

Institution: Queen Mary University of London
Unit of Assessment: A1 (Clinical Medicine)
Title of case study: Cervical screening
<p>1. Summary of the impact</p> <p>Professor Peter Sasieni's team at Queen Mary showed that the efficacy of cervical screening was age-dependent. Their recommendations were adopted as policy in England in 2003 and led many other countries, including the USA, to raise the recommended age of first screening. This research was central to the 2009 re-evaluation of the most appropriate age for first screening in England, resulting in some 300,000 fewer screening tests per year in women aged 20-24, with a cost saving to the NHS of some £15 million annually. Annually, 45,000 fewer women now have an abnormal cervical screening test, of which an estimated 8,500 would have received unnecessary surgical treatment. The estimated annual saving to the NHS is £17.5 million.</p>
<p>2. Underpinning research</p> <p>Globally, cervical cancer is estimated to be the third commonest cancer in women with 530,000 cases and 275,000 deaths annually (Globocan data). Unlike other common cancers, it is not a disease of old age: most cases in England in 2009 were aged 25-49. Cervical screening has been effective in controlling cervical cancer in many countries, but results were mixed: whereas cervical cancer incidence fell by 77% in Finland (between 1962-65 and 1988-93); in England (Birmingham: 1960-66 to 1983-86) and Scotland (1963-66 to 1983-87), rates increased slightly (Gustafsson et al 1997). Recommendations also varied considerably: In the USA women were advised to go for annual screening starting "within 3 years of onset of sexual activity or age 21 (whichever comes first)" (American Cancer Society); whereas Finland recommended 5-yearly screening between ages 30 and 60 (Anttila, Nieminen EJC 2000). In the UK, there was what the media called a "postcode lottery". Some women were first invited on their 20th birthday and then 3-yearly, others 5-yearly from age 24. In Scotland, women were not invited after age 60 but in the rest of the UK screening continued until age 64.</p> <p>In 2003 Sasieni's group published a paper analysing the screening histories of 1305 women with cervical cancer and 2532 age-matched controls [1]. Five-yearly screening offered considerable protection (83%) against cancer at ages 55-69 years and even annual screening offered only modest additional protection (87%). Three-yearly screening offered additional protection (84%) over 5-yearly screening (73%) for cancers at ages 40-54 years, but was almost as good as annual screening (88%). In women aged 20-39 years, even annual screening was not as effective (76%) as 3-yearly screening was in older women. Based on these findings and the observation that screening abnormalities were particularly common in women aged 20-24 but cervical cancer was very rare under age 25, Sasieni et al recommended that the screening programme should start at age 25 and comprise 3-yearly screening to age 49 and 5-yearly screening from age 50 to 64. This publication was the first to suggest that cervical screening worked less well in young women, which was both surprising and controversial. The findings raised the possibility that cervical screening might do more harm than good in some younger women [2].</p> <p>The initial study used a case-control design [3]. Sasieni argued that this should become a routine systematic audit of the screening programme [4]. Since 2007, the audit has covered the whole of England and Wales with about 95% completeness – about 85% of cervical cancers are entered in the audit within 12 months of diagnosis [5]. Screening histories are extracted from prospectively recorded data, eliminating recall bias; controls are randomly selected from population lists and anonymously included without seeking consent, eliminating selection bias. A similar approach to auditing cervical screening has been adopted in Sweden (see reference 25 below under 'Impact').</p> <p>The decision not to screen at age 20-24 remained controversial. In 2009, the team published two further papers. One addressed the argument that screening young women must be beneficial because it leads to the treatment of thousands of cases of high-grade CIN [6]. Prof Sasieni's team demonstrated that these 'high grade CIN' were largely over-treated. The second paper looked</p>

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more closely at the impact of screening in women age 20-24 [7]. It confirmed that there was no significant benefit from screening at ages 20-24 (despite substantial benefit at older ages).

Other studies undertaken by this team in the area of cervical cancer prevention have included

- a review of epidemiological studies to establish the optimum interval for repeat testing following treatment for cervical intraepithelial neoplasia [8]
- a predictive modeling study of the impact of HPV vaccination on cancer incidence [9]
- a critical review of the literature on cervical screening in young women [10] and
- a national audit of invasive cervical cancer [5]

3. References to the research

10 papers listed of 25 relevant from this group (authors from Queen Mary in **bold**):

