THE IMPACT OF CERVICAL SCREENING ON YOUNG WOMEN: A CRITICAL REVIEW OF THE LITERATURE 2002–2009

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THE IMPACT OF CERVICAL SCREENING ON YOUNG WOMEN: A CRITICAL REVIEW OF THE LITERATURE 2002–2009

Until 2003 the age at which the English Cervical Screening Programme invited women for their first cervical screening ranged from 20 to 24, depending on local screening policy. In 2003 the age of first invitation was standardised at 25, on the grounds that normal changes in the cervix before age 25 could lead to unnecessary treatment with potentially negative consequences for women's childbearing, while abnormal changes could be easily detected and treated at this later age.

Since that time there have been a number of publications addressing the impact of cervical screening on young women. This review offers a critical overview of papers published on the topic since 2002, and includes a tabular summary of the main findings of each paper.

The published studies can be divided into six broad categories

a. case-control (or cohort) studies with individual-level information on cervical screening
b. case-only descriptive studies
c. analyses of trends in cervical intraepithelial neoplasia (CIN) and cervical cancer
d. studies of the natural history of human papillomavirus (HPV) infection and/or cervical neoplasia in young women
e. studies examining the risk of preterm delivery after excision of the cervical transformation zone
f. studies assessing the impact of treatment for cervical disease on fertility.

A number of commentaries and editorials responding to specific studies are also included.

This review, which aims to be focused rather than exhaustive, encompasses relevant publications known to the authors and others identified through PubMed searches.

a. Case-control (or cohort) studies with individual-level information on cervical screening

The 2003 publication arising from the UK audit of screening histories (Sasieni et al[1]) found that screening was far less effective in preventing stage 1B or worse cervical cancer in women aged 20–34 than it was in preventing cervical cancer in older women. It also noted that the period of low risk following a negative cervical sample was shorter in younger women than in older ones. Zappa et al[2] conducted a case-control study in Florence, Italy, in response to the UK audit publication. This compared the efficacy of screening women aged <40 and those aged ≥40. It concluded that the protection offered by screening was of shorter duration in women under the age of 40 but that this difference did not result from a greater incidence of adenocarcinoma in these younger women. Sasieni and Castanon[3] provided further analysis of the UK audit data, demonstrating that women aged 20–29 with cervical cancer were no less likely than age-matched controls to have been screened. The study also considered cervical cancer rates in a variety of populations. While rates were low among older women in countries with good quality cervical screening, the study found little correlation in women aged 20–29 between screening activity and cervical cancer rates.

In a personal response to Sasieni et al's 2003 UK audit paper, Fiander[4] commented that it 'did not include micro-invasive cancers, for which fertility-sparing options for treatment may be feasible – an advantage of early screen-detected tumours'. The authors concur, which is why their analysis focused explicitly on more advanced cancers in women whom screening had failed. The sole advantage of screen-detecting a microinvasive cancer is that doing so is likely to prevent more advanced cancers: if microinvasive forms were being detected in very young women one would expect screening to prevent the development of more advanced forms.

In her response, Fiander also observed that 'if we accept that protection from current cervical screening is poor in young women then perhaps the response should not have been to start screening later but to find a better method of screening in young women?'. While few would deny the desirability of more effective cancer screening techniques, cases of cervical cancer in women under age 25 are extremely rare. Although it is the most common cancer in women aged 20–24, there are other cancers that are significantly more common among women aged 30–34 than is cervical cancer among women of 20–24. While the drive for finding new methods of screening derives from the magnitude of the health problem, screening programme policies are based on balancing risks and benefits.

The findings from Sweden's first nationwide audit of cervical screening and cervical cancer were published in 2008. In this age-matched case-control study, Andrae et al[5] found an odds ratio (OR) of 0.42 (=1/2.37) (95% confidence interval (CI) 0.24–0.74) for the effect of three-yearly screening on cancer incidence at ages 21–29. The odds ratios given in the paper are similar for all age groups. Apparent inconsistencies between the results of the UK audit, the Italian case-control study and the Swedish audit reflect important methodological differences. Andrae et al consider a woman aged 20–52 to have been screened if she had a cervical sample taken between 3.5 years and six months before the cancer is diagnosed. Their analyses include stage 1A cancers, most of which will have been screen detected, as well as screen-detected stage 1B cancers. Consequently, in a screen-detected case with two samples taken 3.5 years apart, if the sample that led to the diagnosis is taken within six months of it the woman will be classed as unscreened. A control who is screened every 3.5 years will have an 86% chance (=3.0/3.5) of having had a sample taken within the three-year interval. As a result, the inclusion of screen-detected cases introduces a considerable bias in favour of screening. Since the proportion of cancers that are stage 1A or screen-detected stage 1B is greater in young women, that bias is particularly strong among this group. Thus the Swedish audit does not demonstrate conclusively that cervical screening has a strong protective effect among women aged 20–29.

A more comprehensive commentary on Andrae et al's study, and an argument for the routine audit of cervical screening programmes, can be found in an editorial by Cuzick[6] published in the same journal issue. In his rapid response[7] to a more recent article[8] discussed below, Andrae provides results which demonstrate protection against cervical cancer in women under the age of 30 even once stage 1A cases have been excluded (OR 0.49, 95% CI 0.24–0.98).

