



**UK National
Screening Committee**

Screening for Anal Cancer

External review against programme appraisal
criteria for the UK National Screening Committee
(UK NSC)

Version: Two

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The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at <http://www.screening.nhs.uk/policies> and the policy review process is described in detail at <http://www.screening.nhs.uk/policyreview>

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Glossary of Acronyms

AIN	Anal Intraepithelial Neoplasia
AIN 1	Mild dysplasia
AIN 2	Moderate dysplasia
AIN 3	Severe dysplasia (sometimes referred to carcinoma in situ)
ASIL	Atypical Squamous Intraepithelial Lesion
APR	Anoperineal resection
ARC	Anal-rectal anoscopy
CMT	Combined modality therapy
CT	Chemotherapy
HSIL	High-grade Squamous Intraepithelial Lesion
HPV	Human papillomavirus
LSIL	Low-grade Squamous Intraepithelial Lesion
MSM	Men who have sex with men
MSW	Men who have sex with women
RT	Radiotherapy
SCC	Squamous cell carcinoma
WLE	Wide local excision

Glossary of Terms

Anal Pap	A screening test that involved inserting a swab into the anal canal in order to secure fixed cell samples for cytological examination.
Anal Intraepithelial Neoplasia (AIN)	An abnormal cell growth that may develop into cancer
Anoscopy	A technique to view the inside of the anus or rectum
Cytology	Study of the origin, structure and function of cells
Dysplasia	The proliferation of abnormal cells
Efficacy	Ability to produce the desired affect
Epidemic	Spreading rapidly and extensively
Epidemiology	The branch of medicine that deals with the study of the causes, distribution, and control of disease in populations
Histology	Study of tissue structure
Incidence	Frequency of a disease
Morbidity	The rate of incidence of a disease
Neutropenic sepsis	Inflammatory infection in normally sterile parts of the body, accompanied by fever, occurring in people with a low neutrophil count. Neutrophils play an important role in maintaining a fully functioning immune system in the body.
Prevalence	Number of cases of a disease
Sensitivity	The proportion of people with a disease who have a result
Specificity	The proportion of people without disease who have a negative test result

Introduction

The Review

1. This paper reviews screening for anal cancer in adults (aged 18 years old plus) in the UK general population. The review was requested by the UK National Screening Committee (UK NSC) to assess whether screening for anal cancer meets the UK criteria for recommending a formal screening programme, following the release of the Czoski-Murray et al. study (2010) which focused on the '*Cost-effectiveness of screening high risk HIV-positive men who have sex with men and HIV positive women for anal cancer*'.

The Methodology

2. This review has followed the standard methodology for assessing the potential for screening the general population for serious health conditions. Its principal aim therefore was to focus on screening studies of the general population rather than high risk groups alone. This focus was adopted to ensure any potential changes in policy or practice as a result of the review are not specific to one particular group in society, and relevant to the general population. As other pre-existing conditions may be present in groups with a higher risk, this area would need to be looked at separate to that of the general population. However, the comprehensive work of Czoski-Murray (2010) covers much of this.
3. The publications included in this review were provided to SERIO by the UK NSC, who identified literature through a systematic search of Medline (OvidSP), Embase, PsychINFO, Cinahl and the Cochrane Library. Potentially relevant grey literature was also identified by SERIO through an online search. Details of both search strategies are provided in Appendix One. All potentially relevant literature was then appraised against the UK NSC criteria.

Appraisal against UK NSC Criteria

The Condition

Criterion 1: The condition should be an important health problem

4. Anal cancer is a disease in which cancer cells are present in the anus. The anus extends from the perianal area to the end of the rectum and is sometimes referred to as the anal canal. It is lined with small flat cells called squamous cells (Cancer Research UK, 2012a). Cancer of these cells, Squamous Cell Carcinomas (SCC), is the most common type, accounting for 80% of anal cancers (Cancer Research UK, 2012b).
5. The type of cells lining the anal canal change from squamous to non-squamous (transitional or glandular) cells at the point at which it meets the rectum. This transitional zone is called the dentate line. A rarer form of anal cancer, adenocarcinoma can develop in the glandular cells in this area. Other rarer types of anal cancer include: Basal Cell Carcinomas (which largely develops in the perianal skin); and, melanoma which develops in the melanin of the anal lining (American Cancer Society, 2012).¹
6. Anal cancer is a rare disease. In 2010, there were 916 registrations of newly diagnosed cases of malignant neoplasm of the anus and anal canal in England, accounting for 0.34% of all malignant neoplasms (ONS, 2012).²
7. The rate of newly diagnosed cases is higher amongst females than males (1.6 per 100,000 of the population compared to 1.2 per 100,000) and increases with age for both genders.³ 51.5% of newly diagnosed males and 50.8% of females are aged over 65 years (ONS, 2012).
8. The incidence of anal cancer is increasing (Castor, 2012; Dindo, 2010; Uronis and Bendell, 2007). For example, Brewster et al. (2006) in an analysis of the Scottish Cancer Registry statistics found that the age-standardised incidence of squamous cell carcinoma of the anus more than doubled between 1975-1979 and 1998-2002. In England, Renehan et al. (2009) found that the age-sex-standardised incidence rates for men were 0.39 in 1971 and 1.11 in 2005, and 0.32 and 1.52 for females.

