ORIGINAL PAPER

Age-specific interval breast cancers in New South Wales and meta-analysis of studies of women aged 40–49 years

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Objective: To compare interval cancers in the 40–49 year age group with other age groups in New South Wales and with published trials and service studies.
Setting: New South Wales data were derived from the population-based biennial mammography screening program, which achieved state-wide coverage in 1995. Women aged 40–49 years screened during 1995–1998 were included.
Methods: Bilateral two-view mammography with reading by two radiologists was employed for biennial screening examinations. Interval cancers were detected by the screening program and by linkage with the state-wide cancer registry. Incidence of interval cancer based on the date of diagnosis was estimated as a proportion of the expected underlying breast cancer incidence for first- and second-year interval cancers. Sensitivity estimates were also calculated. Comparative data for the 40–49 year age group were derived from the published literature for meta-analyses of trial and service studies.
Results: Interval cancer rates for New South Wales decreased with increasing age, with the highest proportional incidence in the 40–49 year age group for first year (56%, 95% confidence interval [CI] 50–62%) and second-year (86%, 95% CI 82–90%) interval cancers. Proportional incidence for women aged 50–69 years for first- and second-year interval cancers was 31% (95%CI 29–33%) and 50% (95% CI 47–52%) respectively. Sensitivity estimates for the program increased significantly with age, with lowest sensitivity estimates evident for women 40–49 years. In women aged 40–49 years the meta-analysed proportional incidence rate for randomised trials of screening for first- and second-year interval cancers was 42% (95% CI 21–62%) and 63% (95% CI 55–71%) respectively, while for service studies it was 44% (95% CI 31–58%) and 72% (95% CI 51–92%). Proportional incidence in the New South Wales program for women aged 40–49 years was not significantly different to the meta-analysed proportional incidences for trial and service studies in the first year, or for service studies in the second year.
Conclusion: Proportional incidence of interval cancer was significantly higher in women aged 40–49 years in New South Wales relative to older age groups, but did not differ significantly from service studies of women in a similar age group. The effectiveness of mammography screening for this age group needs to be examined in view of the comparatively high rate of interval cancers.

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INTRODUCTION

Mammography screening for women aged 40–49 years has shown mortality reductions of 15–25% in randomised trials,[1–5] but this reduction is of marginal statistical significance and determining whether screening in this age group is effective has not been without controversy.[6] Compared with women aged 50–69 years, women aged 40–49 years have lower breast cancer incidence and mortality rates[4,7] and a longer period (10–14 years) before mammography screening shows breast cancer mortality reduction.[2,4] Faster tumour progression, higher rates of ductal carcinoma *in situ* (DCIS) found at mammography and lower sensitivity of mammography screening compared with older women, as well as previously small sample sizes in this age group (relative to older age groups) are other factors limiting an unqualified conclusion regarding the efficacy of mammography screening in women aged 40–49 years.[2,4,5]

Low interval cancer rates per woman screened are correlated with significant reductions in mortality from breast cancer in the screened population.[8–10] Interval breast cancers are cancers diagnosed after a mammography screen with a non-malignant result and before the next scheduled screen. Interval cancers can be classified by diagnosis (after the first [prevalent] or a subsequent [incident] screen, or in the first, second or third year following a normal mammogram), by age group, and by period.

Since the underlying rate of breast cancer incidence varies between populations and across age groups, interval cancer rates per woman screened are not directly comparable either internationally or by age. For this reason, interval cancer incidence is often expressed as a proportion of the cancer incidence that would have been expected in a similar population in the absence of screening. This statistic can be used to compare outcomes of major screening trials and service studies.[8,9] Another approach is to use program sensitivity where an interval cancer is considered as a false negative.

Data on interval cancer occurrence from trials of mammography screening are important in setting objectives that screening services could be expected to achieve. On the other hand, interval cancer data from mammographic screening services indicate what has been achieved in the

context of routine service provision. A previous Australian study in New South Wales (NSW) that compared interval cancer rates in women aged 50–69 years found significant differences in proportional incidence between trials and service studies.[11] The purpose of this paper is to compare interval breast cancer proportional incidence and sensitivity estimates in women aged 40–49 years with other age groups from the NSW mammography screening program and with meta-analysed interval cancer rates in women aged 40–49 years from published trials and service studies.

METHODS

Screening

The study population consists of women who attended for mammography screening at BreastScreen NSW during 1995–1998. This ensured that complete two-year follow-up data were available on all women screened (to the end of 2000). BreastScreen NSW is part of BreastScreen Australia and consists of 10 screening and assessment services targeting women aged 50–69 years. Women aged 40–49 years (and ≥70 years) are not actively recruited but are screened on request. This study considers interval cancers in the younger age group and compares incidence with that in older age groups (50–69 and ≥70 years). DCIS was not included. Women who attend for screening undergo bilateral two-view mammography and all films are read independently by two radiologists. If the two radiologists do not agree on a recommendation of either routine rescreen or recall for assessment, then the final recommendation is based on either the consensus opinion of the two radiologists after discussion, or the recommendation of a third radiologist.

Interval cancers

The definition of primary breast cancer used for this study includes invasive cancer, but excludes DCIS and lobular carcinoma *in situ* (LCIS). For the purposes of this study, interval cancers were cases of primary cancer of the breast diagnosed up to 24 months after a screening mammogram from the first or subsequent screening rounds. This definition includes invasive cancers diagnosed at early review – that is, at a repeat assessment following an equivocal assessment visit.

