

Appendix 3

Systematic review of rationale for choice of screening intervals and age groups in breast cancer screening

A number of studies which investigated the effects of the association of screening intervals and age groups with the likelihood of detection of cancer have been reviewed. None of these studies were performed in Ireland and therefore caution should be exercised in interpreting the results.

Screening Intervals

Cowen et al aimed to define the biological nature and malignant potential of interval cancers presenting to a unit within the UK National Health Service (NHS) screening programme.¹ Interval cancers (n=112) were compared with matched, screen-detected (SD) (n=112) and symptomatic cancers (n=112) in terms of their radiographic, histopathological, and immunohistochemical features.

Interval cancers showed no characteristic radiographic pattern. In terms of size, vascular invasion, lymph node status, and prognosis they were intermediate between SD and symptomatic cancers. The interval cancers comprised of an excess of grade one and grade three tumours, and lesions with a high Ki67 index but immunohistochemistry otherwise failed to discriminate between the three groups. It was concluded that interval cancers are more aggressive than SD cancers but in general less aggressive than symptomatic cancers.¹

Bucchi et al examined to what extent the excess risk of lymph node metastases for interval cancers in each screen interval year depends on their larger tumour size (higher chronological age).² In the study area, mammography screening was introduced between 1990 and 2001 for women aged 50 to 69 years. Case records of breast cancer patients (n= 41 370) registered between 1988 and 2001 were reviewed. The Odds Ratio(OR) for interval cancers (n=791) versus the SD cancers (n=1211) having lymph node metastases was modelled using forward stepwise logistic regression analysis. The screening interval was divided into one to 12, 13 to 18, and 19 to 24 months.

The prevalence of lymph node metastases was 28% among SD cancers. With a prevalence of 38%, 42%, and 44%, the OR of lymph node metastases for cancers diagnosed between one to 12, 13 to 18, and 19 to 24 months of interval was 1.41 (95% CI: 1.06-1.87), 1.74 (1.31-2.31), and 1.91 (1.43-2.54), respectively. Histologic type, tumour grade, and tumour size were investigated. Histologic type had modest effects. With adjustment for tumour grade, the ORs decreased to 1.23 (0.92-1.65), 1.58 (1.18-2.12), and 1.73 (1.29-2.32). Adjusting for tumour size decreased the ORs to 0.95 (0.70-1.29), 1.34 (0.99-1.81), and 1.37 (1.01-1.85).

A relationship was confirmed between the time since last negative screen and the biological aggressiveness of interval cancers. The strength of confounding by tumour

size suggested that the excess risk of lymph node metastases for first-year interval cancers reflected only their higher chronological age. The second interval year, but not the first, was associated with an excess risk of lymph node metastases that was independent from tumour size and grade and was partly accounted for by intrinsic biological aggressiveness.²

Burrell et al reviewed the mammographic features of screening interval breast cancers to compare the tumour size, histologic grade, and lymph node involvement with SD and unscreened symptomatic cancers.³ Mammography was performed in 72,773 women aged 50 to 64 years.

Ninety interval cancers were identified in 89 women. Interval cancers were larger, of higher grade, and more likely to have lymph node involvement than SD tumours and were of similar size, histologic grade, and stage of lymph node involvement as symptomatic tumours. It was concluded that the prognosis of interval cancers is similar to that of symptomatic, unscreened tumours and significantly worse than that in SD cancers.³

A UK cohort study was undertaken to describe outcomes from breast cancer in women aged ≤ 54 years when first invited for breast screening.⁴ Two populations, 5,125 and 10,750 women invited for multiple rounds of screening in Wigan and Manchester respectively, were included. The main outcome measures were rates of advanced disease and mortality from breast cancer. In Wigan, 4,028 (78.6%) and in Manchester, 5,485 (51.0%) women accepted all invitations.

The incidence of invasive cancer was higher in Wigan than in Manchester (24.78 vs. 21.11 per 10,000 person-years; $\chi^2=2.11$, 1 df, $P=0.15$), but the rate of advanced disease was significantly lower (2.49 vs. 4.73 per 10 000 person-years; $\chi^2=4.36$, 1 df, $P=0.04$). Mortality was lower in Wigan than in Manchester (2.46 vs. 4.31 per 10,000 person-years; $\chi^2=3.25$, 1 df, $P=0.07$).

A significant difference was detected in the rate of advanced disease between two programmes with different cancer detection and attendance rates. The incidence of advanced disease in non-attendees and the prevalence of advanced disease at the first screening were similar in the two populations. It was concluded that more effective screening, either as a result of higher detection rates or greater attendance at screening, was a likely explanation for the lower rate of advanced disease in Wigan.⁴ The paper highlighted that the degree of benefit from a breast screening programme is highly dependent on its quality.

Alexander et al for the Edinburgh Randomised Trial of Breast Cancer Screening recruited 44,288 women aged 45 to 64 years during 1978 to 1981.⁵ A total of 22,944 women were randomised into the study group and were offered screening for seven years; the remaining women formed the control group.

After 10 years, breast cancer mortality was 14% to 21% lower in the study group than in the controls depending on the precise definition of the end point. Those women who accepted the final invitation to screening were monitored over the three-year period prior to their first screen under the UK service screening programme. Interval cases,

expressed as a proportion of the control incidence, increased from 12% in the first year to 67% in the third year.⁵

In the NHS breast screening programme women are screened every three years.⁶ Interval cancers occurring before 31 March 1994 in women screened from 1 April 1988 to 31 March 1993 at the Manchester and Wigan breast screening services were identified, and a mammogram taken at the time of diagnosis was sought for all these cancers.