A smaller case-control study in New South Wales, Australia,[9] found that screening every two years appeared to give more protection to women aged over 30 than to those aged 20–29. It nevertheless found substantial benefit from screening women aged 20–29. This benefit appears more substantial than in studies by Sasieni et al, perhaps because the Australian controls were selected from women who had been screened (albeit possibly only after the date of diagnosis of the cases).

A later publication by Sasieni et al[8] confirmed the findings of the 2003 UK audit paper. This 2009 study comprised almost double the number of cases used in the earlier paper and applied a different statistical method to the data. It found no evidence that screening women aged 22–24 reduced the incidence of cervical cancer at ages 25–29 (OR 1.11, 95% CI 0.83–1.50). Similar results were

seen when cancers were limited to squamous carcinoma and/or FIGO stage IB or worse, although the numbers were too small to provide narrow confidence intervals. The study was designed to minimise biases and the likelihood of confounding. The authors therefore suggest that the associations observed are causal, concluding that cervical screening in women aged 20–24 has little or no impact on invasive cervical cancer rates up to age 30. However, some uncertainty still surrounds its impact on advanced stage tumours in women under age 30, owing to the small number of these cancers. In their report of a case-control study of cervical screening in Manitoba, Canada, Decker et al[10] do not consider whether the relative protection offered by screening is age dependent.

b. Case-only descriptive studies

Leyden et al[11] studied cases of invasive cancer among members of seven prepaid health plans in the USA and reviewed their medical records for the three years before diagnosis. Odds ratios were calculated to establish whether demographic characteristics were associated with the likelihood of a case being classified as a Failure to Screen: that is, the woman had had no Pap smears in the 4–36 months before diagnosis. Compared with women aged 16–39 years at diagnosis, the authors found that patients aged 40–92 were more likely to have their diagnosis attributed to Failure to Screen (OR 6.48, 95% CI 3.89–10.79). Thus unless screening uptake in young women is much higher than in older women (and data from the UK would suggest that it is, in fact, lower), screening is significantly less effective in younger women.

Prussia et al[12] and Bano et al[13] both presented data on the screening histories of women aged under 25 in specific populations. They concluded that screening should be offered to women aged 20–24, among whom precancerous lesions are very common. However, no data were provided on the incidence of invasive disease in this group.

Reick et al[14] reviewed the colposcopy notes of women in Wales aged 20–24 with cervical cancer and reported on the screening programme results. Approximately 6.3% of screened women in this age group were referred to colposcopy. (In fact, the figure might have been higher, as some of those screened at age 24 would not have been referred until they were 25.) Of those referred, 1.9% were treated by removing tissue from their cervix and fewer than one in 10 000 was found to have a screen-detected cancer. Of the 10 cases of cancer diagnosed in women aged 20–24 over five years, eight were screen detected and (as far as can be ascertained from the paper) all 10 cases had been well screened previously. Thus it would appear that all these cases occurred despite screening.

UK-based studies by Herbert et al[15] and Nair et al[16] collated information on women under age 25 diagnosed with cervical cancer and assessed their screening history. Both papers conclude that the majority of cervical cancer in young women is screen detected.

c. Natural history studies

Moscicki et al[17] published a US-based longitudinal study in 2004 of HPV infection in female adolescents aged 13–22. The young women were examined every four months by cytology, colposcopy and HPV DNA testing. Prevalent and incident cases of low grade squamous intraepithelial lesions (LSIL) were included in the analysis. Median follow up for the 187 women with LSIL was 61 months (interquartile range 34–80). The probability of regression for the entire cohort was 61% (95% CI 53–70) at 12 months and 91% (95% CI 84–99) at 36 months' follow up. Only 3% (95% CI 0.7–6.0) progressed to high grade disease. The authors suggest that cytological follow up for young women is sufficient and that colposcopy should be avoided.

In an accompanying editorial, Szarewski and Sasieni[18] commented 'we should not lose sight of the purpose of screening, which is to prevent cervical cancer by detecting lesions that have a high probability of becoming cancer. With such high regression rates there is no point specifically screening for HPV infection or LSIL. … Evidence suggests that there is considerable anxiety and psychosexual morbidity associated with cervical screening and colposcopy. Since there is no point in treating young women with LSIL, we should reflect on the basic tenet of medicine: at least do no harm.' Evidence from the TOMBOLA study (Trial of Management of Borderline and Other Low grade Abnormal Smears) confirms that women with low grade smears report anxiety levels similar to those found by other studies in women with high grade smears.[19] The TOMBOLA study also found that younger women with low grade smears were at greater risk than older women of suffering anxiety.

A later study by Moscicki et al[20] investigated risk factors for developing high grade disease in a group of young women aged 13–24 who had been referred to colposcopy following a cytological abnormality. The authors found that the most significant risk factor for high grade disease was infection with HPV16 or 18. They concluded that CIN3 was rare, that no case of cancer was found, and that conservative care for young women is therefore warranted.