¹ Please note that the literature abstracts do not consistently specify the type of anal cancer studied. References to anal cancer in this report are assumed to be SCC unless otherwise stated.

² Excluding non-melanoma skin cancer.

³ Age standardised.

Criterion 2: The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

9. Anal cancer is preceded by Anal Intraepithelial Neoplasia (AIN) (Abbas et al. 2010; Ajaz et al. 2007; Gaisa and Goldstone, 2011). Low grade AIN is not considered pre-cancerous and often does not require treatment; high grade versions however are considered at risk of becoming cancerous. The most advanced stage of AIN (carcinoma in Situ), is considered by some as the early stages of cancer (American Cancer Society, 2012).
10. Although there are similarities between cervical and anal cancer (Fox, 2006), the natural history of anal cancer is unclear (see Ajaz et al. 2007; Czoski-Murray et al. 2010; Pineda et al. 2008; Shepherd, 2007). More specifically, the rate of progression from AIN to invasive anal cancer (SCC) is largely unknown (Darragh, 2011).
11. Anal cancer warning symptoms are also, at times, non-existent, with 20% of patients having no tumour-specific symptoms (Abbas, 2010). However, between 50% and 69% of sufferers experience rectal bleeding, and around 30% experience pain or sensation of a rectal mass (Abbas et al, 2010; Wong, 2011). A further complication in the diagnosis of anal cancer is that while the majority of anal cancers progress slowly, some are commonly mistaken for benign conditions such as haemorrhoids (Wietfeldt and Thiele, 2009).
12. Similar to cervical cancer, Human papillomavirus (HPV) is a causal agent and associated risk factor for anal cancer; HPV prevalence rates in the diagnosis of this condition have been reported to range between 76% and 97% (Khalid et al. 2011; Chaturvedi, 2010; De Vuyst et al, 2009; Franceschi, 2009). There are more than 100 HPV strains, with approximately 30 affecting the genital tract through sexual transmission; HPV types are divided into high and low risk types based on the risk of developing cancer (Olsen, et al, 2011). HPV16, followed by HPV18, are the most common types found in cases of anal cancer. Abramowitz et al. (2011) found that HPV16 and 18 was present in 78% of all cases and Hoots et al. (2009) reported their prevalence in 72% of cases.
13. Although still small numbers, some groups have been identified as being at a higher risk of anal cancer. These are discussed below, although it must be highlighted that much of the literature on anal cancer risk groups relate to SCC; anal melanoma has no known risk factors/groups (Singer, 2006).
14. Men who have sex with men (MSM) are at a higher risk of contracting HPV, compared to men who have sex with women (MSW). Anal cancer rates among this group are increasing as stated by Darragh (2011) "although rare, the incidence of anal cancer is alarmingly high and continues to increase in high-risk populations, particularly men who have sex with men". Nyitray et al. (2011) found HPV in the anal canal in 47.2% of the 176 MSM in their study, compared to 12.2% of MSW. Ortoski and Kell (2011) also stated that most MSM, with a history of anal receptive intercourse, will carry HPV, but also reported that it is not just receptive anal

intercourse that is a risk factor for contracting HPV. Nonsexual behavioural risk factors include hand carriage, as in hygiene care, from the genitals to the anus and transference from objects of any kind used to manage genital HPV infection. Further research will be needed to follow up this recent finding. Frisch et al. (2003) (as reported in Czoski-Murray et al. 2010) in a retrospective cohort study in Denmark also found that the overall risk of cancer among 3391 men in registered homosexual partnerships increased twofold (RR = 2.1, 95% CI 1.8 to 2.5, n = 139) compared to men not in a homosexual partnership.