The proportion of true interval cancers increased significantly with year from screening: 40% in year one post-screening, 70% in year two, 80% in year three ($X^2=12.75$; $df=2$; $P<0.002$). Almost half of all interval cancers were diagnosed in the third year after screening. The authors noted that the proportion of true interval cancers occurring in the first two years after screening in their series was 60% and similar to that reported in the Nijmegen programme (58%) and Stockholm trial (64%) in women aged 50 to 64. The authors stated that shortening the screening interval is the only way to reduce the number of true interval cancers.⁶

A U.S. observational study was performed to investigate whether women (40 to 89 years) diagnosed with breast cancer after biennial screening ($n=2,440$) are more likely to be diagnosed with late-stage disease (positive lymph nodes or metastases) than women diagnosed with breast cancer after annual screening ($n=5,400$).⁷ Analyses were stratified by age and breast density.

Little evidence was found to indicate that biennial screening was associated with an increased risk of late-stage breast cancer compared with annual screening, except for women in their forties. Among women age 40 to 49 years, those with a two-year interval were more likely to have late-stage disease at diagnosis than those with a one-year screening interval (28% versus 21%; $OR=1.35$, 95% $CI: 1.01-1.81$). There was no increase in late-stage disease for women ≥ 50 years with a two-year versus a one-year interval (women age 50-59 years: $OR=0.97$, 95% $CI: 0.75-1.25$; women age 60-69 years: $OR=0.99$, 95% $CI: 0.72-1.35$; women age 70 years or older: $OR=0.88$, 95% $CI: 0.64$ to 1.19). There was no indication that women with dense breasts would benefit more from a one-year versus two-year screening interval than women with fatty breasts.⁷

Woodman et al reported the detection rate of interval cancers in women screened by the National Health Service Breast Screening Programme in the UK (NHSBSP) in the North Western Regional Health Authority.⁸ The cohort consisted of 137,421 women screened between 1 March 1988 and 31 March 1992 who had a previous negative screening result.

In total 297 invasive interval cancers were detected. The rate of detection of interval cancers expressed as a proportion of the underlying incidence was 31% in the first 12 months after screening, 52% between 12 to 24 months, and 82% between 24 to 36 months. The authors concluded that the incidence of interval cancers in the third year after breast screening approaches that which would have been expected in the absence of screening and suggests that the three-year interval is too long.⁸ In light of this research Hobgen suggested that the most probable best frequency for screening is between 18 months to two years.⁹

Outcomes among women subject to different screening frequency policies were compared within the Screening Mammography Programme of British Columbia (SMPBC) during 1988-2005.¹⁰ The SMPBC changed its policy for women aged 50 to 79 years from annual to biennial mammography in 1997, but retained an annual recommendation for women aged 40 to 49 years. Data was obtained on 658,151 women comprising of two groups (ages 40 to 49 and 50 to 79 years) participating in a screening programme before and after 1997.

Comparing pre-1997 and post-1997, the median screen interval increased by 11.1 months in women 50 to 79 years but by only 0.3 months in women aged 40 to 49 years. Excluding those detected at initial screen, 6,291 breast cancers were identified. Comparing pre-1997 and post-1997: the relative rates (RR) of screen detected cancer increased in women aged 40 to 49 (RR=1.32) and the rate of invasive cancers ≥ 20 mm at diagnosis decreased (RR=0.83); the rate of cancers with axillary node involvement increased in women aged 50 to 79 (RR=1.23). Cancer survival improved after 1997 for women diagnosed at ages 40 to 49 years (HR=0.62), but was unchanged for women aged 50 to 79 years. Breast cancer mortality rates did not change between the periods in either age group.¹⁰

The UK Co-ordinating Committee on Cancer Research (UKCCCR) trial of Breast Screening Frequency performed a randomised trial directly comparing different screening intervals.¹¹ Women aged 50 to 62 years (n=99,389) who had been invited to a prevalent screen were randomly allocated after the scheduled prevalent screen date to the study arm (three further annual screens), or to the control arm (single screen three years later). There were 37,530 women in the study arm and 38,492 in the control arm. The endpoint was predicted breast cancer deaths. The prediction was based on both the Nottingham Prognostic Index (NPI) and the Swedish Two-County screening trial Index (2CS). Both indices were based on the size, lymph node status and histological grade of the invasive tumours diagnosed in the two arms of the trial.

The tumours diagnosed in the study arm were significantly smaller than those diagnosed in the control arm (P=0.05). The relative risk of death from breast cancer for the annual compared with the three-yearly group was 0.95 (95% CI: 0.83-1.07, P=0.4) using the NPI and 0.89 (95% CI: 0.77-1.03, P=0.09) using the 2CS. Shortening of the screening interval in this age group was predicted to have a relatively small effect on breast cancer mortality.¹¹

In the UK Breast Screening Frequency Trial, 49,173 women aged 50 to 62 years were randomised to three annual incidence screens after their prevalence screen date (study group) and 50,162 to one incidence screen three years after the prevalence screen (control group).¹² Mortality results to the end of 2006 (median follow-up 162 months) were recorded.