In a 2009 paper, Sasieni et al[21] studied the progression from CIN3 to cancer in young women by modelling the rates of cervical cancer that would have resulted had CIN3 not been detected by screening and treated. The study concluded that the progression rate of around 3% per year assumed by many authors is far too high; the progression rate within five years of diagnosis can be no greater than 1% per year and is more likely to be around 0.5% per year. The assumption that a substantial proportion (30–50%) of CIN3 would, if untreated, progress to invasive cervical cancer within 10–15 years is based on the New Zealand cohort reported by McIndoe et al[22] and McCredie et al.[23] One explanation for the high rate of progression from CIN3 to cancer observed in this cohort is that disease diagnosed 30 years ago was more likely to progress than is disease detected more recently. This could be related to improvements in screening that enable smaller CIN3 lesions to be detected. Another possible explanation is that CIN3 in young women is less likely to progress than is CIN3 in older women. This could simply be a reflection of persistence: if most CIN3 starts in young women, lesions that have not regressed by age 30–40 may be more likely to progress. Ostör[24] estimated that 32% of CIN3 (all ages) regress.

d. Trend studies

Rieck et al[14] collated Welsh national statistics on CIN3 and invasive cancer in young women, and additionally women diagnosed aged 20–24 had their colposcopy notes reviewed. The authors concluded that incidence rates of cervical cancer in this age group have been reduced by 58% since the introduction of systematic screening and that deaths from the disease have fallen by 50%. The paper also reviewed a variety of evidence relating to the effectiveness of cervical screening in women aged 20–24 years.

Rieck's literature review does not provide any direct evidence that cervical screening in women aged 20–24 leads to a reduction in cervical cancer incidence or mortality. It is noted that interval cancers (those diagnosed following a negative cervical sample) were more likely in younger women. Indeed, in one US study nine of the 11 cancers in women aged 20–29 were diagnosed within three years of a negative smear. Most of the evidence cited is indirect and does not distinguish the very young (under age 25) from those aged 25–34. There was a substantial fall in cervical cancer registrations in women aged 20–24 and 25–29 in Wales between 1984–88 and subsequent years. However the quality of the data collected by the Wales Cancer Registry was variable in the 1980s and 1990s,[25] and these falls cannot be attributed uniquely to screening.

Herbert et al[15] collated national registrations of invasive and in situ carcinoma from the Office of National Statistics. They are concerned that the increasing rate of CIN3 in very young women will mean that, without screening and treatment of the CIN, more women in their early twenties will develop cervical cancer. Herbert et al use these data to argue in favour of screening from age 20. However, screening under age 25 is worthwhile only if it prevents cancers by treating screen-detected lesions at age 20–24 among women who would have developed cervical cancer despite screening from the age of 25. The most likely benefit will be from treating CIN3 that, untreated, would have become cancer before age 25. We also note that CIN3 rates in young women in the UK are some 50 times greater than the highest rates of cervical cancer in women of the same age[21] anywhere in the world. Given that for every 10 CIN3 biopsies there are six CIN2 biopsies and that the latter plus some women with persistent CIN1 will be treated, the number of women treated who do not have CIN3 registered is probably as great as the number who do.[26] Additionally UK cervical cancer rates in women aged 20–24 are very high when compared with other countries. Thus, for every 100 women treated aged 20–24, at best one case of cancer is prevented that would not have been prevented had screening been delayed until age 25.[21] In practice, however, the benefit is likely to be far less. Much indirect evidence suggests that in the very rare cases where CIN3 does progress to cancer before age 25 it does so very quickly. This reduces opportunities for preventing the cancer by screen detecting a precancerous lesion, and explains why there are so many interval cancers in very young women. It also explains why cancers are often screen detected in slightly older women: as older women are unlikely to develop cancer within 3–5 years of a negative cervical sample, regular screening prevents not only interval cancers but also screen-detected cancers.

Herbert et al[15] argue that delaying the start of screening 'carries a risk of CIN becoming more extensive, and therefore more difficult to excise'. The majority (80%) of CIN can be treated without a general anaesthetic as an outpatient procedure, and serious complications are very rare.[27] The authors suggest that the risk of preterm delivery following a deep LLETZ (large loop excision of the transformation zone) is greater than the risk following a shallow one.[28] The impact of any increased risk of preterm delivery needs to be balanced against the reduction in such deliveries if fewer LLETZ were carried out, particularly among very young women who are more likely to have children after treatment.

In the Netherlands, the cervical screening programme invites women from age 30. Van der Aa et al[29] analysed cancer incidence trends in the Netherlands from 1989 to 2003 to assess the desirability of lowering the national screening age. As incidence and mortality rates for women under age 30 were low and not increasing, the authors felt unable to recommend such a reduction. This contrasts with a study by Sigurdsson and Sigvaldason[30] which looked at the Icelandic National Screening Programme before and after its expansion in 1988 to include women aged 20–24. The study analysed time trends for age-specific incidence and detection rates for CIN2 and CIN3. It found that rates of CIN2 and CIN3 on histology at age 20–24 increased until 1994–98 and levelled out thereafter. The same pattern was observed for low grade and high grade cytology abnormalities in this age group. Detection of low grade cervical samples during 1989–2003 was 40% higher in the 20–24 age group than in women aged 25–29. In 1989–2003, the rate of a repeat low grade cervical sample in women aged 20–24 was double that at age 25–29, and almost triple that at age 30–34. However, 80% of cases regressed with adequate observation and no treatment. Despite these last findings the authors conclude that women will benefit from starting screening soon after age 20.