Interval cancers were identified by linking BreastScreen NSW records to the NSW Central Cancer Registry data for incident breast cancers using the date of diagnosis (not onset of symptoms), the date of the first pathology report, or the date of the first hospital admission (whichever was the earliest) as the definition of date of incidence. DCIS and LCIS were not routinely coded in the NSW Central Cancer Registry data for the study period and were excluded from the analysis of proportional incidence. Some interval cancers were also reported directly to BreastScreen NSW *via* Screening and Assessment Services. Completeness of enumeration is difficult to determine precisely for cancer registries, but the standard indicators, such as the histological verification and the death certificate only rates, suggest good completeness for breast and other cancers in NSW,[12,13] and data are routinely included in the Cancer Incidence in Five Continents publication.[14]

The matching of records from the screening database with the cancer registry was accomplished with the aid of probabilistic linkage[15,16] using a multi-pass Automatch algorithm.[17] The algorithm made use of available identifying information, including the woman's name, address and date of birth. To maximise the sensitivity of matches, the passes in the algorithm alternated between blocking and weighting on combinations of identifying variables. Partial matches were sent to the regional screening services for clerical resolution.

Interval breast cancer rates per 10,000 women screened were calculated for the following ten-year age groups: 40–49, 50–59, 60–69 and 70–79 years. The Poisson method was used to calculate 95% confidence intervals (CIs) for the interval cancer rate.[18] Annual interval cancer rates were examined, though no consistent trends were evident, and aggregate rates for the period 1995–1998 are presented. Tests for trend in interval cancer rates across age groups were completed using Poisson regression models with a logarithmic link function and Poisson error distribution. Age group was specified as an ordinal variable, and models were offset by the natural logarithm of the number of women screened. The following model was specified (where d is the number of interval cancers, p the number of women screened, β_1 the regression co-efficient, and k the constant):

$$\ln(d/p) = \beta_1 \text{age} + k$$

Underlying breast cancer rate

Using the rate of breast cancer for the whole state as an underlying rate[19] is no longer possible in NSW because of widespread population screening. Widespread population mammographic screening initially inflates the incidence of breast cancer because of increased early detection.[11] The underlying age-specific incidence of breast cancer in NSW has been adjusted to discount for the period effect of increased detection using Age, Period, Cohort (APC) modelling, which is described elsewhere.[20,21] The estimated underlying population incidence derived from annual estimates for the period 1995–1998 was 14.9 per 10,000 for women aged 40–49 years, 24.0 per 10,000 for women aged 50–59 years, 28.0 per 10,000 for women aged 60–69 years, and 29.7 per 10,000 for women aged 70–79 years.

Proportional incidence

The interval cancer incidence as a proportion of the underlying breast cancer incidence rate was calculated and the exact method for the binomial distribution[18] was used to calculate the 95% CIs. Tests for trend in proportional incidence across age groups were completed by logistic regression, with outcome probability specified as events/trials. Age group was specified as an ordinal variable. Preliminary analyses showed a curvilinear relationship between proportional incidence and age; both linear and quadratic functions were therefore examined and assessed according to goodness-of-fit statistics. A logarithmic model was specified of the following form (where p is the proportional incidence, β_1 the regression co-efficient, and k the constant):

$$\text{logit}(p) = \beta_1 \ln(\text{age}) + k$$

Sensitivity

Program sensitivity is defined as the number of screen detected cancers expressed as a proportion of total cancer incidence (screen detected plus interval cancers) in women screened. Sensitivity was calculated for the NSW program for all age groups (initial, subsequent and all screens), and also for all trials and service studies where the relevant data could be extracted. The 95% CIs were based on the exact binomial. Tests for trend in program sensitivity across age

groups were completed by logistic regression, with outcome probability specified as events/trials. Age group was specified as an ordinal variable. Both linear and quadratic functions were examined. A logarithmic model was specified of the following form (where p is the sensitivity, β_1 the regression co-efficient, and k the constant):

$$\text{logit}(p) = \beta_1 \ln(\text{age}) + k$$

Comparisons

All studies concerning interval cancers in mammographic screening programs for women aged 40–49 years (or similar age groups) published since 1975 were derived from the literature by electronic searching (Medline) and secondary searching of bibliographies of these and related articles. Studies were included in the review if they contained numbers of interval cancers occurring in the first and/or second year following screening and the underlying incidence rate, or information that enabled these to be calculated (to calculate proportional incidence); or if they contained numbers of interval cancers occurring in the first and/or second year following screening and the number of screen detected cancers, or information that enabled these to be calculated (to calculate sensitivity). Two of the authors (R Taylor and A Page) undertook the extraction of data.

Comparisons of NSW interval cancer rates in relation to underlying incidence and screen detected cancers in women aged 40–49 years were made with international studies from Sweden,[9,10,22,26] Canada,[27] the Netherlands,[28] Italy[29] and the US,[30] as well as Australia.[19,31] The Swedish studies were all randomised trials, as was the Canadian study. The remaining studies from Italy, the Netherlands, the US and Australia were studies carried out in a service context.

Meta-analysis

Meta-analysis was performed by the fixed or random effects model,[32] depending on whether there was significant heterogeneity within the data.[18] A modification of the meta-analysis calculations suitable for rates derived from small numbers of cases was used.[33,34] For the Swedish two county trial, only data that combined results from Kopparberg and Ostergotland counties were used.

Data from all countries were meta-analysed to compare proportional incidence between trial and service situations in women aged 40–49 years for first-and second-year proportional interval cancer incidence.[11,33] Prevalent and incident screens were combined as this data was not presented separately in some studies. The exact binomial was used to calculate 95% CIs for the derived proportional incidence.[18]

RESULTS

Interval breast cancer rates (per 10,000 women screened) were similar across age groups in the NSW screening program, though were slightly higher in women aged 40–49 years for initial screens for both first- and second-year interval cancers. The interval cancer rate in NSW generally declined with increasing age (Table 1, Figure 1a). This decline was much greater for proportional incidence estimates, which account for the underlying incidence in each age group (Table 1, Figure 1b).