There were 373 breast cancer deaths in the study group as a whole and 374 in the control group (RR = 1.02, 95% CI: 0.88-1.17, p = 0.8). In the prevalence screen attendees, there were 209 breast cancer deaths in the study group and 231 in the control group (RR = 0.89, 95% CI: 0.73-1.07, p = 0.2). When mortality only from cancers diagnosed during the three-year screening period of the trial was considered,

there was no significant difference between the study and control group (RR = 0.96, 95% CI: 0.67-1.37, $p = 0.8$). This remained the case when restricted to those who had attended the prevalence screen (RR = 0.93, 95% CI: 0.63-1.37, $p = 0.7$). The authors concluded that there is no evidence in favour of shortening the NHS three-year screening interval.¹

Age Range

A randomised controlled trial investigated the effect of screening in women <50 years of age in Sweden.¹³ Between September 1983 and April 1984, 11,724 women ages 39 to 49 years were invited to screening every 18 months. Fourteen thousand two hundred and seventeen women in the same age range were randomized to a control group. The control group were not invited for screening until the fifth screen of the study group (six to seven years after randomisation). Women with breast carcinoma diagnosed up to the time of the first screen of the control group were followed for death from diagnosis until the end of December 1994.

A 45% reduction in mortality from breast carcinoma was observed in the study group compared to the control group (RR=0.55, $P=0.035$, 95% CI: 0.31–0.96). A conservative estimate based on removal of the tumours detected at the first screen of the control group gave a mortality reduction of 44% (RR=0.56, $P=0.046$, 95% CI: 0.31–0.99). In both cases, the effect was statistically significant. The authors concluded that 18-month mammographic screen interval can reduce mortality from breast carcinoma in women <50 years.¹³

The Edinburgh Randomised Trial of Breast Cancer Screening as previously described,⁵ found that after 10 years follow up, breast cancer mortality was 14% to 21% lower in the screened study group (than in the non-screened controls). The reduction in breast cancer mortality for older women (≥ 50 years) was the same as that for the total study group for this duration of follow up. For analyses of breast cancer mortality in younger women, updates recruited to the trial from 1982 to 1985 (10,383 women with six to eight years follow-up) were included. The reduction in breast cancer mortality for women aged 45 to 49 years was 22% (RR = 0.78, 95% CI: 0.46-1.31).⁵

Buseman et al report on the association between cancer stage at diagnosis and screening history in women aged 42 to 49 years.¹⁴ Previous mammographic screening for 247 breast cancer patients 42 to 49 years of age who were diagnosed during 1994 to 2000 was evaluated relative to cancer stage. Cancer stage was dichotomized into early (American Joint Committee on Cancer (AJCC) Stages 0 and I) and late (AJCC Stages II-IV), and previous screening was defined as at least one normal screening mammogram within 24 months before diagnosis.

Women who were screened were less likely to be diagnosed at a late stage than women who were not screened (40% versus 52% late stage, respectively). Adjusted for age, year of diagnosis, and family history, screened women were 0.56 (95% CI: 0.32-0.97) times as likely as unscreened women to be diagnosed at a late stage. It was concluded that women (42 to 49 years) with breast carcinoma who undergo regular screening mammography have a more favourable cancer stage than women

with breast carcinoma who do not undergo regular screening and this down-staging is likely to translate into improved survival.¹⁴

The association between age and the efficacy of screening mammography in protecting against breast cancer death was investigated in a multicentre case-control study.¹⁵ ORs were calculated to estimate the relative mortality rates from invasive breast cancer among women with at least one prior screening mammogram in the two years compared to non-screened women. The cohorts comprised of 553 women diagnosed during 1994 to 1998 who died in the following five years, and 4,016 controls without breast cancer.

Efficacy for reducing the rate of breast cancer death within five years after diagnosis was greater at ages 50 to 64 years (OR=0.47, 95% CI: 0.35-0.63) than at ages 40 to 49 years (OR=0.89, 95% CI: 0.65-1.23), and greater among postmenopausal (OR=0.45, 95% CI: 0.33-0.62) than premenopausal women (OR=0.74, 95% CI 0.53-1.04). It was concluded that despite the persistence of age differences in efficacy of mammography screening, with greater observed benefit for women aged 50 to 64 years further progress could be made in reducing mortality from breast cancer by increasing the use of screening mammography, especially among women aged 40 to 49 years.¹⁵

In 1996 the Swedish Cancer Society and the Swedish National Board of Health and Welfare reviewed data from all randomised trials of breast cancer screening that included women aged 40 to 49 years, and all identifiable substantial databases on service screening in women in the same age group.¹⁶

Results from the Swedish overview of mammographic screening trials indicated a relative mortality associated with invitation to screening of 0.77 (95% CI: 0.59-1.01) compared to no invitation. Combining all population-based randomised trials gave the relative-mortality figure of 0.76 (0.62-0.93), and combining all trials gave 0.85 (0.71-1.01). Detailed analysis suggested faster tumour progression in the age group 40 to 49 years compared with groups aged ≥ 50 years. It was concluded that mammographic screening of women aged 40 to 49 years was likely to reduce subsequent mortality from breast cancer, and in order to obtain substantial benefit it was probably necessary to screen every 12 to 18 months.¹⁶

A multicentre randomised controlled trial aimed to compare breast cancer mortality in 40 to 49 year old women who received either screening with annual mammography, breast physical examination, and instruction on breast self-examination on four or five occasions (n=25,214) or community care after a single breast physical examination and instruction on breast self examination (n=25,216).¹⁷ Women who had no previous breast cancer diagnosis, and had not had mammography in the preceding 12 months were recruited between 1980 and 1985.

