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SHORT COMMUNICATION

No strong evidence for increased risk of breast cancer 8–26 years after multiple mammograms in their 30s in females at moderate and high familial risk

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Objective: To assess the risks of induction of breast tumours from frequent screening mammography in younger females.

Methods: A study group of 853 females was identified who had at least 5 mammograms starting before 37 years of age, with 4 or more before the age of 40 years. These were followed up from their 40th birthday or 8 years from their first mammogram, and their cancer incidence was compared with that of a control group of 1103 females who had an average of 5 mammograms between the ages of 40 and 46 years. All females in the study were previously assessed to be at moderate familial risk or higher.

Results: There were 43 incident breast cancers in the study group after the 8-year start point, whereas 38.3

were expected from life-table calculations (RR 1.12; 95% CI: 0.83 to 1.51). In the control group, 50 incident breast cancers developed some time after their first mammogram in follow up to age 60 years. The observed, expected ratio from life tables in this group was 0.94 (95% CI: 0.71–1.24), similar to that in the study group.

Conclusion: There was no trend to greater cancer incidence in those receiving mammograms earlier.

Advances in knowledge: This study shows that there is no substantial effect on the induction of additional primary breast tumours from frequent mammography starting at <37 years of age. Further work on larger numbers of females is necessary to assess longer term risks and determine whether a small excess cancer effect may be present.

INTRODUCTION

Mammographic screening below the age of 40 years raises concern about the induction of new primary breast cancers and whether the benefit of surveillance in denser breasts with lower sensitivity is justified. There are also concerns about females with high familial risk who may carry mutations in genes such as the Breast cancer genes 1 or 2 (*BRCA1* or *BRCA2*) which are associated with DNA repair. Radiation-induced tumours usually occur 7–30 years after exposure, with a peak latent period of around 15 years.^{1,2} A recent meta-analysis revealed an increased risk of breast cancer among high-risk females exposed to low-dose radiation [odds ratio (OR) = 1.3, 95% CI: 0.9–1.8]. Exposure before the age of 20 years (OR = 2.0, 95% CI: 1.3–3.1) or a mean of ≥ 5 exposures (OR = 1.8, 95% CI: 1.1–3.0) was significantly associated with higher breast cancer risk

and the authors concluded that a careful approach is needed when using low-dose radiation on high-risk females.³ One study suggested using single-view mammography to detect calcifications in those undergoing MRI screening.⁴ Although MRI is widely advocated in some countries in females with lifetime risks as low as 20–25%,⁵ in many countries, its use is limited by cost and availability. In the UK, the National Institute for Health and Care Excellence guidance effectively limits screening to females with at least a 30% likelihood of mutations in *BRCA1/2* or the tumour protein 53 gene (*TP53*).⁶ Hence, the majority of females aged 30–39 years at high-risk of breast cancer would not be eligible for MRI screening. We have recently shown that mammography screening between 35 and 39 years of age detects breast cancer at an early stage similar to screening females at increased familial risk in their 40s,

although more work is necessary to show definite benefit.⁷ A further assessment of potential benefit of mammography has been proposed as a cancer detection: induction ratio of at least 10:1.⁸ Using this definition, mammography was deemed potentially beneficial in females aged 30–39 years at moderate risk with a mother or sister with breast cancer in their 30s but is more marginal in females aged 30–34 years with a mother or sister with breast cancer in their 40s.⁸ In keeping with the National Institute for Health and Care Excellence guidance,⁶ the ratios drop markedly below 30 years of age and mammography was not recommended.^{6–9} To assess the effect of mammography alone, we have examined potential breast cancer induction in females exposed to ≥ 5 mammograms starting before 37 years of age compared with females exposed at least 10 years later.

METHODS AND MATERIALS

Females attending the Genesis Breast Cancer Family History Clinic in Manchester, UK, with at least moderate ($\geq 17\%$) lifetime breast cancer risk were assessed for the study. In this clinic, females at moderate risk or higher are offered annual mammography until at least the age of 50 years. After 2004, no females were offered mammograms prior to their 30th birthday.⁶ A study group of females was identified consisting of those who had undergone at least five mammograms, with at least four of them before the age of 40 years and the first before their 37th birthday. Follow-up was assessed from their 40th birthday or 8 years from the first mammogram, whichever was later, or 1 August 2011 when all females were checked against the regional cancer registry. A control group consisted of females at similar moderate ($\geq 17\%$) breast cancer risk with no mammography exposure under 40 years of age who underwent risk assessment aged 40–46 years. The control group was therefore 8 years older than the study group at first exposure to mammography. The control group was followed from date of first mammogram to date of last follow-up as in the study group. Follow-up was censored at the date of diagnosis or risk-reducing mastectomy. Expected cancers were calculated for both the study and control groups using a manual life-table approach that was previously shown to be accurate.¹⁰ Cancers identified at first mammogram in the control group were excluded as this was the beginning of the study period and failure to do so would not allow for lead time. The main purpose of the control group was as an internal validation of the life-table predictions.