Proportional incidence of interval breast cancer in NSW for all screens was 56% and 86% in the 40–49 year age group for first- and second-year interval cancers respectively, and was significantly higher compared to all other age groups for initial, subsequent, and all screens (Table 1a,b). Proportional incidence was significantly higher for all age groups in the second year following the prevalent screen compared to the first year. A significant decreasing logarithmic trend from younger to older age groups was evident for both first-year and second-year interval cancers (Table 1a,b; Figure 1b). Interval cancer proportional incidence was not significantly different for initial and subsequent screens and these were aggregated for meta-analysis.

Comparison of the NSW screening program with other studies for first-year interval cancers in women aged 40–49 years show a slightly higher proportional incidence when

Table 1a First- and second-year interval breast cancers by age group in the NSW mammography screening program in women screened 1995–1998 (0–12 months)

Age group	Women screened *a*	Screen detected cancers *b*	Interval cancers *c*	Expected cancers† *d*	Rate /10,000 screens‡ (95% CI) § *c/a*	Proportional Incidence (%)¶ (95%CI) †† *c/d*	Sensitivity (%)§ (95% CI) †† *b/(b+c)*
First year (0–12 months)							
Initial							
40–49	116,463	243	97	174	8.3 (6.8–10.2)	55.7 (48.0–63.3)	71.5 (66.4–76.2)
50–59	141,703	644	102	338	7.2 (5.9–8.7)	30.2 (25.3–35.4)	86.3 (83.7–88.7)
60–69	90,962	599	65	251	7.1 (5.5–9.1)	25.9 (20.6–31.8)	90.2 (87.7–92.4)
70–79	37,558	399	28	110	7.5 (5.0–10.8)	25.5 (17.6–34.7)	93.4 (90.7–95.6)
Trend					β = –0.05	β = –1.05***	β = 1.22***
50–69	232,665	1,243	167	589	7.2 (6.1–8.4)	28.4 (24.8–32.3)	88.2 (86.4–89.8)
Subsequent							
40–49	94,262	144	79	140	8.4 (6.6–10.4)	56.4 (47.8–64.8)	64.6 (57.9–70.8)
50–59	178,329	625	171	431	9.6 (8.2–11.1)	39.7 (35.0–44.5)	78.5 (75.5–81.3)
60–69	171,889	691	128	485	7.4 (6.2–8.9)	26.4 (22.5–30.6)	84.4 (72.5–78.5)
70–79	80,043	393	49	240	6.1 (4.5–8.1)	20.4 (15.5–26.1)	88.9 (85.6–91.7)
Trend					β = –0.12*	β = –1.22***	β = 1.03***
50–69	350,218	1,316	299	916	8.5 (7.6–9.6)	32.6 (29.6–35.8)	81.5 (79.5–83.4)
All screens							
40–49	210,725	387	176	314	8.4 (7.2–9.7)	56.1 (50.4–61.6)	68.7 (64.7–72.6)
50–59	320,032	1,269	273	769	8.5 (7.5–9.6)	35.5 (32.1–39.0)	82.3 (80.3–84.2)
60–69	262,851	1,290	193	736	7.3 (6.3–8.5)	26.2 (23.1–29.6)	87.0 (85.2–88.7)
70–79	117,601	792	77	350	6.5 (5.2–8.2)	22.0 (17.8–26.7)	91.1 (89.1–92.9)
Trend					β = –0.08*	β = –1.11***	β = 1.06***
50–69	582,883	2,559	466	1,505	8.0 (7.3–8.8)	31.0 (28.6–33.4)	84.6 (83.3–85.9)

*p<0.05, **p<0.01, ***p<0.001. †Expected cancers are the estimated number of cancers during the period in the absence of screening, estimated by age, period, cohort (APC) modelling. ‡Test for trend is of the form $\ln(d/p) = \beta_1 \text{age} + k$. §95% Confidence intervals calculated using Poisson distribution. ¶Test for trend is of the form $\text{logit}(p) = \beta_1 \ln(\text{age}) + k$. ††95% Confidence intervals calculated using the exact binomial

Table 1b First– and second–year interval breast cancers by age–group in the NSW mammography screening program in women screened 1995–98 (13–24 months)

Age group	Women screened *a*	Screen detected cancers *b*	Interval cancers *c*	Expected cancers† *d*	Rate /10,000 screens‡ (95% CI)§ *c/a*	Proportional Incidence (%)¶ (95% CI)†† *c/d*
Second year (13–24 months)						
Initial						
40–49	110,583	243	144	165	13.0 (11.0–15.3)	87.4 (81.2–92.0)
50–59	133,903	644	172	319	12.8 (11.0–14.9)	53.8 (48.3–59.5)
60–69	86,486	599	102	239	11.8 (9.6–14.3)	42.8 (36.3–49.2)
70–79	35,022	399	47	103	13.4 (9.9–17.8)	45.8 (35.8–55.7)
Trend					β = –0.02	β = –1.54**
50–69	220,389	1243	274	558	12.4 (11.0–14.0)	49.1 (44.9–53.3)
Subsequent						
40–49	85,485	144	108	127	12.6 (10.4–15.3)	84.8 (77.6–90.8)
50–59	180,778	625	259	438	14.3 (12.6–16.2)	59.2 (54.4–63.8)
60–69	154,020	691	179	435	11.6 (10.0–13.5)	41.2 (36.5–45.9)
70–79	71,041	393	68	213	9.6 (7.4–12.1)	32.0 (25.7–38.6)
Trend					β = –0.10*	β = –1.77***
50–69	334,798	1316	438	872	13.1 (11.9–14.4)	50.2 (46.9–53.6)
All screens						
40–49	196,068	387	252	292	12.9 (11.3–14.5)	86.3 (81.8–90.0)
50–59	314,681	1269	431	757	13.7 (12.4–15.1)	56.9 (53.3–60.5)
60–69	240,506	1290	281	673	11.7 (10.4–13.1)	41.7 (38.0–45.6)
70–79	106,063	792	115	315	10.8 (9.0–13.0)	36.5 (31.2–42.1)
Trend					β = –0.07*	β = –1.67***
50–69	555,187	2559	712	1430	12.8 (11.9–13.8)	49.8 (47.2–52.4)