After 11 to 16 years of follow-up, the 105 breast cancer deaths in the mammography group and 108 breast cancer deaths in the usual care group yielded a cumulative rate ratio of 1.06 (95% CI: 0.80 to 1.40). A total of 592 cases of invasive breast cancer and 71 cases of in-situ breast cancer were diagnosed by 31 December 1993 in the mammography group compared with 552 and 29 cases, respectively, in the usual

care group. It was concluded that four or five annual screenings with mammography, breast physical examination and breast self-examination had not reduced breast cancer mortality compared with usual community care after a single breast physical examination and instruction on breast self-examination.¹⁷

The efficacy of population screening mammography for the age group of 50 to 74 years has been demonstrated. However, only limited data are available regarding women aged 75 years and over, and recommendations for breast cancer screening in this age group vary in different countries.¹⁸

An overview, based on 282,777 women followed for five to 13 years in randomised trials in Malmö, Kopparberg, Östergötland, Stockholm, and Gothenburg, reveals a significant 24% (95% CI: 13-34%) reduction of breast cancer mortality among those invited to mammography screening compared with those not invited.¹⁹ There was a consistent risk reduction associated with screening in all studies, although the point estimate of the relative risk for all ages varied non-significantly between 0.68 and 0.84. The cumulative breast cancer mortality by time since randomisation was estimated at 1.3 per 1,000 within six years in the invited group compared with 1.6 in the control group. The corresponding figures after nine years are 2.6 and 3.3 and after 12 years 3.9 and 5.1. The largest reduction of breast cancer mortality (29%) was observed among women aged 50 to 69 years at randomisation. Among women 40 to 49 years there was a non-significant 13% reduction. In this younger age group cumulative breast cancer mortality was similar in the invited and control group during the first eight years of follow-up. After eight years there was a difference in favour of the invited women. There was no evidence of any detrimental effect of screening in terms of breast cancer mortality in any age group. Among women aged 70 to 74 years screening seems to have had only a marginal impact.¹⁹

McPherson et al aimed to determine an upper age limit or quantifiable level of co-morbidity that would render mammography screening ineffectual in decreasing mortality in women ≥ 65 years.²⁰ A retrospective cohort analysis comprised of 5,168 women aged 65 to 101 years diagnosed with invasive breast cancer from 1986 to 1994.

Patients with mammographically detected tumours and no co-morbidity experienced significantly lower RRs of death in every age group ($P < 0.001$ to $P = 0.039$). Women with mammographically-detected tumours and mild to moderate co-morbidity had RRs of death as follows: age 65 to 69 (RR=0.32; 95% CI: 0.15-0.69), age 70 to 74 (RR=0.45; 95% CI: 0.22-0.91); age 75 to 79 (RR=0.47; 95% CI: 0.25-0.88), age 80 or over (RR= 0.52; 95% CI: 0.33-0.8). Women with severe or multiple co-morbidities experienced no improvement in survival. It was concluded that mammographic detection of breast cancer may be associated with a significantly decreased risk of death for older women of all ages, even for women with mild to moderate levels of co-morbidity, but for older women with severe or multiple co-morbidities, mammography is not associated with an improvement in overall survival.²⁰

McCarthy et al investigated the relationship between prior mammography use, cancer stage at diagnosis and breast cancer mortality among older women with breast

cancer.²¹ A retrospective cohort consisted of 9,767 women (≥ 67 years) with a first primary diagnosis of breast cancer. Non-users of mammography were defined as having no screening mammogram, while regular users were defined as having two screening mammograms within the two years preceding their diagnosis.

Older women who were non-users were diagnosed with breast cancer at Stage II or greater more often than regular users (OR=3.12; 95% CI: 2.74-3.58). This association was present within all age groups. Non-users were at a significantly greater risk of dying from breast cancer than regular users (HR=3.38; 95% CI: 2.65-4.32) for women within each age group. The finding was statistically significant for the age groups 67 to 74 years and 75 to 85 years, but was not for the ≥ 85 years group. The authors concluded that the use of mammography in older women was recommended and suggested that it can reduce breast cancer mortality in older women even those aged ≥ 85 years.²¹

Van Dijck et al evaluated whether regular mammographic screening of women ≥ 65 years affected breast cancer mortality.²² Women over 64 years of age were selected from the population-based screening programme. Eighty-two had died from breast cancer. For these cases, 410 age matched population controls were selected.

The ratio of breast cancer mortality rates of the women who had participated regularly (i.e. in the two most recent screening rounds prior to diagnosis) versus women who had not was 0.56 (95%; CI 0.28-1.13). The rate ratio was 0.45 (95%; CI: 0.20-1.02) in the 65 to 74 year group and was 1.05 (95%; CI 0.27-4.14) in the ≥ 75 year group. The authors concluded that regular screening of women over 65 years (at least up to 75 years) can reduce breast cancer mortality.²²

Summary

In Ireland screening is recommended every two years for women aged 50 to 64 years.²³ The European Union Advisory Committee on Cancer Prevention recommends that women, aged 50 to 69 years, without symptoms of breast cancer be offered mammography examination every two to three years.²⁴

A number of studies have been evaluated for this review. None of these studies were performed in Ireland and therefore caution should be exercised in interpreting the results.