Peto et al[31] analysed trends in cervical cancer mortality both in England and Wales and internationally. They found that the pattern of mortality in birth cohorts was consistent with a substantial benefit from screening, and that the younger the cohort when first offered screening the greater this benefit was. They argue that regular cervical screening should start at a young age, but do not specify what that age should be.

e. Studies examining the risk of preterm delivery after excision of the cervical transformation zone

In 2007 Kyrgiou et al[32] published an extensive systematic review and meta-analysis of 27 studies addressing the risk of preterm delivery after excisional treatment for cervical disease. They found that LLETZ was significantly associated with preterm delivery (relative risk (RR) = 1.70, 1.24–2.35), low birth weight (RR = 1.82, 1.09–3.06) and preterm premature rupture of membranes (pPROM) (RR = 2.69, 1.62–4.46).

Since this meta-analysis, five further primary research articles have been published in the area. Bruinsma et al[33] found that women referred for assessment of precancerous changes in the cervix were at an increased risk of preterm birth when compared with the general population while, within the cohort, those receiving treatment were significantly more likely to have a preterm delivery (OR = 1.23, 1.01–1.51). Himes and Simhan[34] used a nested case-control study including 114 treated and 962 untreated women to assess whether the time from treatment to subsequent pregnancy was associated with a risk of preterm birth. They concluded that increased risk for preterm delivery was limited to women with a short interval between conisation and conception. Sjoborg et al[35] combined treatment with laser conisation and LLETZ to find a statistically significant association between treatment and preterm delivery (RR = 3.4, 2.3–5.1), low birth weight (RR = 3.9, 2.4–6.3) and pPROM (RR = 10.5, 3.7–29.5). Nøhr et al[36] found the relative risk of preterm delivery to be 1.8 (1.1–2.9) in women who underwent a LLETZ before pregnancy. Jakobsson et al[37] found an increased risk of preterm delivery after conisation (RR = 1.99, 1.81–2.20), and this estimate did not change after adjustment for confounding factors. In a subsequent publication Jakobsson et al[38] observed that women who had a delivery after LLETZ had a higher rate, before treatment, of preterm delivery (6.5%) than the general population (4.6%). However once the women had been treated the risk of preterm delivery nearly doubled (12%; RR = 1.94, 1.10–3.40). These estimates did not change after adjusting for maternal age, parity or both. They also found that the preterm birth rates increased with cone size and repeat treatments. Albrechtsen et al[39] investigated the risk of preterm delivery in three groups of women: those who gave birth after conisation; those who gave birth before conisation; and those who did not receive treatment. The proportion of preterm deliveries in each group was 17.2%, 6.7% and 6.2% respectively. The study also found that the relative risk of preterm delivery in the treated group when compared with the untreated group was 4.4 (3.8–5.0) at 24–27 weeks, 3.4 (3.1–3.7) at 28–32 weeks and 2.5 (2.4–2.6) at 33–36 weeks. The authors also observed that the excess risk of a delivery before 32 gestational weeks decreased significantly between the start of the period studied in 1967 and its end in 2003. This reduction in risk was especially marked among those delivered under 28 weeks. The decreasing trend was most apparent up to the 1990s and coincided with the decreasing use of knife cone biopsy, a more radical treatment than LLETZ which has since displaced it to become the norm in the UK. This finding was borne out in 2008, when Arbyn et al[40] published a meta-analysis looking at the risk of severe adverse pregnancy outcomes after treatment for cervical disease. They found that cold knife conisation was associated with an increase in perinatal mortality, while laser ablation, cryotherapy and LLETZ were not (RR = 1.17, 0.74–1.87). In the most recent publication from the UK, Shanbhag et al[41] used routinely collected data from Scotland to estimate the risk of preterm delivery in women with CIN3. They found that women diagnosed with CIN3 were more likely to have preterm deliveries (OR 1.52, 1.29–1.80) and pPROM (OR = 1.27, 1.09–1.48). However, treatment per se was not associated with an increased risk of preterm delivery: the small group who did not receive treatment for CIN3 had similar rates of preterm delivery to those who were treated.

f. Studies assessing the impact of treatment for cervical disease on fertility

Several studies have been published that consider the impact on fertility of treatment for cervical disease. The largest of these, by Cruickshank et al,[42] included a cohort of 1000 treated women and their controls. When asked at 18–54 months following their treatment, over 27% said that they had become pregnant or were trying to conceive. None of the women investigated for infertility was found to have cervical stenosis or amucorrhoea, which would be related to treatment for cervical disease; other causes for their infertility were identified. Three further studies, although small, found no difference in the pregnancy rates between treated women and their controls[43,44] and one found that most of the women treated went on to conceive within a year of treatment.[45]

Summary

We review four types of studies looking at screening and cervical cancer: case-control (and cohort) studies, case-only studies, trends studies and natural history studies. We also take into account views expressed in editorials. Additionally we look at studies evaluating the adverse events of treatment for cervical disease all of which use a case-control design.

Case-control (and cohort) studies

Three main studies published since 2003 consider the effects of screening in different age groups.