*p<0.05, **p<0.01, ***p<0.001. †Expected cancers are the estimated number of cancers during the period in the absence of screening, estimated by age, period, cohort (APC) modelling. ‡Test for trend is of the form ln(d/p)= $\beta_1$age+k. §95% Confidence intervals calculated using Poisson distribution. ¶Test for trend is of the form logit(p)= $\beta_1$ln(age)+k. ††95% Confidence intervals calculated using the exact binomial

Table 1c First– and second–year interval breast cancers by age–group in the NSW mammography screening program in women screened 1995–98 (0–24 months)

Age group	Women screened *a*	Screen detected cancers *b*	Interval cancers *c*	Expected cancers† *d*	Rate /10,000 screens‡ (95% ci)§ *c/a*	Proportional incidence (%)¶ (95% ci)†† *c/d*	Sensitivity (%)¶ (95%ci)†† *b/(b+c)*
First and Second year (0–24 months)							
Initial							
40–49	227,046	486	241	339	10.6 (9.3–12.0)	71.1 (66.0–75.9)	66.9 (63.3–70.3)
50–59	275,606	1,288	274	657	9.9 (8.8–11.2)	41.7 (37.9–45.6)	82.5 (80.5–84.3)
60–69	177,448	1,198	167	490	9.4 (8.0–11.0)	34.1 (29.9–38.5)	87.8 (85.9–89.5)
70–79	72,580	798	75	213	10.3 (8.1–13.0)	35.3 (28.8–42.0)	91.4 (89.4–93.2)
Trend					β = –0.03	β = –1.20***	β = 1.18***
50–69	453,054	2,486	441	1,147	9.7 (8.8–10.7)	38.4 (35.6–41.3)	84.9 (83.6–86.2)
Subsequent							
40–49	179,747	288	187	267	10.4 (9.0–12.0)	70.0 (64.2–75.5)	60.6 (56.1–65.1)
50–59	359,107	1,250	430	869	12.0 (10.9–13.2)	49.5 (46.1–52.9)	74.4 (72.3–76.5)
60–69	325,909	1,382	307	920	9.4 (8.4–10.5)	33.4 (30.3–36.5)	81.8 (79.9–83.6)
70–79	151,084	786	117	453	7.7 (6.4–9.3)	25.8 (21.9–30.1)	87.0 (84.7–89.2)
Trend					β = –0.11***	β = –1.43***	β = 1.04***
50–69	685,016	2,632	737	1,788	10.8 (10.0–11.6)	41.2 (38.9–43.5)	78.1 (76.7–79.5)
All screens							
40–49	406,793	774	428	606	10.5 (9.5–11.6)	70.6 (66.8–74.2)	64.4 (61.6–67.1)
50–59	634,713	2,538	704	1,526	11.1 (10.3–11.9)	46.1 (43.6–48.7)	78.3 (76.8–79.7)
60–69	503,357	2,580	474	1,409	9.4 (8.6–10.3)	33.6 (31.2–36.2)	84.5 (83.2–85.8)
70–79	223,664	1,584	192	665	8.6 (7.4–9.9)	28.9 (25.5–32.5)	89.2 (87.7–90.6)
Trend					β = –0.07***	β = –1.31***	β = 1.05***
50–69	1,138,070	5,118	1,178	2,935	10.4 (9.8–11.0)	40.1 (38.4–41.9)	81.3 (80.3–82.3)

*p<0.05, **p<0.01, ***p<0.001. †Expected cancers are the estimated number of cancers during the period in the absence of screening, estimated by age, period, cohort (APC) modelling. ‡Test for trend is of the form ln(d/p)= $\beta_1$age+k. §95% Confidence intervals calculated using Poisson distribution. ¶Test for trend is of the form logit(p)= $\beta_1$ln(age)+k. 95% Confidence intervals calculated using the exact binomial

compared with all trials (56 *versus* 42%) and when compared with all service studies (56 *versus* 44%) when meta-analysed separately (Table 2, Figure 2a). These differences were not statistically significant. For second-year interval cancers, proportional incidence in the NSW program was significantly higher than all trials (86 *versus* 63%), but not significantly higher than all service studies (86 *versus* 73%; Table 2, Figure 2b).

Sensitivity estimates for the NSW program increased significantly across age groups, from 72 to 93% for the first year post screening and from 63 to 90% for the second year (Table 1a,c). A significant difference between 0–12 month and 0–24 month interval cancers for those aged 50–69 years was evident for invasive cancers (Table 1a,c).

DISCUSSION

Data from the NSW mammography screening program on first- and second-year interval breast cancers in women aged 40–49 years showed a proportional incidence of 56 and 86% respectively for all screens during the period 1995–1998. Proportional incidence for both first- and second-year interval cancers was significantly higher in women aged 40–49 compared to women >50 years old. A significant

