Grilli R, Grimshaw JM, Harvey E, Oxman AD, Thomson MA. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. The Cochrane Effective Practice and Organization of Care Review Group. *BMJ* 1998; **317:** 465–68.

14 Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. *Lancet* 1993; **342:** 1317–22.

15 Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J. Clinical guidelines: potential benefits, limitations, and harms of clinical guidelines. *BMJ* 1999; **318:** 527–30.

16 Institute of Medicine. Clinical practice guidelines we can trust. Washington, DC, USA: The National Academies Press, 2011.

17 Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Version 3.0, 2008. http://www.survivorshipguidelines.org/ (accessed April 5, 2011).

18 Dutch Childhood Oncology Group. Richtlijn follow-up na kinderkanker meer dan 5 jaar na diagnose. SKION, Den Haag/ Amsterdam, the Netherlands, 2010. http://www.skion.nl/bestanden/richtlijn_follow-up_na_kinderkanker_deel_1_boekje_met_aanbevelingen_1.pdf (accessed April 5, 2011).

19 Scottish Intercollegiate Guidelines Network. Long term follow up of survivors of childhood cancer. A national clinical guideline, 2004. http://www.sign.ac.uk/guidelines/fulltext/132/index.html (accessed April 5, 2011).

20 United Kingdom Children's Cancer Study Group Late Effects Group. Therapy based long term follow up practice statement, 2011. http://www.cclg.org.uk/treatment-research/guidelines (accessed April 5, 2011).

21 Landier W, Bhatia S, Eshelman DA, et al. Development of risk-based guidelines for pediatric cancer survivors: the Children's Oncology Group Long-Term Follow-Up Guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. *J Clin Oncol* 2004; **22:** 4979–90.

22 Kremer LC, Mulder RL, Oeffinger KC, et al. A worldwide collaboration to harmonize guidelines for the long-term follow-up of childhood cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Pediatr Blood Cancer* 2013; **60:** 543–49.

23 Gibbons RJ, Smith S, Antman E. American College of Cardiology/ American Heart Association clinical practice guidelines: part I: where do they come from? *Circulation* 2003; **107:** 2979–86.

24 GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004; **32:** 1490–94.

25 van der Weijden T, Boivin A, Burgers J, Schunemann HJ, Elwyn G. Clinical practice guidelines and patient decision aids. An inevitable relationship. *J Clin Epidemiol* 2012; **65:** 584–89.

26 Guibout C, Adjadj E, Rubino C, et al. Malignant breast tumors after radiotherapy for a first cancer during childhood. *J Clin Oncol* 2005; **23:** 197–204.

27 Inskip PD, Robison LL, Stovall M, et al. Radiation dose and breast cancer risk in the childhood cancer survivor study. *J Clin Oncol* 2009; **27:** 3901–07.

28 Taylor AJ, Winter DL, Pritchard-Jones K, et al. Second primary neoplasms in survivors of Wilms' tumour—a population-based cohort study from the British Childhood Cancer Survivor Study. *Int J Cancer* 2008; **122:** 2085–93.

29 Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. *JAMA* 2003; **290:** 465–75.

30 van Leeuwen FE, Klokman WJ, Stovall M, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. *J Natl Cancer Inst* 2003; **95:** 971–80.

31 Friedman DL, Rovo A, Leisenring W, et al. Increased risk of breast cancer among survivors of allogeneic hematopoietic cell transplantation: a report from the FHCRC and the EBMT-Late Effect Working Party. *Blood* 2008; **111:** 939–44.

32 de Bruin ML, Sparidans J, Van't Veer MB, et al. Breast cancer risk in female survivors of Hodgkin's lymphoma: lower risk after smaller radiation volumes. *J Clin Oncol* 2009; **27:** 4239–46.

33 Travis LB, Hill D, Dores GM, et al. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. *J Natl Cancer Inst* 2005; **97:** 1428–37.

34 Bhatia S, Yasui Y, Robison LL, et al. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. *J Clin Oncol* 2003; **21:** 4386–94.

35 Kenney LB, Yasui Y, Inskip PD, et al. Breast cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. *Ann Intern Med* 2004; **141:** 590–97.

36 Metayer C, Lynch CF, Clarke EA, et al. Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. *J Clin Oncol* 2000; **18:** 2435–43.

37 Taylor AJ, Winter DL, Stiller CA, Murphy M, Hawkins MM. Risk of breast cancer in female survivors of childhood Hodgkin's disease in Britain: a population-based study. *Int J Cancer* 2007; **120:** 384–91.