- Zappa et al[2] included 208 cases and 832 controls and showed that the effect of screening between three and six years before diagnosis was greater in women over the age of 40 than in women under age 40 (OR = 0.26, 95% CI 0.14–0.48, and OR = 0.63, 95% CI 0.26–1.52, respectively).
- Andrae et al[5] included 1230 cases and 6150 controls. They found that the Swedish screening programme was equally effective for women of all ages.
- Sasieni et al[8] included 4012 cases and 7889 controls. Cervical screening in women aged 20–24 was found to have little or no impact on invasive cervical cancer rates up to age 30.

Natural history studies

Three groups have published important results since 2003.

- McCredie et al[23] used data from an untreated cohort diagnosed in New Zealand between 1955 and 1976 to show that 30% of women over 25 years of age with untreated CIN3 developed invasive cancer during 30 years of follow up.
- Sasieni et al[21] studied CIN3 and cervical cancer rates from around the world and argued that the risk of progression to invasive cancer within five years of diagnosis of CIN3 in women aged 20–24 is no more than 5%.
- Moscicki et al[17] found that 91% of low grade cytology in women under age 23 regresses spontaneously. In a subsequent publication they present indirect evidence of CIN3 regressing in young adults.[20]

Case-only and trend studies

These studies show clear evidence of high levels of CIN3 in young women, suggesting that women are becoming infected with HPV earlier. There is no direct evidence from these studies to suggest that the age at which women are screened affects cancer rates under age 30.

Studies of adverse effects

- No demonstrable effect of treatment is found on subsequent fertility, but most studies are small.
- An association is consistently found between treatment (including LLETZ) and subsequent preterm delivery (RR = 1.99, 1.81–2.20) in a large cohort study.[37]
- The risk of a preterm delivery seems to increase with the depth of excision.[32]
- There is no significant association between treatment with LLETZ and perinatal mortality (although 95% CI allows an effect up to 1.87) nor for severe adverse pregnancy outcomes, including extreme preterm delivery and low birth weight.[40]

Conclusion

The literature published since 2002 has not fully resolved the controversy regarding the value of screening in women aged 20–24. Those in favour of screening young women point out the high detection rate for CIN3 and the lack of biological evidence to suggest that the effect of screening is age dependent. They also question whether the association between treatment of CIN and subsequent preterm delivery is causal. Nevertheless the evidence published since 2002 shows little, if any, benefit from screening women under 25 as far as the prevention of cervical cancer or of advanced cervical cancer is concerned. Indeed the balance of evidence suggests that if screening is beneficial under age 25, the benefit is at best modest. Several papers published since 2002 confirm earlier findings that women treated for cervical lesions prior to childbearing are at increased risk of preterm delivery. Further work is needed to understand this association more fully. Despite these uncertainties the Advisory Committee on Cervical Screening (England) was unanimous in its decision not to lower the age at first invitation from 25 to 20.

Summary of papers published on the effectiveness of cervical screening in young women 2002–2009

Author/year	Methods	Results	Conclusions
Case-control (or cohort) studies with individual-level information on cervical screening			
Sasieni 2003[1]	Case-control study in the UK. Screening histories of 1305 women aged 20–69 years diagnosed with stage 1B+ cervical cancer and 2532 age-matched controls were obtained from national screening programme databases. Data were analysed in terms of time since last negative, and time since last cervical screening.	Five-yearly screening offers considerable protection (83%) against cancer at ages 55–69 years and even annual screening offers only modest additional protection (87%). Three-yearly screening offers additional protection (84%) over five-yearly screening (73%) for cancers at ages 40–54 years, but is almost as effective as annual screening (88%). In women aged 20–39 years, even annual screening is less effective (76%) than three-yearly screening in older women, and three years after screening cancer rates return to those seen in unscreened women.	The authors suggested that there was little point screening women under the age of 25, and that women aged 25–49 should be screened three-yearly, while woman age 50–64 could be screened five-yearly.
Zappa 2004[2]	Case-control study in Florence, Italy ($n=208$), to evaluate the efficacy of cytological screening in preventing cervical cancer in women under age 40, compared with those aged 40 or older.	Odds ratios were very similar for women of any age for screening intervals of less than three years before the date of diagnosis (OR=0.35, 95% CI 0.13–0.95, for women under age 40; OR=0.22, 95% CI 0.12–0.42, for women over age 40). However odds ratios were higher for women under age 40 with screening intervals between three and six years before diagnosis (OR=0.63, 95% CI 0.26–1.52) than they were for women over age 40 (OR=0.26, 95% CI 0.14–0.48).	The duration of the protective effect of screening was shorter in women under the age of 40. This difference did not result from a greater proportion of adenocarcinoma in young women.
Sasieni 2006[3]	Analysis of call and recall screening programmes in the UK, focusing on screening intervals and age limits.	Analysis of the UK audit data showed that women aged 20–29 with cervical cancer were as likely as their age-matched controls to have been screened. The study also found that, among women aged 20–29, 65% of cases of stage 1B+ and 72% of controls had had a negative cervical sample within five years of diagnosis. Cervical cancer rates were compared in a variety of populations, screened and unscreened.	The authors concluded that while cervical cancer rates in older women were low in countries with good cervical screening, there was little association between screening activity and cervical cancer rates in women aged 20–29.