1. **Sasieni P, Adams J, Cuzick J**. Benefit of cervical screening at different ages: evidence from the UK Audit of Screening Histories. *British Journal of Cancer* 2003; 89: 88-93.
2. **Szarewski A, Sasieni P**. Cervical screening in adolescents – at least do no harm. *Lancet* 2004; 364: 1642-1644.
3. **Sasieni PD, Cuzick J**, Lynch-Farmery E. Estimating the efficiency of screening by auditing smear histories of women with and without cervical cancer. *British Journal of Cancer* 1996; 73: 1001-1005.
4. **Sasieni PD**. Routine audit is an ethical requirement of screening. *BMJ* 2001; 322:1179.
5. **Sasieni P, Castanon A, Louie KS**, Eds. *NHSCSP Audit of Invasive Cervical Cancer National Report 2007–2010*. NHS Cancer Screening Programmes. Sheffield 2011.
6. **Sasieni P, Castanon A, Parkin DM**. How many cervical cancers are prevented by treatment of screen-detected disease in young women? *International Journal of Cancer* 2009; 124: 461-4.
7. **Sasieni P, Castanon A, Cuzick J**. Effectiveness of cervical screening with age: population based case-control study of prospectively recorded data. *BMJ* 2009; 339: b2968. Erratum in *BMJ* 2009; 339: b3115.
8. Soutter WP, **Sasieni P**, Panoskaltzis T. Long-term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. *International Journal of Cancer* 2006; 118: 2048-55.
9. **Cuzick J, Castañón A, Sasieni P**. Predicted impact of vaccination against human papillomavirus 16/18 on cancer incidence and cervical abnormalities in women aged 20-29 in the UK. *British Journal of Cancer* 2010; 102: 933-939.
10. **Sasieni P, Castañón A, Cuzick J**. *The Impact of Cervical Screening on Young Women: A Critical Review of the Literature 2002-2009*. NHSCSP Publication No 31, February 2010. Sheffield, UK: NHS Cancer Screening Programmes, 2010.

The main funder for this work was Cancer Research UK.

4. Details of the impact

In sum, this research [a] quantified the benefit of cervical screening at different ages; [b] quantified the benefit of screening at different intervals; [c] quantified the harms of screening at different ages. The impacts listed below have been divided into impact on policy and guidance; impact on practice; reduction in harms; economic impacts; and impact on research internationally.

4a: Change in policy / guidance

UK: The cervical screening programme in England changed in 2003 to adopt the ages and intervals recommended by Sasieni's team. Policy was reviewed in 2009 and remained the same. In 2012, the National Screening Committee (representing all four nations of the UK) recommended that cervical screening should start at age 25 [11]. This was as a direct result of Sasieni's research. Reference [1] was published in July 2003. It was discussed by the Advisory Committee on Cervical Screening and, in October 2003, the Minister for Public Health announced changes to the cervical screening programme in England, including the changes to the age-range and screening intervals that the Queen Mary researchers recommended [12]. Sasieni spoke at the Minister's press conference to explain the research. Sasieni and Cuzick presented their epidemiological findings

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(references 1,2,5,6) and modelling of impact of HPV vaccination on cervical screening and cervical cancer in young women (reference 9) to an extraordinary meeting of the Advisory Committee on Cervical Screening in 2009. In line with their research, the Committee unanimously recommended against a proposal to change the age at first screen from 25 back to 20 [13].

USA: In 2012, a national guideline produced jointly by the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology recommended changing the screening interval from yearly to 3-yearly in women aged 21-29 and not screening women under 21 regardless of age of onset of sexual activity [14, 15]. The USSPTF made similar recommendations [16]. This represents a marked change in policy as a result of Sasieni et al's research. In 2002, the recommendation in USA was that cervical screening should occur from age 18 or soon after the onset of sexual activity. Adoption of the recommendations in the USA has taken longer, perhaps because of a long tradition of annual screening. Whilst US guidance is still not exactly in line with the research evidence, it was influenced by the findings of Sasieni's team and represented a shift in a more evidence-based direction.

4b: Change in public health practice

The percentage of women screened in different age groups in 2002-03 in England was 22.4% at age 20-24, 25.6% at age 25-29, and 18.8% at age 55-59, representing a mix of three- and five-yearly screening from age 20-64 [17]. In 2010-11 (and 2011-12) those percentages were 2.1% (1.7%) (age 20-24), 27.8% (28.3%) (age 25-29), and 15.3% (15.1%) (age 55-59) [18, 19]. Thus this research has not only resulted in a new policy but that policy has been implemented and has had a clear impact on cervical screening in England.

4c: Reduction in harms

There were some 53,000 abnormal (ie borderline changes or worse) screening tests in women aged 20-24 in England in 2002-03 [17]. It is reasonable to infer that most of these women would have been anxious. In 2010-11 there were fewer than 8,000 such tests [18], a reduction of around 45,000. All women with moderate dyskaryosis or worse (N=9702 aged 20-24 in 2002-03) were referred to colposcopy and approximately 22% of women with borderline changes (N=23,020) and 43% of those with mild dyskaryosis (N=20,950) were referred (after a repeat abnormal test) [17]. Thus it is estimated that some 20,000 fewer women aged 20-24 will have been referred to colposcopy in 2010-11 compared to 2002-03. At all ages in 2002-03, 16.8% of women referred with persistent low-grade cytology and 73.4% of women referred with moderate dyskaryosis or worse had high-grade disease on histology (CIN2 or worse) [17]. Certainly all these women would have been offered treatment. Consequently, as a result of this research an estimated 8,500 women aged 20-24 will have avoided having unnecessary treatment each year. The team has quantified the harms and benefits of starting screening at 20 rather than at age 25 and a table laying out the numbers affected; this is available on the National Screening Committee website [20]. A recent US editorial 'Primum non nocere' acknowledged the potential harms of cervical screening in inappropriate groups and/or at over-frequent intervals [21].