Mean glandular radiation doses¹¹ were estimated from the mammography technique in use at the time of examination. Prior to 2004, females underwent single-view film-screen mammography, with two-view film-screen mammography in use from 2004 to the introduction of two-view digital mammography (2009). An assessment of the lifetime risk of radiation-induced cancers was made for the study and control groups using the individual estimated dose and age at exposure together with the risk factors currently used to justify the national breast screening programme.¹²

RESULTS

In total, 853 females underwent at least 8 years of follow-up and at least 5 mammograms starting < 37 years. In the control group, 6/1109 females (0.54%) with prevalence breast cancers

were excluded. Eight females were censored for risk-reducing mastectomy in the study group and 23 in the controls. 14 deaths unrelated to breast cancer in the control group lead to censoring as opposed to 2 in the study group. In the study group, there were 5972.9 years of follow-up from the start point (40th birthday or 8 years from the first mammogram, whichever was later), with females undergoing a total of 8899 (10.43 mean per female) mammograms additional to those they would have had in the general population-screening programme aged 50–69 years. There were 43 incident breast cancers during follow-up when 38.3 were expected from life-table calculation (RR 1.12; 95% CI 0.83–1.51; Table 1). Follow-up time from the first mammogram was 8.01–28.02 (median 15.59) years. Some females received further views following recall for assessment; thus some had more frequent than annual mammograms. The 43 breast cancers occurred from 8.38 to 21.98 years (median: 12.66 years) after the first mammogram, reflecting the overall distribution of follow-up rather than a skew to higher later incidence. 64 females received their first mammogram at an age < 30 years, the last in 2003. Four breast cancers occurred in this group aged 40.45–45.93 years, with two being mutation carriers (*BRCA1*, *BRCA2*). Table 1 shows the subdivision of the study group into three: starting aged < 33 , 33–34 and 35–36 years. There was no evidence of a stepwise decrease in observed: expected (O:E) ratios with an O:E of 0.86 (0.46–1.60) in the youngest exposed group. In the 43 incident breast cancers, there were 9 *in situ* carcinomas, 21 Stage 1 cancers, 7 Stage 2a cancers and 2 Stage 2b. Full pathology details were not available for four cancers occurring in females who had left the programme. After a total of 227.6 years of follow-up, four deaths occurred 2.1–6.3 years post diagnosis. All but 231 of the 799 (29%) uncensored females received a follow-up mammogram in the previous 3 years, therefore recent follow-up data are available for the majority. There was no evidence of higher proportions of breast cancers in the high-risk group. 30 breast cancers occurred in 550 females when 26.6 were expected (OR: 1.13, 95% CI: 0.79–1.61).

The control group consisted of 1103 females who underwent an average of 5 additional mammograms (to population screening but none < 40 years). Within the group, 50 incident breast cancers developed after the first mammogram in 9696 years of follow-up to a maximum of 60 years of age. The O:E ratio from life tables was 0.94 (95% CI 0.71–1.24; Table 1), similar to that in the study group. 552 (50%) of the females not censored for other reasons had not received a mammogram in the past 2 years. There were seven breast cancer deaths (14%). In the first 8 years from initial exposure in the control group when no induced cancer were likely, there were 30 breast cancers when 31.29 (O:E 0.96) would have been expected in 6608 females years of follow-up.

In terms of radiation dose, females in the study group were estimated to have received a median mean glandular dose¹¹ of 30.5 mGy (range 22.5–40.5 mGy) in the period before follow-up started (40th birthday or 8 years from the first mammogram), whereas the control group had no exposure in the equivalent period. Individual dose estimates were calculated using mammography examination radiation doses considered typical at the time (2.5 mGy for single-view examination and 4.5 mGy for

Table 1. Follow-up and characteristics of the study and control groups with expected and observed breast cancers

Group	Number	Years of follow-up	Breast cancers	Mean (median) age at first mammogram (years)	Mean (median) lifetime risk (%)	Expected cancers from manual model	O : E ratio (95% CI)	Cancers in high risk (%)	O : E ratio, high risk (95% CI)	Cancers in <i>BRCA1/2</i> carriers (%)
Study group	853	5972.9	43	33.83 (34.74)	28% (33)	38.30	1.12 (0.83–1.51)	30/550 (5.45)	1.13 (0.79–1.61)	15/44 (34.1)
Control group	1103	9696	50	42.49 (42.43)	24% (33)	53.27	0.94 (0.71–1.24)	25/561 (4.46)	0.84 (0.57–1.24)	9/46 (19.6)
Study group, first mammogram <33 years	264	1802.6	10			11.65	0.86 (0.46–1.60)	7/175 (4.00)		6/16 (37.5)
Study group, first mammogram 33–34 years	220	1685.2	16			11.10	1.44 (0.88–2.36)	12/149 (8.05)		3/10 (30.0)
Study group, first mammogram 35–36 years	369	2485.05	17			15.62	1.09 (0.68–1.75)	11/226 (4.87)		6/18 (33.3)

O : E, observed : expected.

two-view examination),¹² accounting for the change to two-view screening mammography in 2004. Using age-dependent breast-cancer-specific risk factors for the UK breast screening population,¹² individual estimated mean glandular dose and age at each exposure, the lifetime excess breast cancer risk was calculated. Summing individual lifetime risks for the 853 females in the study group, 0.43 radiation-induced cancers would be predicted. Radiation exposure in the control group, having mammography only after the age of 40 years, was similarly analysed. Females in this group were estimated to have received a median mean glandular dose of 17.8 mGy (range 5.0–40.5 mGy). Summation of individual lifetime risks for the 1103 females in this group predicts 0.31 radiation-induced cancers. These risk evaluations are in line with the method presently used to justify radiation exposure in the national breast screening programme and do not account for any hypothesized higher radiosensitivity in high-risk females.