The effects of screening intervals have been evaluated. Cowen et al concluded that interval cancers are more aggressive than SD cancers but in general less aggressive than symptomatic cancers.¹ Bucchi et al confirmed that a relationship exists between the time since last negative screen and the biological aggressiveness of interval cancers.² Burrell et al concluded that the prognosis of interval cancers is similar to that of symptomatic, unscreened tumours and significantly worse than that in SD cancers.³

Alexander et al found that interval cases, expressed as a proportion of the control incidence, increased from 12% in the first year to 67% in the third year.⁵ The NHS breast screening programme has shown that the proportion of true interval cancers

increased significantly with year from screening: 40% in year one post-screening, 70% in year two, 80% in year three. The authors stated that shortening the screening interval is the only way to reduce the number of true interval cancers.⁶ White et al found that among women age 40 to 49 years, those with a two-year interval were more likely to have late-stage disease at diagnosis than those with a one-year screening interval.⁷ Woodman et al concluded that the incidence of interval cancers in the third year after breast screening approaches that which would have been expected in the absence of screening and suggests that the three-year interval is too long.⁸ In light of this Hobgen suggested that the most probable best frequency for screening is between 18 months to two years.⁹ Conversely, the UKCCCR predicted that shortening of the screening interval from every three years to every year in the 50 to 62 year age group would have a relatively small effect on breast cancer mortality¹¹ and this was later confirmed.¹²

The impact of age range in screening has also been evaluated for this review. Bjustam et al concluded that an 18-month mammographic screen interval can reduce mortality from breast carcinoma in women <50 years.¹³ Buseman et al concluded that women (42 to 49 years) with breast carcinoma who undergo regular screening mammography have a more favourable cancer stage than women with breast carcinoma who do not undergo regular screening and this down-staging is likely to translate into improved survival.¹⁴ Norman et al concluded that despite the persistence of age differences in efficacy of mammography screening, with greater observed benefit for women aged 50 to 64 years, further progress could be made in reducing mortality from breast cancer by increasing the use of screening mammography, especially among women aged 40 to 49 years.¹⁵ The Swedish Cancer Society and the Swedish National Board of Health and Welfare concluded that mammographic screening of women aged 40 to 49 years was likely to reduce subsequent mortality from breast cancer, and in order to obtain substantial benefit it was probably necessary to screen every 12 to 18 months.¹⁶ Conversely Miller et al concluded that four or five annual screenings with mammography, breast physical examination and breast self-examination had not reduced breast cancer mortality compared with usual community care after a single breast physical examination and instruction on breast self-examination.¹⁷ Nystrom et al found that among women, 40 to 49 years, there was a non-significant 13% reduction in breast cancer mortality among those invited to screening and those who were not. After eight years follow up however there was a difference in favour of the invited women. There was no evidence of any detrimental effect of screening in terms of breast cancer mortality in any age group. Among women aged 70 to 74 years screening seems to have had only a marginal impact.¹⁹ McPherson et al concluded that mammographic detection of breast cancer may be associated with a significantly decreased risk of death for older women of all ages, even for women with mild to moderate levels of co-morbidity, but for older women with severe or multiple co-morbidities, mammography was not associated with an improvement in overall survival.²⁰ McCarthy et al concluded that the use of mammography in older women was recommended and suggested that it can reduce breast cancer mortality in older women even those aged ≥ 85 years.²¹ Van Dijck et al concluded that regular screening of women over 65 years (at least up to 75 years) can reduce breast cancer mortality.²²

A recommendation on decreasing the current screening intervals or narrowing the age

range cannot be made based on the available literature. It would be appropriate to extend the age range to 69 years to meet with current European Union Advisory Committee on Cancer Prevention Recommendations.

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Appendix 4

Systematic review of rationale for choice of screening intervals and age groups in cervical cancer screening

Screening Intervals

The World Health Organization International Agency for Research on Cancer has reported on statistical models, which have been developed to explore the effect of screening test, policy and programme characteristics on the expected reductions in incidence and mortality. The main findings derived from these models were that, with increasing numbers of tests, the marginal gains become smaller with each additional test. With few tests, the optimal age to start screening is around the age of 35 years, and as more tests are added to the schedule, the optimum age at start diminishes but less than the addition of years for examination at older ages.¹

A matched case-control study comparing the risks of developing invasive squamous cell cervical cancer associated with screening intervals of one, two, and three years after a negative smear was published in 2003.² Patients (n=482) were matched with 934 controls. The odds ratio (OR) for a two-year versus a one-year interval was 1.72 (95% confidence interval (CI): 1.12, 2.64, P=0.013) and for a three-year versus a one-year interval was 2.06 (95% CI: 1.21, 3.50, P=0.007). The OR for a three-year versus a two-year interval was 1.20 (95% CI: 0.65, 2.21, P= 0.561). Thus the relative risks of invasive squamous cell cervical cancer were significantly greater for two-year and three-year cervical cancer screening intervals versus a one-year interval but not for a three-year interval versus a two-year interval.²