Author/year	Methods	Results	Conclusions
Andrae 2008[5]	Case-control study in Sweden. Cases were diagnosed from 1 January 1999 to 31 December 2001 and reported to the Swedish Cancer Registry ($n=1230$). Age-matched controls were identified from the National Population Register. Screening histories were reviewed for a six-year period.	Women who did not have a Pap smear within the recommended screening interval (0.5–3.5 years in women under age 53 and 0.5–5.5 years for women aged 53 or older) had a higher risk of cervical cancer than women who had been screened. This association was observed regardless of the age at diagnosis. Women who were not screened and were diagnosed at age 21–29 had an OR of 2.37 (95% CI 1.36–4.13), those diagnosed at age 30–65 had an OR of 2.51 (95% CI 2.14–2.94) and those diagnosed at age ≥66 had an OR of 2.7 (CI 1.89–4.11).	The screening programme in Sweden was equally effective for women of all ages.
Yang 2008[9]	Case-control study in New South Wales, Australia. Cases were diagnosed between 2000 and 2003 and reported to the New South Wales Central Cancer Registry ($n=877$). Three age-matched controls were selected using the Pap Test Register (1996–2004). Screening histories were reviewed from 1996 for all women.	Screening intervals were defined as: none (no smear in the last four years); irregular (one smear in the last four years); or regular (two or more smears in the last four years). Compared with no screening, irregular screening reduced the risk of invasive cervical cancer by 76% in women aged 20–29 (OR 0.24, 95% CI 0.11–0.54), by 81% in women aged 30–49 (OR 0.19, 95% CI 0.14–0.26) and by 90% in women aged 50–69 (OR 0.10, 95% CI 0.06–0.15). The effect of regular screening is greater, but the same pattern is observed of decreased risk with increased age.	Although the effect is less marked in young women, having a Pap test in the last four years substantially reduced the risk of invasive cancer in women under the age of 30.
Sasieni 2009[8]	Population-based case-control study using prospectively recorded data on cervical screening in the UK. Cases were diagnosed in women ($n=4012$) aged 20–69 and two controls were individually matched by age and area of residency. Screening histories were available for all women from 1988.	No evidence was found that screening women aged 22–24 reduced the incidence of cervical cancer at ages 25–29 (OR = 1.11, 95% CI 0.83–1.50). Similar results were seen when cancers were restricted to squamous carcinoma and/or FIGO stage IB or worse, but the numbers were insufficient to provide narrow confidence intervals. Screening was associated with a 60% reduction in cancers in women aged 40, increasing to 80% at age 64. Screening was particularly effective in preventing advanced stage cancers.	Cervical screening in women aged 20–24 was found to have little or no impact on invasive cervical cancer rates up to age 30. Some uncertainly still exists regarding its impact on advanced stage tumours in women under age 30.

Author/year	Methods	Results	Conclusions
Case-only descriptive studies			
Leyden 2005[11]	Cases of invasive cancer were analysed among members of seven prepaid comprehensive health plans in the USA diagnosed between 1 January 1995 and 31 December 2000. Medical records were reviewed for the three years before diagnosis. Demographic characteristics were independently associated with the odds of a case being ascribed to 'Failure to Screen' (patient has no Pap tests during the 4–36 months prior to diagnosis).	The study identified 833 women with invasive cancer. Of these, 24% were aged 16–39, 31% aged 40–49, 28% aged 50–64 and 17% aged ≥65. Compared with women aged 16–39 at diagnosis, older women had higher odds of having their diagnosis attributed to 'Failure to Screen' (OR = 6.48, 95% CI 3.89–10.79).	In the majority of women in this case series, cervical cancer was attributed to a lack of recent Pap screening.
Prussia 2002[12]	Retrospective study in Barbados to determine the types of Pap test abnormalities and their clinical implications in girls aged 18 and under during the five-year period January 1995 to December 1999. Gynaecological history and histology reports for these patients were analysed.	Two hundred and sixty-five Pap smears were examined from 236 patients. Of the 236 first-visit samples 94 (39.8%) were abnormal with 58 (24.5%) reported as atypical cells of undetermined significance (ASCUS), 33 (14%) reported as low grade squamous intraepithelial lesions (LSIL) and three (1%) reported as high grade squamous intraepithelial lesions (HSIL). Twenty-two (23.4%) of the 94 patients who had abnormal smears (either ASCUS or LSIL) were re-evaluated within 6–12 months of the initial abnormal diagnosis. Eight of these 22 patients (36.4%) had a histological diagnosis of LSIL, including cervical intraepithelial neoplasia grade 1 (CIN1) and condylomata. High risk HPV DNA types were detected in two of these eight patients (25%).	Authors recommend screening of sexually active teenage girls as they are at risk of developing preinvasive cervical disease.

