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Focus On

Screening for breast cancer in women with previous mantle radiotherapy for Hodgkin's disease

G. Ralleigh

Department of Radiology, King's College Hospital, Denmark Hill, London, UK.

Abstract There is an established increased risk of secondary malignancy following radiation therapy for cancer in childhood or as a young adult. Breast cancer poses a particular problem as the population risk is significant and screening methods are available raising the question of possible screening interventions for women who are at high lifetime risk.

Keywords: Breast cancer; Hodgkin's disease; Screening; Supradiaphragmatic irradiation

Breast cancer in women treated for Hodgkin's disease

Relative risk and age at irradiation

Long-term follow-up of Hodgkin's disease (HD) survivors has revealed an increased incidence of secondary malignancy. More specifically, the relative risk of breast cancer after supradiaphragmatic irradiation (SDI) for HD is significantly increased [1–15], predominantly in those under the age of 30 years at the time of irradiation. Studies have shown a relative risk of 15–25 with greater risks for those treated between the ages of 10 and 16 years [1,4,9,10]. For women aged over 30 years at the time of treatment the relative risk is less significant, some studies have shown no excess risk while others have shown a relative risk of 2.4–3.7 [4,5,9,12]. Caution must be exercised in interpreting studies with incomplete follow-up as these may overestimate apparent risk (incomplete data is more likely to relate to subjects who have not had a second malignancy).

Correspondence to: Dr Gita Ralleigh, Department of Radiology, King's College Hospital, Denmark Hill, London, SE5 9RS, UK. E-mail: Gita.Ralleigh@kingsch.nhs.uk; Tel: +44 207 346 3875; Fax: +44 207 346 4363

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Latency

The median induction period for breast cancer following SDI for HD in adults is long, around 15 years (range 4–20) [1,3,5,7–10,13]. However, this may be shorter in those patients treated in childhood. There is sparse follow-up data beyond 20 years, but Dores *et al.* [2] have followed a cohort of patients for greater than 25 years and shown a significant continuing risk of breast cancer.

Radiation dose and chemotherapy

Radiation dose and the radiation field significantly influence risk, with most cases of breast cancer following mantle radiotherapy, which includes the neck, supraclavicular fossae, axillae and mediastinum, and increased risk with high-dose regimes [11,15,16]. Chemotherapy may modify the radiotherapy-induced risk due to the hormonal consequences of ovarian toxicity.

Characteristics of breast cancer developing after irradiation for HD

Histopathology

Breast cancers developing after SDI for HD are biologically and pathologically similar to sporadic breast cancer [7,17–21]. Cutuli *et al.* found in a retrospective

analysis of 133 breast cancers that 108 were invasive ductal carcinomas, 15 were ductal carcinoma *in situ* (DCIS) and 4 were lobular carcinoma with 6 other subtypes [20].

Location of tumours and bilaterality

Breast cancers developing after irradiation for HD differ from those observed sporadically in that tumours are more commonly bilateral [7,17–21] (9–29% synchronous and metachronous) and are more likely to be located in the medial part of the breast [7].

Minimising the risk of disease development

Breast cancer is a common disease and therefore an increase in relative risk raises the issue of counselling patients of their increased risk and possible benefits of screening and prevention strategies.

Published results from large randomised-controlled trials testing tamoxifen for chemoprevention in women at high risk of developing breast cancer have shown a risk reduction of 38%. This may have implications for the management of women following irradiation for HD [22].

Possible surveillance strategies

In the absence of conclusive data and the lack of randomised-controlled trials of possible screening methods in these women, a pragmatic approach is to consider the available options of self-examination, clinical examination, mammography, ultrasound and magnetic resonance imaging (MRI).

Self-examination/clinical examination

Randomised-controlled trials have shown that breast self-examination or clinical breast examination by a trained health professional has relatively low sensitivity (around 50–60%) both in population screening and in high-risk groups [23,24]. More importantly no demonstrable mortality benefit has been shown.

Mammography

The mortality benefits of mammography for population screening over the age of 50 years (of the order of 25% in women who take up screening) have been long established [25–28]. There is some mortality benefit in women aged 40–49 years [29–31]. There is however insufficient evidence of the effectiveness of mammography for either population or high-risk screening of women under age 40 years. Mammography generally demonstrates reduced sensitivity in young women partly due to increased breast density. Post SDI breast cancers are generally visible on mammography (in 87–100% of cases) [18–21]. The high sensitivity in such a young population is due to the high prevalence of microcalcification (62–72%) in those with abnormal mammograms [19,21].