38 Wolden SL, Hancock SL, Carlson RW, Goffinet DR, Jeffrey SS, Hoppe RT. Management of breast cancer after Hodgkin's disease. *J Clin Oncol* 2000; **18:** 765–72.

39 Diller L, Medeiros NC, Shaffer K, et al. Breast cancer screening in women previously treated for Hodgkin's disease: a prospective cohort study. *J Clin Oncol* 2002; **20:** 2085–91.

40 Kwong A, Hancock SL, Bloom JR, et al. Mammographic screening in women at increased risk of breast cancer after treatment of Hodgkin's disease. *Breast J* 2008; **14:** 39–48.

41 Lee L, Pintilie M, Hodgson DC, Goss PE, Crump M. Screening mammography for young women treated with supradiaphragmatic radiation for Hodgkin's lymphoma. *Ann Oncol* 2008; **19:** 62–67.

42 Dershaw DD, Yahalom J, Petrek JA. Breast carcinoma in women previously treated for Hodgkin disease: mammographic evaluation. *Radiology* 1992; **184:** 421–23.

43 Howell SJ, Searle C, Goode V, et al. The UK national breast cancer screening programme for survivors of Hodgkin lymphoma detects breast cancer at an early stage. *Br J Cancer* 2009; **101:** 582–88.

44 Oestreicher N, Lehman CD, Seger DJ, Buist DS, White E. The incremental contribution of clinical breast examination to invasive cancer detection in a mammography screening program. *AJR Am J Roentgenol* 2005; **184:** 428–32.

45 Elmore JG, Barton MB, Moceri VM, Polk S, Arena PJ, Fletcher SW. Ten-year risk of false positive screening mammograms and clinical breast examinations. *N Engl J Med* 1998; **338:** 1089–96.

46 Bobo JK, Lee NC, Thames SF. Findings from 752 081 clinical breast examinations reported to a national screening program from 1995 through 1998. *J Natl Cancer Inst* 2000; **92:** 971–76.

47 Elmore JG, Armstrong K, Lehman CD, Fletcher SW. Screening for breast cancer. *JAMA* 2005; **293:** 1245–56.

48 Kriege M, Brekelmans CT, Boetes C, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. *N Engl J Med* 2004; **351:** 427–37.

49 Warner E, Plewes DB, Hill KA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. *JAMA* 2004; **292:** 1317–25.

50 Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. *Ann Intern Med* 2008; **148:** 671–79.

51 Lord SJ, Lei W, Craft P, et al. A systematic review of the effectiveness of magnetic resonance imaging (MRI) as an addition to mammography and ultrasound in screening young women at high risk of breast cancer. *Eur J Cancer* 2007; **43:** 1905–17.

52 Kriege M, Brekelmans CT, Obdeijn IM, et al. Factors affecting sensitivity and specificity of screening mammography and MRI in women with an inherited risk for breast cancer. *Breast Cancer Res Treat* 2006; **100:** 109–19.

53 Sardanelli F, Podo F, Santoro F, et al. Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the high breast cancer risk Italian 1 study): final results. *Invest Radiol* 2011; **46:** 94–105.

54 Li CI, Nishi N, McDougall JA, et al. Relationship between radiation exposure and risk of second primary cancers among atomic bomb survivors. *Cancer Res* 2010; **70:** 7187–98.

55 Preston DL, Mattsson A, Holmberg E, Shore R, Hildreth NG, Boice JD Jr. Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. *Radiat Res* 2002; **158:** 220–35.

56 van Ravesteyn NT, Miglioretti DL, Stout NK, et al. Tipping the balance of benefits and harms to favor screening mammography starting at age 40 years: a comparative modeling study of risk. *Ann Intern Med* 2012; **156:** 609–17.

57 National Breast Cancer Organization Netherlands. Evidence-based richtlijn mammacarcinoom, version 2.0, 2012. http://www.oncoline.nl/richtlijn/item/index.php?pagina=/richtlijn/item/pagina.php&richtlijn_id=885 (accessed April 5, 2011).

58 Cutuli B, Borel C, Dhermain F, et al. Breast cancer occurred after treatment for Hodgkin's disease: analysis of 133 cases. *Radiother Oncol* 2001; **59:** 247–55.

59 Elkin EB, Klem ML, Gonzales AM, et al. Characteristics and outcomes of breast cancer in women with and without a history of radiation for Hodgkin's lymphoma: a multi-institutional, matched cohort study. *J Clin Oncol* 2011; **29:** 2466–73.