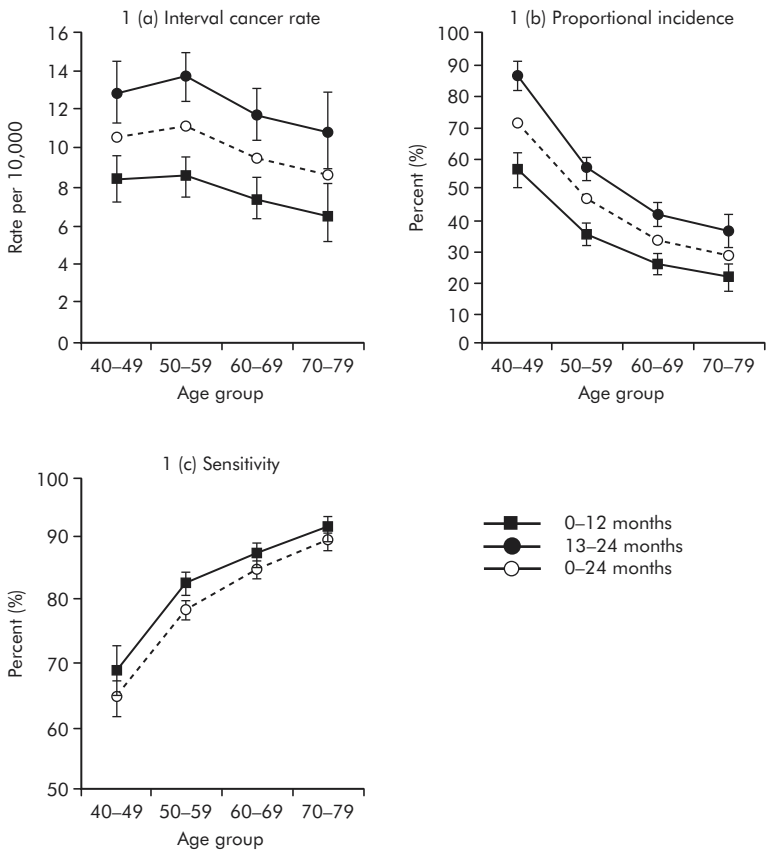

Figure 1 Proportional Incidence of interval breast cancers in New South Wales, 1995–1998

Table 2 International comparisons of first– and second–year interval breast cancer in women 40–49 years, as a proportion of underlying incidence

	Year 1 (0–12 months)			Year 2 (13–24 months)			Years 1 & 2 (0–24 months)		
Study	O	E	PI (95% CI)*	O	E	PI (95% CI)*	O	E	PI (95% CI)*
Trials									
Tabar *et al*, 1987 (Two Counties, Sweden)§	15	40	37.5 (22.7–54.2)	23	34	67.7 (49.5–82.6)	38	74	51.4 (39.4–63.2)
Andersson *et al*, 1988 (Malmo, Sweden)§	–	–	–	–	–	–	6	14	42.9 (17.7–71.1)
Miller *et al*, 1992 (NBSS, Canada)§	19	28	67.9 (47.7–84.1)	16	25	64.0 (42.5–82.0)	61	108	56.5 (46.6–66.0)
Tabar *et al*, 1992 (Two Counties, Sweden)§	25	54	46.3 (32.6–60.4)	36	54	66.7 (52.5–78.9)	35	53	66.0 (51.7–78.5)
Bjurstam *et al*, 1997 (Gothenburg, Sweden)	16	90	17.8 (10.5–27.3)	19	37	51.4 (34.4–66.1)	33	127	26.0 (18.6–34.5)
Frisell *et al*, 1987, 1997 (Stockholm, Sweden)	–	–	–	–	–	–	21	38	55.3 (38.3–71.4)
Bjurstam *et al*, 2003 (Gothenburg, Sweden)	–	–	–	–	–	–	33	152	21.7 (15.4–29.1)
Service studies									
Paci *et al*, 1990 (Florence, Italy)§	4	14	28.6 (8.4–58.1)	6	13	46.2 (19.2–74.9)	10	28	35.7 (18.6–55.9)
Brekelmans *et al*, 1992 (Utrecht, Netherlands)§	8	19	42.1 (20.3–67.6)	25	37	67.6 (50.2–82.0)	33	56	58.9 (45.0–71.9)
Rickard *et al*, 1998 (Sydney, Australia)§	5	17	29.4 (10.3–56.0)	–	–	–	–	–	–
Kavanagh *et al*, 1999 (Victoria, Australia)	28	48	58.3 (43.2–72.4)	23	25	92.0 (74.0–99.0)	40	49	81.6 (68.0–91.2)
BreastScreen, 1995–1998 (NSW, Australia)	176	314	56.1 (50.4–61.6)	252	292	86.3 (81.8–90.0)	428	606	70.6 (66.8–74.2)
Summary statistics									
Trials	75	212	41.7 (21.2–62.2)†	94	150	62.9 (55.2–70.7)‡	227	566	40.2 (36.1–44.3)†
Service studies	221	412	44.4 (30.7–58.0)†	306	367	71.9 (51.4–92.3)†	511	739	69.2 (65.6–72.8)†
All studies	296	624	42.6 (30.4–54.7)†	400	517	67.4 (55.1–79.8)†	738	1305	51.7 (38.4–65.1)†

O, Observed interval cancers; E, Expected incident cancers; PI, Proportional Incidence, PI=O/E, *95% Confidence Intervals calculated using the exact binomial, † Random effects model, ‡ Fixed effects model, § Includes ductal carcinoma *in situ*.