Sawaya et al employed a Markov model to estimate the importance of intervals.³ Among 31,728 women 30 to 64 years, who had had three or more consecutive negative tests, the prevalence of biopsy-proven cervical intraepithelial neoplasia (CIN) grade two was 0.028 % and grade three was 0.019%; no women had invasive cervical cancer. It was estimated that compared with annual screening for three years, screening performed once every three years was associated with an average excess risk of cervical cancer of approximately three in 100,000. To avert one additional case of cancer by screening 100,000 women annually for three years rather than once three years after the last negative test, an average of 69,665 additional pap tests and 3,861 colposcopic examinations would be needed in women 30 to 44 years of age and an average of 209,324 additional pap tests and 11,502 colposcopic examinations in women 45 to 59 years of age. Annual screening reduced this risk of cervical cancer, but required substantial resources and the difference in the risk of cancer was small.³

Schindeler et al investigated the association of two to three year screening intervals with the likelihood of detection of a high-grade cervical abnormality and cancer.⁴ Data on 1,213,295 Human papillomavirus (HPV) unvaccinated women aged 20 to 69 years (minimum of two negative smear tests) was obtained from a Test Register and Central Cancer Registry. For each year increase in the screening interval, the odds

of a histologically confirmed high-grade abnormality increased significantly in women aged 20 to 29 years (OR =1.24, 95% CI: 1.20-1.28) and in women aged 30 to 49 years (OR 1.11, 95% CI: 1.06-1.16), but not in women aged 50 to 69 years (OR 1.08, 95% CI: 0.89-1.32). Similarly the interval was significantly and positively associated with a cytological prediction of cervical cancer (OR 1.40, 95% CI: 1.28-1.54) and a confirmed cervical cancer diagnosis (OR 1.66, 95% CI: 1.33-2.07) in women aged 20 to 69 years.

If the interval was increased from two to three years, and the number of women participating in triennial screening was the same as for biennial participation, it was estimated that 267 (95% CI: 186-347) extra cases of high-grade abnormalities would be detected annually by cytology and 225 extra cases (95% CI: 160-291) confirmed by histology, mostly confined to women aged 20 to 49 years. Equivalently, 2.3 (95% CI: 1.8-2.8) and 1.9 (95% CI: 1.5-2.4) extra cases of high-grade cytology and histology, respectively, would be expected per 1,000 women with initially negative cytology. It was recommended that the screening interval be retained at two years.⁴

Sasieni et al reviewed the screening histories of 1,305 women (20 to 69 years), with frankly invasive cervical cancer and data on 2,532 controls.⁵ Five-yearly screening offered considerable protection (83%) against cancer at ages 55-69 years and annual screening offered only modest additional protection (87%). In women aged 40-54 years, three-yearly screening offered additional protection (84%) over five-yearly screening (73%), but was almost as effective as annual screening (88%). In women aged 20-39 years, even annual screening was not as effective (76%) as three-yearly screening in older women, and three years after screening cancer rates returned to those in unscreened women. The policy of having a uniform screening interval from age 20 to 64 years was questioned. The value of screening in middle-aged women was stressed.⁵

Historically women in the UK aged 20 to 64 years had been invited for cervical cancer screening every three to five years. Since 2003, women aged 25 to 49 years in England are invited for screening every three years, while those aged 50 to 64 years are invited every five years. Women less than 25 years are no longer screened.⁶ Canfell et al constructed a model to examine the potential effects of these changes.⁷

The predicted cumulative lifetime incidence of invasive cervical cancer was 1.70% in the absence of screening and 0.77% with the pre-2003 screening practice. A reduction in lifetime incidence to 0.63% was predicted following the implementation of the 2003 recommendations. It was estimated that extending screening to women aged 65-79 years would further reduce the lifetime incidence to 0.56%. Screening women aged 20-25 years would have minimal impact, with the cumulative lifetime incidence decreasing from 0.63 to 0.61%. The study supported the 2003 recommendations.⁷

Vinkesteijn et al performed a retrospective follow up to assess the effects of extending the screening interval from three to five years.⁸ The results were collected of the first and second rounds of a five-year interval programme. Histoscores for CIN 3 and squamous cell carcinoma (n/100 women investigated) and the hit count (sum of the CIN 3 histoscores, adenocarcinoma in situ and invasive cervical carcinoma) were calculated. The results of the five-year programme (commenced 1996) were compared with those of the three-year interval programme (commenced in 1976).

From the first to the second round of the three-year programme, the histoscores for CIN 3 (3.33, 1.88) and squamous cell carcinoma (0.53, 0.19) and the hit count (3.92, 2.15) all diminished significantly.⁸ The five-year programme showed low starting values for all three parameters, comparable to those in the second round of the three-year programme; a further reduction (0.16, 0.08; $p < 0.01$) was seen only in the histoscore for squamous cell carcinoma and the hit count of serious abnormalities remained constant.⁸

Siemens et al concluded that screening at five-year intervals may result in stabilization of positive cytology and of the incidence of CIN and invasive squamous cell carcinoma and may be more cost effective than the three-year programme.⁹

Age Range

In an unscreened population, the incidence of cervical cancer reaches its maximum around the age of 50 years. In screened populations, the incidence tends to be highest for women above 60 years.¹

Sasieni et al reviewed prospectively recorded data on cervical screening from selected centres in the UK¹⁰ The cohort comprised of 4,012 women aged 20 to 69 years with invasive cancer and two controls per case. There was no evidence that screening women aged 22 to 24 years reduced the incidence of cervical cancer at ages 25 to 29 years (OR 1.11, 95% CI: 0.83 to 1.50). Similar results were seen for cancers restricted to squamous carcinoma or FIGO (International Federation of Gynaecology and Obstetrics) stage IB or worse, but the numbers were insufficient to provide a narrow CI. Screening was associated with a 60% reduction of cancers in women aged 40 years, increasing to 80% at age 64 years.