Mammography screening may therefore be of benefit to these women but is unproven.

Furthermore mammography involves the use of ionising radiation with a consequent risk of cancer induction, which is higher in younger women. Women who have had SDI may understandably resist the use of further X-rays to detect a possible radiation-induced cancer.

Assuming a 15% risk of SDI-induced breast cancer (and that breast cancers developing are detectable with mammography), for a 30-year-old woman with average size breasts having yearly mammograms until age 50 years, the calculated potential benefit exceeds the risk of cancer induction by a factor of 100 (Faulkner K, personal communication).

Ultrasound

Bilateral whole-breast ultrasound can be used as an adjunct to mammographic screening in women with radiographically dense breasts. The quality of breast ultrasound has undoubtedly improved in the last 20 years with a consequent reduction in the false positive biopsy rate from 7.5% to 2.4% with an added cancer detection rate of approximately 0.3% in population screening [24,32–34]. At present European Consensus guidelines do not recommend breast ultrasound as a primary screening technique because of the high false negative and positive rates [35]. The problems of high operator dependence, difficulty covering the whole breast and low sensitivity for microcalcifications and thus DCIS, have also curtailed use of ultrasound for screening. The advantages of breast ultrasound are that it is widely available at a relatively low cost and does not use ionising radiation. It may have a role as an adjunct to other techniques or where other methods are contraindicated rather than as a primary screening test.

MRI

MRI has a high sensitivity for the early detection of breast cancer in young women at genetic risk particularly when performed with optimum technique and reported by radiologists experienced in interpretation [36,37]. A prospective multicentre cohort study of 649 women with a strong family history or who were either carriers of a BRCA1, BRCA2 or TP53 genetic mutation or a first degree relative of a carrier were examined with mammography and MRI. The sensitivity of MRI was 77% compared to 40% for mammography and 94% when both methods were used. However MRI has a reduced sensitivity for DCIS (60–88%) compared to mammography [38,39].

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Table 1. Surveillance for women at risk of breast cancer after treatment for HD with supradiaphragmatic irradiation.

Age (years)	Recommended surveillance	
<25	*No imaging*	
25–29	*Annual MRI* but if contraindications *annual ultrasound* (mammography is not recommended for this age group)	
30–50	*Baseline two-view mammogram.* Women should then be divided into two groups:	
	Predominantly fatty breast tissue	**Dense breast tissue**
	Annual two-view mammography	*Annual two-view mammography plus MRI*: Unless there are contraindications when the patient should be offered
		Annual mammography plus ultrasound: If breast tissue becomes predominantly fatty prior to the age of 50 years the patient should move into group 1 (i.e. annual mammography only)
>50	*Three-yearly mammography* should be offered within the NHS Breast Screening Programme (NHSBSP)	

The specificity of MRI is variable [40,41], benign masses and normal breast parenchyma may enhance in young women leading to false positives (a problem compounded by the difficulties of MR-guided biopsy). The pathology of breast cancer in women at genetic risk is different from sporadic breast cancer, which may influence the choice of screening method [42], but this is not the case for SDI-induced breast cancer [43].

MRI is also significantly more expensive than mammography or ultrasound, less available and is not tolerated by some patients.

Screening age and interval

The average age of breast cancer presentation in women post SDI is around 40 years but may be younger for those treated in childhood. Any method of screening should therefore begin at a younger age than population screening for sporadic breast cancer. For those treated under the age of 17 years screening from age of 25 years is appropriate, for those treated between 17 and 35 years screening should begin 8 years after the completion of treatment for HD.

Breast cancer in younger women has a shorter sojourn time (1–2 years aged 40–49 vs. 3 years in over 50s) [44,45] and annual screening is therefore advised.

Conclusion

Women treated with SDI for HD under age 35 years are at increased risk of subsequent breast cancer. No screening method is of proven efficacy in these women.

Screening causes adverse effects; anxiety and costs are associated with false-positive diagnosis and false reassurance. There is a balance between the potential benefit of mortality reduction and the risks, and the magnitude of both is unclear. Women should be counselled to allow an informed decision about surveillance and alternative risk reduction strategies such as surgery or chemoprevention. For those who opt for surveillance a recommended schedule has been developed by expert consensus from available evidence (Table 1).

Centres organising such surveillance for women with previous SDI for HD should record screening methods and outcomes. Only evaluation of such screening activity will allow future calculation of risks and benefits.

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