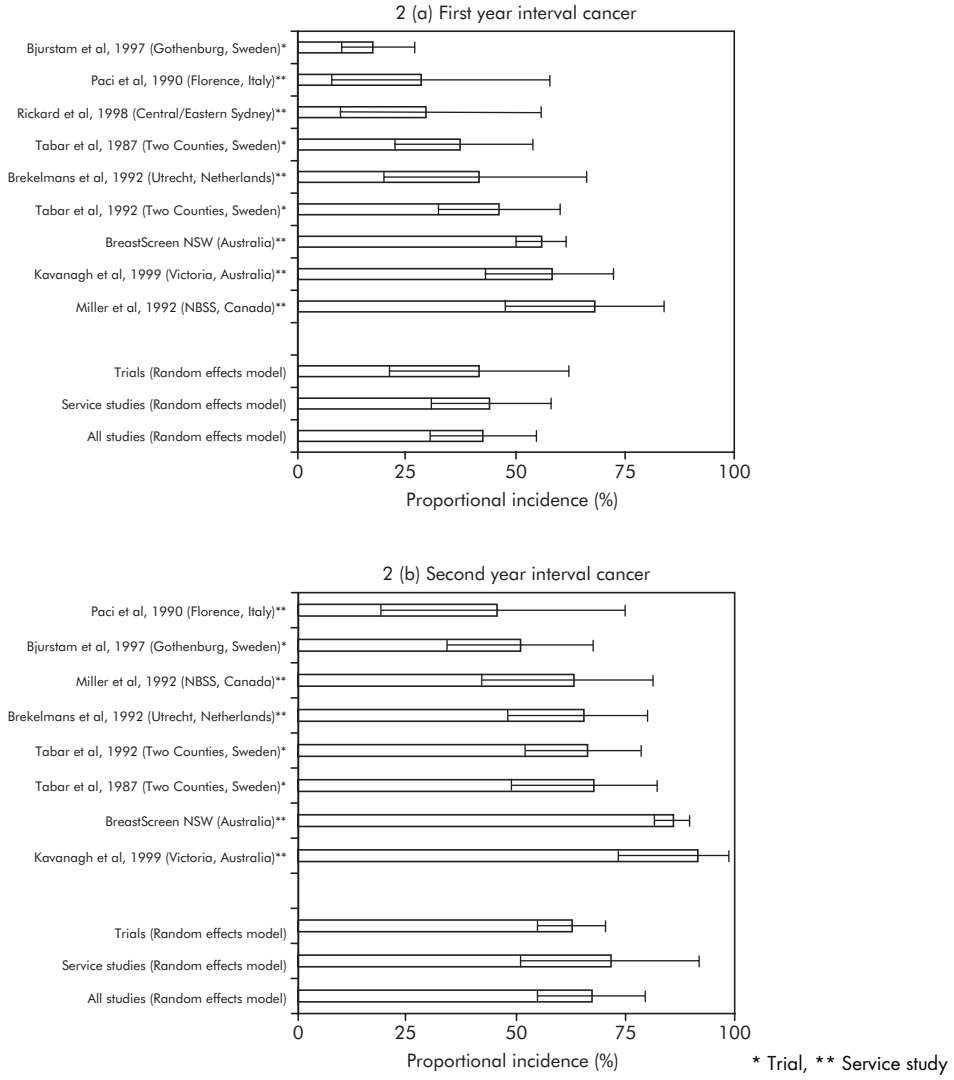

Figure 2 First– and second–year interval breast cancer as a proportion of underlying incidence (40–49 years): International comparisons.

decreasing logarithmic trend in proportional incidence with increasing age was also evident for both first- and second-year interval cancers. Interval cancer rates (per 10,000 women screened) in women aged 40–49 years were similar to older groups, although interval cancer rates were slightly lower in older age groups. Proportional incidence is a better a measure of interval cancer incidence than the interval cancer rate as the underlying rate of breast cancer incidence varies between age groups, making interval cancer rates not directly comparable. Lower proportional incidence in the 12 months following screening is more an indicator of the quality of screening ('missed' cancers) compared to the second 12–month period, where intervals are likely to be true interval cancers – that is, cancers that develop subsequent to screening.[35,36]

Studies included in the meta-analysis showed a wide range of proportional incidences for women aged 40–49 years: from 18 to 68% for first-year interval cancers and from 46 to 92% for second-year interval cancers. All studies included in the meta-analysis had a proportional incidence for first-year interval cancer rates of >25%, with the exception of the Gothenburg trial (18%).[22] The Victorian service study[31] and the Canadian NBSS trial[27] both had a proportional incidence >50%. Two service studies, one in Australia[19] and one in Italy,[29] both had a proportional incidence of 29%.

Sensitivity estimates for first-year interval cancers in NSW women aged 40–49 years were significantly lower than those in the Canadian[27] and Swedish trials,[10] as well as an Australian service study.[19] No significant differences in sensitivity were evident for second-year interval cancers in NSW women aged 40–49 years.

Sensitivity by age group in NSW women showed the same (but inverse) trend seen for proportional incidence of interval cancers by age. Sensitivity does not depend on the calculation of the underlying rate of breast cancer, which becomes more problematic the greater the duration of service population screening.

The accuracy of interval cancer identification in mammographic screening programs depends on the completeness of cancer registration in the area and the precision of matching of mammographic screening data with cancer registry data. In the present study, discrepancies in the assignment of cancer to the categories of interval and screen detected may exist for women who had an early biennial screen (e.g. in the 21–24 month period). Published reports of interval cancers in mammography screening trials and services emanate from populations with good mammography and cancer data collections. If errors occur they are most likely to lead to under-enumeration of interval cancers and hence lower interval cancer rates.

Proportional incidence of interval cancers depends on an estimate of the expected number of cancers in the popu-

Table 3 International comparisons of sensitivity (%) in trial and service studies in women 40–49 years: first and second year

Study	Year 1 (0–12 months) a	b	Sensitivity (%) (95% CI*) a/(a+b)	Year 1 & 2 (0–24 months) a	b	Sensitivity (%) (95% CI*) a/(a+b)
Trials						
Frissell *et al*, 1987 (Stockhom, Sweden)	–	–	–	21	21	50.0 (34.2–65.8)
Andersson *et al*, 1988 (Malmo, Sweden)¶	–	–	–	16	6	72.7 (49.8–89.3)
Miller *et al*, 1992 (NBSS, Canada)¶	99	19	83.9 (76.0–90.0)	139	35	79.9 (73.2–85.6)
Tabar *et al*, 1992 (Two Counties, Sweden)¶	115	25	82.1 (74.8–88.1)	230	58	79.9 (74.8–84.3)
Bjurstam *et al*, 1997,2003 (Gothenburg, Sweden)	–	–	–	66	33	66.7 (56.5–75.8)
Service studies						
Paci *et al*, 1990† (Florence, Italy)¶	–	–	–	36	49	42.4 (31.7–53.6)
Brekelmans *et al*, 1992 (Utrecht, Netherlands)¶	26	8	76.5 (58.8–89.3)	50	33	60.2 (48.9–70.8)
Kerlikowske *et al*, 1996†† (California, United States)	39	6	86.7 (73.2–95.0)	–	–	–
Rickard *et al*, 1998 (Sydney, Australia)¶	36	5	87.8 (73.8–95.9)	–	–	–
Kavanagh *et al*, 1999 (Victoria, Australia)	71	28	71.7 (61.8–80.3)	40	40	50.0 (38.6–61.4)
BreastScreen, 1995–98 (NSW, Australia)	387	176	68.7 (64.7–72.6)	270	98	73.4 (68.5–77.8)
Summary statistics						
Trials	214	44	83.0 (78.4–87.5)§	472	153	71.0 (61.7–80.4)†
Service studies	559	223	76.5 (68.7–84.4)‡	396	220	56.8 (41.4–72.3)†
All studies	1332	267	78.8 (72.0–85.6)‡	868	373	64.3 (55.5–73.1)†