60 Janov AJ, Tulecke M, O'Neill A, et al. Clinical and pathologic features of breast cancers in women treated for Hodgkin's disease: a case-control study. *Breast J* 2001; **7:** 46–52.

61 Sanna G, Lorizzo K, Rotmensz N, et al. Breast cancer in Hodgkin's disease and non-Hodgkin's lymphoma survivors. *Ann Oncol* 2007; **18:** 288–92.

62 Yahalom J, Petrek JA, Biddinger PW, et al. Breast cancer in patients irradiated for Hodgkin's disease: a clinical and pathologic analysis of 45 events in 37 patients. *J Clin Oncol* 1992; **10:** 1674–81.

63 Warner E. Clinical practice. Breast-cancer screening. *N Engl J Med* 2011; **365:** 1025–32.

64 Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L. Screening for breast cancer: an update for the US Preventive Services Task Force. *Ann Intern Med* 2009; **151:** 727–42.

65 Fenton JJ, Barton MB, Geiger AM, et al. Screening clinical breast examination: how often does it miss lethal breast cancer? *J Natl Cancer Inst Monogr* 2005; **35:** 67–71.

66 de Koning HJ. Mammographic screening: evidence from randomised controlled trials. *Ann Oncol* 2003; **14:** 1185–89.

67 Fracheboud J, Otto SJ, van Dijck JA, Broeders MJ, Verbeek AL, de Koning HJ. Decreased rates of advanced breast cancer due to mammography screening in the Netherlands. *Br J Cancer* 2004; **91:** 861–67.

68 Groenewoud JH, Otten JD, Fracheboud J, et al. Cost-effectiveness of different reading and referral strategies in mammography screening in the Netherlands. *Breast Cancer Res Treat* 2007; **102:** 211–18.

69 Otto SJ, Fracheboud J, Looman CW, et al. Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. *Lancet* 2003; **361:** 1411–17.

70 Leach MO, Boggis CR, Dixon AK, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). *Lancet* 2005; **365:** 1769–78.

71 Bijker N, Peterse JL, Duchateau L, et al. Risk factors for recurrence and metastasis after breast-conserving therapy for ductal carcinoma-in-situ: analysis of European Organization for Research and Treatment of Cancer Trial 10853. *J Clin Oncol* 2001; **19:** 2263–71.

72 Tunon-de-Lara C, Lemanski C, Cohen-Solal-Le-Nir C, et al. Ductal carcinoma in situ of the breast in younger women: a subgroup of patients at high risk. *Eur J Surg Oncol* 2010; **36:** 1165–71.

73 Virnig BA, Tuttle TM, Shamliyan T, Kane RL. Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. *J Natl Cancer Inst* 2010; **102:** 170–78.

74 Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. *Lancet* 2012; **380:** 1778–86.

75 Berrington de Gonzalez A, Berg CD, Visvanathan K, Robson M. Estimated risk of radiation-induced breast cancer from mammographic screening for young BRCA mutation carriers. *J Natl Cancer Inst* 2009; **101:** 205–09.

76 US Food and Drug Administration, Center for Devices and Radiological Health. Trends in mammography dose and image quality 1974–2005. http://www.fda.gov/Radiation-EmittingProducts/MammographyQualityStandardsActandProgram/FacilityScorecard/ucm113352.htm (accessed April 4, 2012).

77 Young KC, Burch A, Oduko JM. Radiation doses received in the UK Breast Screening Programme in 2001 and 2002. *Br J Radiol* 2005; **78:** 207–18.

78 Griebsch I, Brown J, Boggis C, et al. Cost-effectiveness of screening with contrast enhanced magnetic resonance imaging vs X-ray mammography of women at a high familial risk of breast cancer. *Br J Cancer* 2006; **95:** 801–10.

79 Norman RP, Evans DG, Easton DF, Young KC. The cost-utility of magnetic resonance imaging for breast cancer in BRCA1 mutation carriers aged 30–49. *Eur J Health Econ* 2007; **8:** 137–44.

80 Plevritis SK, Kurian AW, Sigal BM, et al. Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging. *JAMA* 2006; **295:** 2374–84.

81 Taneja C, Edelsberg J, Weycker D, Guo A, Oster G, Weinreb J. Cost effectiveness of breast cancer screening with contrast-enhanced MRI in high-risk women. *J Am Coll Radiol* 2009; **6:** 171–79.

82 Pijpe A, Andrieu N, Easton DF, et al. Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations: retrospective cohort study (GENE-RAD-RISK). *BMJ* 2012; **345:** e5660.