DISCUSSION

Potential rates of radiation-induced breast cancer from multiple mammograms before 40 years of age have been assessed in females at moderate and high risk of breast cancer. Although the study does not cover the entire lifetime of the females, it does cover the peak period for radiation-induced cancers of 8–25 years post exposure.^{1,2} The results effectively rule out the 1.8-fold relative risk estimated for >5 exposures from the Dutch meta-analysis,³ as this estimate lies outside the 95% confidence intervals obtained here. Although our study is not powered to detect smaller effects, there is reassurance that females undergoing mammograms in their early 30s do not have a greatly increased risk of radiation-induced breast cancers. The O:E of 1.12 implies a detection:induction ratio close to the 10:1 ratio suggested as beneficial.⁸ Nearly all the breast cancers detected had excellent prognostic features, with 26/39 (67%—4 no longer screened) detected by screening and only 10 (26%) occurring as true interval cancers (3 were found incidentally at risk-reducing mastectomy). Taking the detection rate into account, there would have been a detection:induction ratio of 6.3:1; however, even this ratio is based on a non-significant potential induction rate and is therefore speculative. Although the major part of the study period for cancer detection was outside the main exposure period of the 30s, we have previously shown that the prognosis of females aged 35–39 years with breast cancers detected in a mammographic screening programme is as good as for those females aged 40–49 years at detection, and significantly better than non-screened controls.^{7,13}

The breasts are known to be particularly radiosensitive in teenage and early adult life, as shown by the marked increased incidence of breast cancer following supradiaphragmatic radiotherapy in young females (typically mantle radiotherapy for Hodgkin's lymphoma).¹⁴ However, in the present study, in addition to finding no evidence for an increased risk of breast cancer from the much smaller diagnostic radiation exposure in females undergoing mammography in their twenties and 30s, there was no stepwise effect with increasing age. Nevertheless, we would not advocate commencing mammography <30, in line with current UK recommendations.¹⁵ The lower sensitivity of mammography in younger females¹⁶ should be taken into

account in determining its potential risks and benefits in these females. There was also no evidence of a greater carcinogenic effect of radiation in those estimated at particularly high breast cancer risk (>30%).

The lifetime risk estimated based on general population estimates indicates only 0.43 induced cancers in the present study based on early exposure. This does not account for higher background risks of breast cancer or increased radiosensitivity suggested for *BRCA1/BRCA2* carriers whose genetic defects give rise to impairment in DNA repair by homologous recombination, once the cell has lost both functioning copies of the gene.¹⁵ However, it still remains to be shown that the cells which are heterozygous for a mutation are more radiosensitive. The current study is not powered to assess any effects in *BRCA1/2* mutation carriers specifically, and as these females qualify for the more sensitive MRI screening, they may not need mammography.^{6,17,18} Using the approximate 6-fold population risk in females in their 30s (0.5% in general population^{1,7}), then without additional radiosensitivity, 1.72 additional breast cancers could have been induced in the study group of 853, whereas there were an expected 18 found in the 30s as well as 28 screen-detected cancers in the 40s, equating to a 26:1 ratio of screen-detected:potential radiation-induced cancers. This study is important for the larger proportion of females who are at high risk of breast cancer not from *BRCA1/2* families and do not qualify for MRI screening in the UK.

The present study employed both a life-table risk approach to assess expected cancers and a control group unexposed to mammography at ages <40 years. Life tables demonstrate an accurate assessment of expected cancers in the large control group who were exposed later to mammography and whose follow-up period was largely outside the main tumour induction period. There are limitations to the present study. It is not sufficiently powered to detect small cancer-induction effects of additional radiation exposure and, in particular, in *BRCA1/2* mutation carriers. The follow-up does not reflect a lifetime risk from early mammography but assesses risk in the main induction period of radiation-induced cancer, as median follow-up was 15 years from the first exposure.

CONCLUSION

This study shows that there is no strong evidence for increased radiation-induced breast cancers 8–26 years after early mammography exposure in females at high and moderate risk of breast cancer. It suggests that detection:induction ratios of females screened are likely to be in line with the lower 10:1 ratio suggested as being beneficial.⁸ As such, it appears reasonably safe to offer females at high risk of breast cancer mammographic surveillance in their 30s, although further research is necessary to verify that screening is effective in this group and that no later effect occurs. Females undergoing such early surveillance should nonetheless have the potential cancer-induction risks explained.

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