a – Screen detected cancers. *b* – Interval cancers. *95% Confidence Intervals calculated using the exact binomial. †Data presented are for 5 years. ‡Random effects model. §Fixed effects model. ¶Includes ductal carcinoma *in situ*. ††Based on 0–13 months.

lation. In a trial, the expected number of cancers can be derived from the incidence rate in the control group. For screening services, the expected number of cancers must be derived from incidence rates in comparable unscreened populations or from projections of cancer incidence in the same population in the absence of screening. If this is not done the proportional incidence will be under-estimated because screening activity causes an increase in recorded incidence (and thus expected cancers), chiefly because of the diagnosis of prevalent cancers in the first round.[21] Additionally, interval cancer rates in NSW may be artificially higher due to over-enumeration of cancers detected in asymptomatic women by short interval *de facto* screening outside of the screening program.

The results indicate that a substantial proportion of cancers in NSW in women aged 40–49 years are not detected at the screen; however, these results are not significantly different from other service trials and are also not substantially different from randomised trials. There may be a number of explanations for this finding. These include the greater density of glandular tissue in younger women's breasts leading to a decrease in mammographic sensitivity and the faster breast cancer sojourn time in younger women.[2,4,5]

As 40–49 year old women are self-selected rather than actively recruited they may have a higher underlying rate of breast cancer related to, for example, family history or high socio-economic status, which may bias the proportional incidence upwards because the underlying rate for this calculation is based on all women aged 40–49 years. However, the sensitivity data also shows a similar, prominent and statistically significant difference between women in the 40–49 years and older age groups and these calculations do not use estimates of underlying rates of breast cancer.

The cost-effectiveness of BreastScreen NSW in reducing breast cancer mortality is dependent on adequate participation rates in the target age group (women aged 50–69 years). Data from clinical trials suggest that mammography screening can achieve up to a 30% reduction in breast cancer mortality,[37] and that achieving a participation rate of 70% can justify the expense of implementing a population screening program.

Multiple factors need to be considered in deciding whether to offer screening to women aged 40–49 years. These include results from randomised trials for this age group (which have been equivocal),[1,3,4,6] although these trials employed biennial screening periods and may have used mammography of lesser quality than contemporary practice. Results from service studies that include women aged <50 years indicate significant breast cancer mortality reduction.[28,29,31,38] The biology of breast cancer and the results of screening trials in women aged <50 years suggest that screening intervals of less than two years would be required for mortality reduction (such as the 18 month interval in the Gothenburg study).[9,10,22–26] One factor for consideration when considering systematic screening of women aged 40–49 years is the magnitude of interval cancer rates achievable locally, because trial results may not be readily replicated in the service context. Although less than two year screening intervals would obviously reduce second year interval cancers, it cannot reduce first year interval cancers and the low proportional incidence for first year interval cancers in the Gothenburg study[9,10,22–26] must be associated with high quality screening.

Randomised trials of women aged 40–49 with sufficient statistical power to detect an effect of mammography in reducing breast cancer mortality are currently being implemented to produce more data on whether mammography

screening in women aged 40–49 years is effective.[39] Previously meta-analysed randomised trials and service studies indicate a modest reduction in breast cancer mortality from mammography screening. Interval cancer rates are a measure of the expected effectiveness of mammography screening. However, rates from actual service situations need to be used for comparative evaluation, since trials may concentrate resources and expertise in ways that may be less replicable in the circumstances of routine service delivery.