Screening was particularly effective in preventing advanced stage cancers.¹⁰ Cervical screening in women aged 20 to 24 years had little or no impact on rates of invasive cervical cancer up to age 30 years. There was some uncertainty regarding the impact of screening on advanced stage tumours in women under age 30 years, however, screening older women led to a substantial reduction in incidence of and mortality from cervical cancer.

Zappa et al evaluated the efficacy of cytological screening in preventing adenocarcinoma as compared to squamous cell cancer by means of a case-control study.¹¹ All women aged below 70 years registered as having a cervical cancer diagnosed between 1994 to 1999 were considered. Each case was matched with four controls. A total of 208 cases and 832 controls were selected. Among cases, 148 (71.1%) had squamous carcinoma, 53 (25.5%) adenocarcinoma and seven (3.4%) other or unspecified types. The ORs of women who had a smear test within the previous three years was 0.65 (95% CI: 0.26–1.64) and 0.15 (95% CI 0.07–0.31), for adenocarcinoma and squamous cancer, respectively. The study showed a lower protection from cytological screening for adenocarcinoma than squamous carcinoma. As far as the association of age with screening efficacy was concerned, the relative protection of screening from invasive squamous carcinoma was shorter in younger (<40 years) than in older (>40 years) women. The authors suggested that a longer interval (five years) could be adopted in older age groups.¹¹

Armaroli et al assessed routine screening to identify CIN2 or worse in women over 50 years in a multicentre retrospective cohort.¹² In all, 287,330 women screened at age 25 to 64 years, with at least two screening tests (the first negative), were followed from their first negative smear until a biopsy proven CIN2 lesion or their last negative smear. The detection rate was significantly lower over 50 years. The cumulative risk (CR) of CIN2 was at least eightfold higher in women <50 years (CR=2.06, 95% CI: 1.88–2.23) than in women >50 years (CR=0.23, 95% CI: 0.00–0.46). Over 50 years of age, after four tests at least three false-positive cases are diagnosed for every true positive. The authors concluded that the benefits arising from cytological screening are uncertain in well-screened older women.¹²

Baay et al tested the hypothesis that women, ≥ 50 years, who are HPV-negative and a normal smear might be able to refrain from further screening.¹³ Although up to 25% of the cases of cervical cancer occur in women over the age of 65 years, a long episode of persistent HPV infection would precede the development of cervical lesions and hence these women should be detected in a screening system combining cytology and HPV detection.

The prevalence of HPV in a population of 1,936 women of ≥ 50 years was investigated. After an initial decline, a slightly higher prevalence was seen with increasing age. There was a decrease in the prevalence of multiple infections with age, paralleled by an increase in single infections, especially of HPV-16 in the eldest-age group. However, neither the decrease in multiple infections nor the increase in single infections was statistically significant. The authors concluded that approximately 94% (99% CI: 92.6–95.4) of women over 50 years could be withdrawn from the cervical cancer screening.¹³ HPV DNA detection is not part of the screening process in Ireland and this paper should be interpreted with caution.

Sigurdsson et al assessed the effect of starting screening at age 20 years in 1988.¹⁴ The average three-year screening attendance at age 20 to 24, 25 to 29 and 30 to 34 was 23%, 62% and 72%, respectively, in 1979 to 1988 and increased to 62%, 78% and 82% in 1989 to 2003. Information on preinvasive disease was gathered for the period 1979 to 2003. All rates on preinvasive diseases were calculated per 1,000 women screened. The incidence of invasive disease was calculated per 100,000 women in the population per year.

Results showed that cancer incidence increased significantly at age 25 to 34 years after 1979 due to early stage squamous cell and adenocarcinoma. After an initial increased rate of preinvasive disease, CIN 3 decreased significantly at age 30 to 34 years after 1988, at age 25 to 29 years after 1993, and levelled out after 1998 at age 20 to 24 years. The rates of CIN 2 levelled out after 1998. The rates of repeat low-grade smears decreased after observation at age 20 to 24 years by 80%. The authors highlighted an increasing rate of preinvasive and invasive disease among younger women and the subsequent benefit of starting organised screening at two- to three-year intervals soon after age 20 years.¹⁴

Van der Aa et al investigated whether the target age for cervical cancer screening should be lowered to below 30 years in view of apparent increases in new cases

of invasive cancer below age 30 years and in age group 30 to 44 years in the Netherlands.¹⁵ All cervical cancer cases diagnosed between 1 January 1989 and 31 December 2003 were selected from the nationwide Cancer Registry. For age group 25 to 39 years, incidence data were also available for 2004 and 2005.