4d: Cost savings to the NHS

The cost saving from not screening some 350,000 women each year is approximately £17.5 million [22]. The impact in the USA has been less dramatic, but because the population is larger and was previously encouraged to have annual screening from age 18, the economic impact has been even greater. The Centre for Disease Control and Prevention [23] reports that an additional 23-24% of 18 and 19 year old women (i.e. some 1 million women) have never had a Pap smear and an additional 16% of 20-24 year old women (about 1.75 million women) have not had a smear in the last year. Thus the change in policy had resulted in about 2.75 million fewer Pap smears in women aged 18-24 in the year 2010. It is difficult to estimate the cost of cervical screening in the USA, but it is likely that the annual saving is over \$200 million.

4e: Informing further research internationally

Soon after the 2003 publication [1], Sasieni was contacted by colleagues in Italy and invited to work with them; the following year a paper was published broadly confirming the UK finding on Italian data [24]. A routine audit of cervical screening has been set up in Sweden [25]. The Wolfson team is coordinating an international collaborative audit of cervical screening programmes and

analysis of routine screening data. The design of the cervical screening audit is now being adapted and employed to evaluate routine breast colorectal screening [26].

5. Sources to corroborate the impact

11. UK National Screening Committee. Cervical cancer consultation Q&A. <http://www.screening.nhs.uk/cervicalcancer-qa>.
12. Advisory Committee on Cervical Screening statement 2003. Modernising the NHSCSP: Introduction of LBC and change in national policy. <http://www.cancerscreening.nhs.uk/cervical/news/009.html>
13. Advisory Committee on Cervical Screening statement 2009. <http://www.cancerscreening.nhs.uk/cervical/cervical-review-minutes-20090519.pdf>
14. National guidelines in USA: Saslow DS et al. Guidelines for the Prevention and Early Detection of Cervical Cancer. *CA Cancer J* 2012; 62: 147-172. <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&listuids=22422631>
15. Kizer N, Peipert JF. Cervical Cancer Screening: Primum Non Nocere. *Annals of Internal Medicine* 2012; 156: 896-897. <http://www.annals.org/content/early/2012/03/14/0003-4819-156-12-201206190-00425.full>
16. Moyer VA. Screening for Cervical Cancer: US Preventive Services Task Force Recommendation Statement. *Annals of Internal Medicine* 2012. <http://annals.org/article.aspx?articleid=1183214>
17. Department of Health Bulletin 2003/24. *Cervical Screening Programme, England: 2002-03*. http://www.dh.gov.uk/en/Publicationsandstatistics/Statistics/StatisticalWorkAreas/Statisticalhealthcare/DH_4080876
18. The NHS Information Centre. *Cervical Screening Programme, England: 2010-11*. 2011. <http://www.ic.nhs.uk/statistics-and-data-collections/screening/cervical-screening/cervical-screening-programme--england-2010-11>
19. The Health and Social Care Information Centre. *Cervical Screening Programme, England: 2011-12*. 2012. <http://www.ic.nhs.uk/statistics-and-data-collections/screening/cervical-screening/cervical-screening-programme--england-2010-11>
20. Sasieni P. Comparison of screening from age 20 and age 25: Table of harms and benefits. 2012. <http://www.screening.nhs.uk/cervicalcancer> (see Appendix 2).
21. Kizer N, Peipert JF. Cervical Cancer Screening: Primum Non Nocere. *Annals of Internal Medicine* 2012; <http://www.annals.org/content/early/2012/03/14/0003-4819-156-12-201206190-00425.full>
22. NHS Cervical Screening Programme. How much does the programme cost and how is it funded? <http://www.cancerscreening.nhs.uk/cervical/publications/pm-04.html>
23. Centers for Disease Control and Prevention. Cervical Cancer Screening Among Women Aged 18–30 Years – United States, 2000–2010. *Morbidity and Mortality Weekly Report* 2013; 61: 1038-42. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6151a2.htm>
24. Zappa M, Visioli CB, Ciatto S, Iossa A, Paci E, Sasieni P. Lower protection of cytological screening for adenocarcinomas and shorter protection for younger women: the results of a case-control study in Florence. *British Journal of Cancer* 2004; 90: 1784-1786. (Analysis of Italian cervical screening data, inspired by Sasieni et al's research and which confirmed their findings).
25. Andrae B, Kemetli L, Sparen P, Silfverdal L, Strander B, Ryd W et al. Screening-preventable cervical cancer risks: evidence from a nationwide audit in Sweden. *Journal of the National Cancer Institute* 2008; 100: 622-629.
26. Research protocol linking cervical with breast and colorectal screening in UK. <http://prp.dh.gov.uk/files/2012/02/PRP-commissioned-projects-Feb-2012.pdf>