Author/year	Methods	Results	Conclusions
Bano 2007[13]	Screening and colposcopy histories were reviewed for women aged 20–24 who had been screened between 1 April 2003 and 31 March 2004 in Lewisham, UK. A prospective study involving a random sample of 215 women of all ages was carried out in the form of a questionnaire. This asked about sexual and smoking habits and contraception used.	Pap test results for 2793 women were analysed. Of these 71.5% were normal, 13.4% were inadequate, 5.1% were borderline, 7.4% had mild dyskaryosis and 2.5% had high grade lesions. Of the 182 women referred to colposcopy 22% did not attend, 16% had a normal colposcopy, 0.5% had inadequate biopsy material, 34% had histological evidence of CIN2/3, 27% had evidence of CIN1 and 0.5% had evidence of koilocytosis. The incidence of CIN in women aged 16–25 was 6.6 per 1000; the incidence of CIN1 was 2.9 per 1000 and that of CIN2/3 was 3.7 per 1000. The questionnaire revealed that five out of seven young women under age 20 with high grade CIN described themselves as heavy smokers. The average age at first sexual intercourse was 17 years 7 months, ranging from 13 to 25.	The high incidence of precancerous lesions among young women in Lewisham suggests that women under age 25 should be screened.
Reick 2006[14]	The authors reviewed the literature on the effectiveness of screening women aged 20–24 and collated Welsh national statistics on CIN3 and invasive cancer in young women between 1981 and 2003. Women diagnosed under age 25 had their colposcopy notes reviewed.	Incidence rates of cervical cancer in women aged 20–24 have fallen by 58% since the introduction of the call and recall screening programme in Wales, while deaths from the disease have fallen by 50%. Screening coverage for this age group was 50%. Ten cancers in women aged 20–24 were reviewed. Six of these had microinvasive cancer and all of these women had been screened at least once before the cervical sample that led to diagnosis.	Women should continue to be invited for screening from age 20.
Nair 2007[16]	Case series of all women under the age of 25 diagnosed with cervical cancer between January 2003 and December 2005 and registered on the East Kent Gynaecological Oncology Centre database.	Six of the 96 cases diagnosed in the region during the study period were in women under age 25. Four of these women had cancer stage 1A1, one had cancer stage 1B1 and all were referred to colposcopy because of abnormal cervical samples. One further woman aged 19 was referred to colposcopy owing to symptoms and diagnosed with cancer stage 2B. She had a Pap test two months before diagnosis, reported as normal. During this three year period, 187 women under the age of 25 were found to have high grade disease.	Delaying screening till age 25 will fail to prevent progression of preinvasive disease or fail to detect cancer at an early stage (allowing for complete treatment and recovery).

Author/year	Methods	Results	Conclusions
Herbert 2008[15]	The authors collated national registrations of invasive and in situ carcinoma from the Office for National Statistics and carried out an audit of cancers diagnosed at Guy's and St Thomas' NHS Foundation Trust to determine the screen-detected cancers.	Recorded rates of CIN3 in women aged 20–24 were high; they increased from the 1980s and 1990s until at least 2003, after which fewer women aged 20–24 were offered screening. The majority of cervical cancer in young women is screen detected. The authors are concerned that the increasing rate of CIN3 in very young women will mean that more such women would develop cervical cancer if screening (and treatment of the CIN) were not offered to those in their early 20s.	Delaying the age for screening eligibility carries a risk of CIN progression.
Natural history studies			
Moscicki 2004[17]	Longitudinal study of HPV infection in female adolescents aged 13–22. Women were examined every four months by cytology, colposcopy and HPV DNA. Prevalent and incident cases of LSIL were included in the analysis.	The median follow up for the 187 women with LSIL was 61 months (interquartile range (IQR) 34–80). The median time they had been sexually active at diagnosis was 3.2 years (IQR 2.6–6.5). The probability of regression for the entire cohort was 61% (95% CI 53–70) at 12 months and 91% (95% CI 84–99) at 36 months' follow up, with only 3% progress to high grade disease.	The authors suggest that cytological follow up for young women is sufficient and that colposcopy should be avoided.
Moscicki 2008[20]	Young women aged 13–24 who were referred to colposcopy following a cytological abnormality in one of 12 participating clinics in North Carolina were recruited into the study. Face to face interviews were carried out on demographics and sexual behaviour. HPV testing was undertaken at the initial examination.	CIN3 was found in 6.6% (95% CI 4.6–8.6) of 622 women enrolled in the study; no cancers were found. Risk for CIN3 compared with CIN1 or less included infection with HPV16 or 18 (OR = 30.9, 95% CI 6.9–137.7), non-16/18 HPV (OR = 6.3, 95% CI 1.3–29.4) and time on oral contraceptives (OR = 1.36 per year of use, 95% CI 1.08–1.71)	The authors conclude that CIN3 was rare, no cases of cancer were found, and conservative care for young women is therefore warranted.