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REFERENCES

1 Glasziou P, Irwig L. The quality and interpretation of mammographic screening trials for women ages 40–49. *J Natl Cancer Inst Monogr* 1997;**22**:73–77.
2 Kerlikowske K, Grady D, Rubin SM, Sandrock C, Ernster VL. Efficacy of screening mammography. A meta-analysis. *JAMA* 1995;**273**:149–54.
3 Kerlikowske K. Efficacy of screening mammography among women aged 40 to 49 years and 50 to 69 years: comparison of relative and absolute benefit. *J Natl Cancer Inst Monogr* 1997;**22**:79–86.
4 Smart CR, Hendrick RE, Rutledge JH, III, Smith RA. Benefit of mammography screening in women ages 40 to 49 years. Current evidence from randomized controlled trials. *Cancer* 1995;**75**:1619–26.
5 Swedish Cancer Society and the Swedish National Board of Health and Welfare. Breast-cancer screening with mammography in women aged 40–49 years. *Int J Cancer* 1996;**68**:693–99.
6 Dickersin K. Breast screening in women aged 40–49 years: what next? *Lancet* 1999;**353**:1896–97.
7 Feig SA. Mammographic screening of women aged 40–49 years. Benefit, risk, and cost considerations. [Review] [54 refs]. *Cancer* 1995;**76**(10:Suppl):Suppl–106.
8 Day NE, Williams DR, Khaw KT. Breast cancer screening programmes: the development of a monitoring and evaluation system. *Br J Cancer* 1989;**59**:954–58.
9 Tabar L, Faberberg G, Day NE, Holmberg L. What is the optimum interval between mammographic screening examinations? An analysis based on the latest results of the Swedish two-county breast cancer screening trial. *Br J Cancer* 1987;**55**:547–51.
10 Tabar L, Fagerberg G, Duffy SW, Day NE, Gad A, Grontoft O. Update of the Swedish two-county program of mammographic screening for breast cancer. *Radiol Clin North Am* 1992;**30**:187–210.
11 Taylor R, Supramaniam R, Rickard M, Estoesta J, Moreira C. Interval breast cancers in New South Wales, Australia, and comparisons with trials and other mammographic screening programmes. *J Med Screen* 2002;**9**:20–25.
12 Coates M, Armstrong B. Incidence and Mortality, 1996. Sydney: New South Wales Cancer Council, 1999.
13 Taylor R, Smith D, Hoyer A, *et al*. Breast Cancer in New South Wales, 1972–1991. Sydney: New South Wales Cancer Council, 1994.
14 Parkin DM, Muir CS, Whelan SL, *et al*. Cancer Incidence in Five Continents, Volume VI. Lyon: International Agency for Research on Cancer (IARC), 1992.
15 Fellegi IP, Sunter AB. A theory of record linkage. *J Am Stat Assoc* 1969;**64**:1183–210.
16 Jaro M. Advances in record linkage methodology as applied to matching the 1985 census of Tampa, Florida. *J Am Stat Assoc* 1989;**84**:414–20.
17 Automatch Generalized Record Linkage System. Silver Spring, Maryland: Matchware Technologies Inc., 1994.
18 Armitage P, Berry G. Statistical Methods in Medical Research. Third Edition ed. Oxford: Scientific Publications, 1994.
19 Rickard MT, Taylor RJ, Fazli MA, El Hassan N. Interval breast cancers in an Australian mammographic screening program. *Med J Aust* 1998;**169**:184–87.
20 Taylor R, Boyages J. Absolute risk of breast cancer for Australian women with a family history. *ANZ J Surg* 2000;**70**:725–31.
21 Taylor R, Boyages J. Estimating risk of breast cancer from population incidence affected by widespread mammographic screening. *J Med Screen* 2001;**8**:73–76.
22 Bjurstam N, Bjorneld L, Duffy SW, *et al*. The Gothenburg breast screening trial: first results on mortality, incidence, and mode of detection for women ages 39–49 years at randomization. *Cancer* 1997;**80**:2091–99.
23 Frisell J, Eklund G, Hellstrom L, Somell A. Analysis of interval breast carcinomas in a randomized screening trial in Stockholm. *Breast Cancer Res Treat* 1987;**9**:219–25.
24 Frisell J, Lidbrink E. The Stockholm Mammographic Screening Trial: Risks and benefits in age group 40–49 years. *J Natl Cancer Inst Monogr* 1997;**22**:49–51.
25 Andersson I, Aspegren K, Janzon L, *et al*. Mammographic screening and mortality from breast cancer: the Malmo mammographic screening trial. *BMJ* 1988;**297**:943–48.
26 Bjurstam N, Bjorneld L, Warwick J, *et al*. The Gothenburg Breast Screening Trial. *Cancer* 2003;**97**:2387–96.
27 Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 1. Breast cancer detection and death rates among women aged 40 to 49 years. *CMAJ* 1992;**147**:1459–76.
28 Brekelmans CT, Collette HJ, Collette C, Fracheboud J, de Waard F. Breast cancer after a negative screen: follow-up of women participating in the DOM Screening Programme. *Eur J Cancer* 1992;**28A**(4–5):893–95.
29 Paci E, Ciatto S, Buiatti E, Cecchini S, Palli D, Rosselli dT. Early indicators of efficacy of breast cancer screening programmes. Results of the Florence District Programme. *Int J Cancer* 1990;**46**:198–202.
30 Kerlikowske K, Grady D, Barclay J, Sickles EA, Ernster V. Effect of age, breast density, and family history on the sensitivity of first screening mammography. *JAMA* 1996;**276**:33–38.
31 Kavanagh AM, Mitchell H, Farrugia H, Giles GG. Monitoring interval cancers in an Australian mammographic screening programme. *J Med Screen* 1999;**6**:139–43.
32 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–88.
33 Berry G. Analysis and interpretation. In: McDonald JC, editor. *Epidemiology of work related diseases*. London: BMJ Publishing Group, 1995: 441–62.
34 Taylor R, Berry G. Quantitative meta-analysis. In: Kerr C, Taylor R, Heard G, editors. *Handbook of Public Health Methods*. Sydney: McGraw Hill, 1998: 449–56.
35 Amos AF, Kavanagh AM, Cawson J. Radiological review of interval cancers in an Australian mammographic screening programme. Radiology Quality Assurance Group of BreastScreen Victoria. *J Med Screen* 2000;**7**:184–89.
36 Vitak B, Olsen KE, Manson JC, Arnesson LG, Stal O. Tumour characteristics and survival in patients with invasive interval breast cancer classified according to mammographic findings at the latest screening: a comparison of true interval and missed interval cancers. *Eur Radiol* 1999;**9**:460–69.
37 World Health Organisation (WHO), International Agency for Research on Cancer (IARC). *IARC Handbooks of Cancer Prevention. Volume 7: Breast Cancer Screening*. Lyon: IARC Press, 2002.
38 Duffy SW, Tabar L, Chen HH, Holmqvist M, Yen MF, Abdsalah S *et al*. The impact of organized mammography service screening on breast carcinoma mortality in seven Swedish counties. *Cancer* 2002;**95**:458–69.
39 Moss S. A trial to study the effect on breast cancer mortality of annual mammographic screening in women starting at age 40. Trial Steering Group. *J Med Screen* 1999;**6**:144–48.