Between 25 to 28 years, the absolute number of new cases of cervical cancer annually varied between 0-9 per age. Significantly decreasing trends in incidence were observed for age groups 35 to 39 years and 45 to 49 years ($p < 0.0001$ and $p=0.01$, respectively). The annual number of deaths fluctuated with a decreasing trend for age groups 30 to 34 years and 35 to 39 years ($p=0.01$ and $p=0.03$, respectively). Because the incidence and mortality rates for cervical cancer among women younger than 30 years were low and not increasing, lowering the age for cervical cancer screening was not considered to be beneficial.¹⁵

Gupta aimed to identify the target age group where screening efforts may be concentrated in developing or poor countries.¹⁶ Although not directly relevant to the Irish situation the mean ages for detection of squamous intraepithelial lesions (SILs) were investigated.

The results of screening in an Indian hospital-based programme were analysed retrospectively. The peak age incidence for squamous intraepithelial lesions (SILs) was in the 30 to 39 years age group while that for malignancies was age >60 years. The mean ages for low grade (LG) SIL, high grade (HG) SIL and cancer were 34.7, 37.7 and 51.8 years respectively. Around 43% LSILs and 48% HSILs presented in the fourth decade.¹⁶

These results have been repeated in studies from other developing countries. Misra et al assessed the feasibility of a single lifetime smear in women between 41-50 years in developing countries.¹⁷ The cervical smears of 31,032 women were evaluated during a span of 32 years (April 1971 to March 2003) for early detection of carcinoma. Approximately 30% of total cancer cases detected belonged to the age group, 41 to 50 years. The maximum numbers of SIL cases were detected in this group (35.3% of total). The maximum incidence of invasive cervical carcinoma was found in women beyond 50 years (1.3%) and the percentage of total occurrence of cervix cancer also was high (45.1%).¹⁷

Ghosh et al reviewed smears taken from January 2000 to June 2004 in a Nepalese population.¹⁸ Samples were analysed to study the patterns of precancerous atypical squamous cell of undetermined significance, LSIL and HSIL and malignant squamocellular carcinoma of the cervix in a total of 2,288 females. Precancerous and malignant lesions were diagnosed in 65 patients. The pattern of lesions was found to be almost same among the age groups of 26 to 35 years and 36 to 45 years. The authors concluded that it would be wise to screen for cervical lesions in women even younger than 26 years to detect precancerous lesions early.¹⁸

This study also described a number of other studies in which the age of diagnosis was investigated. In North America the median age at diagnosis of cervical cancer was 47 years but nearly half of the cases were diagnosed before the age of 35 years. In active duty U.S. Air Force women, the disease was associated mainly with those < 30 years,

SILs being found at ages 21 to 25 years and atypical squamous cell of undetermined significance in those < 30 years.¹⁸

Summary

In Ireland, screening is carried out every three years for women aged 24 to 44 years and every five years for women aged 45 to 60 years once they have had two “no abnormality detected” smear test results at the three-yearly intervals.¹⁹ The European Union Advisory Committee on Cancer Prevention recommends that women from 20 to 25 years up to 59 to 64 years should be targeted, but states that if limited screening resources are available these should be concentrated in the age range of 30 to 60 years. Screening should be undertaken with a three- to five-year interval.²⁰

A number of studies have been evaluated for this review. None of these studies were performed in Ireland and therefore caution should be exercised in interpreting the results.

The effects of screening intervals have been investigated. Grisham-Miller et al found that the relative risks of invasive squamous cell cervical cancer were significantly greater for two-year and three-year cervical cancer screening intervals versus a one-year interval but not for a three-year versus a two-year interval.² Schindeler et al found that if the interval was increased from two to three years, an estimated 267 extra cases of high-grade abnormalities would be detected annually and 225 extra cases confirmed by histology.⁴ Equivalently, 2.3 and 1.9 extra cases of high-grade cytology and histology, respectively, would be expected per 1,000 women with initially negative cytology. A two-year interval was recommended.⁴ Sasieni et al found that five-yearly screening offered considerable protection (83%) against cancer at ages 55 to 69 years.⁵ In women aged 40 to 54 years, three-yearly screening offered additional protection (84%) over five-yearly screening (73%).⁵ Siemens et al, however, concluded that screening at five-year intervals may result in stabilization of positive cytology and of the incidence of CIN and invasive squamous cell carcinoma and may be more cost-effective than the three-year programme.⁹

The impact of age range in screening has also been evaluated for this review. Sasieni et al states that there was some uncertainty regarding the impact of screening on advanced stage tumours in women under age 30 years, however, screening older women led to a substantial reduction in incidence of and mortality from cervical cancer.¹⁰ Zappa et al found that the relative protection of screening from invasive squamous carcinoma was shorter in younger (<40 years) than in older (>40 years) women and suggested that a five-year interval be adopted in the older age group.¹¹ Armaroli et al found that the screen detection rate was significantly lower over 50 years and concluded that the benefits arising from cytological screening are uncertain in well-screened older women.¹² Sigurdsson et al highlighted an increasing rate of preinvasive and invasive disease among younger women and the subsequent benefit of starting screening at two to three year intervals soon after age 20 years.¹⁴ Ghosh et al concluded that women younger than 26 years should be screened to detect precancerous lesions early.¹⁸

Conversely, Van-der-Aa did not recommend lowering the screening age to below 30 years based on low and non-increasing incidence and mortality rates for cervical cancer among women younger than 30 years.¹⁵

A recommendation on decreasing the current screening intervals or narrowing the age range cannot be made based on the available literature. It may be appropriate to extend the three-year screening interval to women up to 54 years.

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