Author/year	Methods	Results	Conclusions
Sasieni 2009[21]	Registrations of carcinoma in situ for England and Scotland were used to project the additional numbers of invasive carcinoma that would have resulted had carcinoma in situ gone untreated. These estimated rates were then compared with rates recorded in *Cancer Incidence in Five Continents.*[46]	In order for the projected rates in England and Scotland at ages 20–24 not to be exceptionally high compared with maximum recorded rates for each registry in *Cancer Incidence in Five Continents*,[47] the progression rate from CIN3 to invasive cancer in women aged 20–24 should not exceed 1% per year. Similar progression rates were reasonable for women aged 25–29.	The authors conclude that at most 1.5% of women treated (equivalent to 3% of CIN3 registrations) would have had cancer by age 25, whereas it is reasonable to assume that over half of them would have regressed by age 25.
Trend studies			
Van der Aa 2008[29]	Cervical cancers diagnosed between 1 January 1989 and 31 December 2003 were selected from the Netherlands Cancer Registry. Cancer incidence trends were calculated.	The absolute number of cases of cervical cancer varies annually between zero and nine per age year for women under 29. Significant decreases in cancer incidence were observed only for the 35–39 age group ($P<0.001$) and the 45–49 ($P=0.012$) age group. In the 25–29 age group a small, non-significant increase in incidence (2%, $P=0.86$) was observed; this was based mainly on the incidence among women aged 29. A decreasing mortality trend was observed for age groups 30–34 and 45–49 ($P=0.01$ and $P=0.03$ respectively).	As incidence and mortality rates for women under age 30 are low and not increasing, lowering the screening age in the Netherlands is not recommended.
Sigurdsson 2007[30]	Data from the Icelandic National Screening Programme database were used to look at time trends in age-specific incidence and detection rates for CIN2 and CIN3.	Age-specific incidence rates in the 20–24 age group did not change substantially between 1955–1978 (2.6/100 000/year) and 1979–2003 (2/100 000/year). The rates of CIN2 and CIN3 on histology increased at age 20–24 until 1994–1998 and levelled out thereafter. The same pattern was observed for low grade and high grade cytology abnormalities in this age group. The screening coverage in this group increased from 23% in 1979–1988 to 62% in 1989–2003. Detection of low grade cervical samples during 1989–2003 was 40% higher in the 20–24 age group than in those aged 25–29. The rate of a repeat low grade sample in women aged 20–24 in 1989–2003 was double that at age 25–29 and almost triple that at age 30–34. However, 80% of these regressed with adequate observation and no treatment.	High rates of preinvasive and invasive disease in young women indicate the benefit of starting screening soon after age 20.

Author/year	Methods	Results	Conclusions
Commentaries			
Szarewski 2004[18]	Commentary on Moscicki et al 2004[17].	The authors counsel against losing sight of the purpose of screening, which is to prevent cervical cancer by detecting lesions that have a high probability of becoming cancer. With such high regression rates it is pointless to screen specifically for HPV infection or LSIL. Moscicki and colleagues demonstrate how common and insignificant LSIL is in young women. They suggest that 'the strategy of colposcopy for all adolescents and young women with LSIL is unwarranted'. Evidence suggests that there is considerable anxiety and psychosexual morbidity associated with cervical screening and colposcopy. Since there is no benefit to treating young women with LSIL, the authors contend, clinicians should reflect on the basic tenet of medicine: at least do no harm.	
Fiander 2008[4]	Personal view.	Fiander notes that CIN3 rates have been increasing since the 1980s and this increase is greatest in women under age 35. She assumes a progression rate to invasive cancer of 1% per year. In Wales 300–350 cases of CIN3 are diagnosed in women aged 20–24 each year; if 1% were to progress to cancer, screening from age 25 would detect 15–17 cases annually in this age group. In England, the author argues, raising the start of screening to age 25 has dramatically reduced coverage in the 25–29 age group and this in turn will affect those aged 30, the age at which cancer incidence is at its highest.	
Cuzick 2008[6]	Editorial on Andrae et al 2008[5].	The proportion of microinvasive cancers decreases with age, from about 50% in women aged 20–29 to less than 10% in women aged over 50. This association of microinvasive tumours with younger women may explain why the overall effectiveness of screening women aged 20–29 was similar to that of screening older women. As a large proportion of microinvasive cancers are screen detected, and virtually 100% are curable, they should be considered screening successes. It would be interesting to see the Swedish data broken down by age for cancers stage IB or worse, to determine whether the protection obtained against these more severe cancers is seen in the youngest age group.	

Author/year	Methods	Results	Conclusions
Other related publications of interest			
Peto 2004[31]	An analysis of mortality trends in England and Wales before 1988 (when the national screening programme was introduced) to estimate what future trends in cervical cancer mortality would have been in the absence of screening.	The authors found that the pattern of mortality seen in birth cohorts between 1922 and 1952 showed a persistent reduction in mortality, and that this was associated with starting screening at an earlier age.	The birth cohorts present strong evidence that women who are screened regularly from a young age have much lower mortality rates than women who are screened for the first time when they are older.
IARC Handbooks 2005[48]	The handbook provides an evidence-based critical evaluation of the efficacy and effectiveness of the types of cervical cancer screening available by the end of 2004.	Sufficient evidence exists that screening every three to five years between the ages of 35 and 64 by conventional cytology in high quality programmes reduces the incidence of invasive cervical cancer by 80%. In women aged 25–34, screening at intervals of three years or less may have more limited impact. There is no evidence that screening annually in either age group results in much greater efficacy.	
Rebolj 2009[49]	A prospective observational study, using national data from the Netherlands, of incidence of cervical cancer after the third consecutive negative result.	After 10 years of follow up, the cumulative incidence rate of cervical cancer was similar in the younger age group (30–40) to that in the older one (45–54): 41/100 000 (95% CI 33–51) and 36/100 000 (95% CI 24–52) women-years at risk respectively ($P = 0.48$). The cumulative risk of CIN1 or worse was twice as high in the younger age group as in the older one.	The risk of cervical cancer after several negative results at age 50 is similar to the risk at a younger age. It is therefore not justifiable to stop screening women with negative results after age 50.

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