15. *Those who are HIV-positive* have also been identified as being at higher risk of anal cancer, largely due to increased likelihood of developing AIN (Ortoski et al. 2011; De Vuyst et al. 2009; Dindo et al. 2010; Uronis, and Bendell, 2007). Porche (2006) reported that while it is estimated that 35 of every 100,000 men who have sex with men will develop anal cancer, a significant 70 of every 100,000 women and men who are HIV positive will develop the disease. As Czoski-Murray et al. (2010, p25) describe, HIV infection has “*a profound effect on the immune system. It is the immune system that fights infection but also this same system guards against dysplastic changes. It is this latter role that explains much of the increase cancer risk in patients with HIV and AIDs.*”. Mitra et al. (2012) have recently stated that anal cancer amongst HIV-positive MSM has reached epidemic proportions.
16. *Post-transplant immunosuppression* also presents an increased risk for this type of cancer. The MAS (2007) study notably reported that the risk of rare, virus associated cancers, in post-transplant patient is increased several hundred fold (compared to age matched populations). It presents particularly higher risks for cancers of the lymphoid system, skin, and the urogenital and anogenital tracts (associated viruses including Epstein-Barr; HPV and Hepatitis B). There is, however, a higher prevalence of these cancers in immunosuppressed females than males, which contrasts with the trend for most other post-transplant cancers (MAS, 2007).
17. *Women who have anal sex* also have an increased risk of anal cancer. Frisch et al. (1997), in a study using population control studies in Denmark and Sweden, showed that of the three groups involved in their research (one control group and two groups having anal cancer or carcinoma in situ) women with anal cancer were more likely to have anal sex. Women with anal cancer were reported to also have more sexual partners and a history of sexual transmitted diseases.
18. *Those with a history of genital dysplasia* are also at a higher risk of developing anal cancer. Goodman et al. (2010) conducted a longitudinal cohort study of 751 sexually active women and found that “*the RR [relative risk] of acquiring an anal HPV infection after a cervical infection with HPV of the same genotype was 20.5 (95% CI, 16.3-25.7), compared with women without a previous anal/cervical infection with HPV.*” (p1331) This led Goodman to suggest that the anus serves as a reservoir for HPV infection at other sites. Similarly, Santoso et al (2010), found that the prevalence of AIN amongst 205 women with intraepithelial neoplasia on the cervix, vagina or vulva was 12.2%. In addition, the MAS (2007) study, reported a 6.3% likelihood of developing secondary anal cancer amongst a study group of women with cervical cancer.

19. Other anal cancer risk factors include the presence of lichen sclerosus (Henquet, 2011); smoking; and a high number of sexual partners (Gorez, et al., 2008).
20. In summary, while the natural history of anal cancer is still not fully understood and symptoms are not always present, there is a detectable risk factor (HPV) which has led to a good level of knowledge of groups in society who have a higher risk of developing the disease.

Criterion 3: All the cost-effective primary prevention interventions should have been implemented as far as practicable

21. The main focus of primary prevention relates to the association between HPV and anal cancer. This was identified as the most commonly investigated primary prevention intervention within the literature provided by the UK NSC.
22. In the UK, a national HPV vaccination programme was introduced in 2008 for 12 and 13 year old females, and also to females aged 13-18 in a three-year catch up programmes to help prevent cervical cancer. The immunisation level is currently at 80% with modelling suggesting that the additional benefits of vaccinating boys is not cost effective. Males, therefore, are not included within the national programme.
23. The benefits of the HPV vaccination go beyond the prevention of cervical cancer and include other HPV related cancers. For example, based on the prevalence of HPV16 or 18 in vulvar, vaginal or anal cancers, Hampl et al. (2006) concluded that the prophylactic HPV vaccination, which protects against these HPV types, could reduce the risk of the intraepithelial lesions in the lower genital tract in women by two thirds. In a further study of vaccinating 12-year old females, it was found *“the potential benefits of preventing anal, vaginal, vulvar, and oropharyngeal cancers offer nontrivial improvements in the estimated cost-effectiveness of the HPV vaccination.”* (Chesson et al. 2008, p249).
24. The effects of extending the HPV vaccination programme have been studied, most frequently in relation to the inclusion of males, and although some benefits have been identified, the impacts of a population-based programme are unclear (Henquet, 2011). It has also been highlighted that the vaccine is only effective in preventing cancers amongst those unexposed to HPV types included in the vaccine, so the actual population impact will be lower on naive populations (Paavonen, 2008).
25. In relation to the inclusion of males within a vaccination programme, the provided evidence indicates that there are benefits in terms of preventing HPV-associated cancers / health conditions. Jenson et al. (2011) showed that the vaccination of males aged 9-26 years old against genital warts is beneficial and cost effective, based on mathematical modelling, but dependant on the vaccination of females in the population being less than 80%. The authors conclude that further research is required to fully understand such benefits.
26. One study conducted in Australia reported that a female-only HPV vaccination programme will positively impact upon males by reducing HPV 16 infections by 68% by 2050, which in turn would lead to a 14% reduction in head, neck and anogenital cancers (Smith et al. 2011). However, the authors concluded that a female-only

programme would provide a maximum vaccine-conferred benefit of 73% to males, relative to a male and female vaccination programme.

27. Garland et al. (2010) in a review of HPV prevention strategies concluded that the most cost-effective strategy is to include men and/or boys within a vaccination programme of 12-year old females (with catch-up vaccination of 12-24 year olds). This strategy is projected to reduce HPV16 infection in females by 88-94% and 68-82% in males by 2050. However, cost-benefit analyses were reported to be needed to determine efficacy at population level.
28. The cost-effectiveness and benefits of extending current HPV vaccination programme is the subject of continuing investigation. It is also important to emphasise that such vaccinations are only effective in preventing HPV related anal cancers. There is less research relating to the primary prevention interventions of non-HPV related anal cancers.

Criterion 4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

This criterion is not applicable.

The Test

Criterion 5: There should be a simple, safe, precise and validated screening test

29. The evidence provided identifies two principle screening methods for the pre-cursors of anal cancer:⁴⁵ anal-rectal cytology (ARC) and anoscopy. ARC is similar to a cervical smear, and therefore often referred to as an anal Pap smear, and uses a swab or cytobrush to collect cells from the anal canal. The cell sample can be prepared either in liquid or the conventional smear test method of fixing the cells onto a glass slide; although Bean and Chieng (2010) state that the former method is preferred. In anal-rectal anoscopy, the wall of the anus and lowest portion of the rectum is visually examined allowing the identification of abnormalities. The use of this screening method has been recommended where ARC identifies an abnormality (Chiao et al, 2006; de Carvalho et al. 2011).
30. In the UK, the conventional Pap smear method has been replaced with Liquid Based Cytology (LBC), involving a swab being taken from the anal canal which is then

⁴ This refers to HGAIN.

⁵ Please note that this section of the review focuses on the pre-cursors of anal cancer largely because this is what screening programmes specifically target. Other sections of the review present data directly for anal cancer (as the fully established condition) due to the underlying nature of the criteria. For example, sections on screening practice will focus on HGAIN as this is the relevant topic, other sections on treatment, however, will focus on treatment for anal cancer, not HGAIN, as anal cancer is the condition which is under review.

preserved in a liquid based solution (offering the added advantage of filtering off any impurities in sample). Although a small number of studies have investigated the use of LBC in high risk groups (see Anderson et al., 2008 or Reynolds et al., 2009), no evidence was found in the literature on the preciseness or validity of its use in general population studies.

31. Different sensitivity and specificity rates were reported in the evidence. A recent meta-analysis of 33 cervical and 11 anal screening studies found that anal cytology was *"somewhat less discriminating than cervical cytological screening"* (Mathews et al, 2011, p249).
32. However at least two studies provided to the review team suggest that ARC is comparable to cervical cytology in both respects (Bean et al. 2010; Chiao et al. 2006). Bean et al., (2010) state that *"the sensitivity and specificity of a single anal-rectal cytology specimen is comparable with that of a single cervical cytology test, but cytological interpretations do not always correlate with lesion severity."* (p538) Chiao et al. (2006) review found that the sensitivity of anal Pap smears ranged from 69% to 93%, and the specificity from 32% to 59% (p225). The authors concluded that although the anal Pap smear has similar accuracy to the cervical Pap smear, the benefits of screening to survival rates were not yet fully understood, warranting the need for further research in this area.
33. Nathan et al (2010) assessed cytology using samples from 395 patients, 212 of whom were HIV-positive. The sensitivity of cytology to detect disease was 70% and specificity 67% (based on 288 histology results). They found that the sensitivity of anal cytology was dependent on the area of disease and HIV infection, and suggested that these factors may explain previously reported sensitivity differences.
34. Perhaps unsurprisingly given the range of groups identified as being at higher risk of anal cancer, many of the provided studies assess screening methods in high risk groups only. Less is known about the sensitivity and specificity of the tests in the general population. There is no evidence to suggest that the test is not safe. Research into the precision of screening tests is on-going and the relationship between screening and outcomes is not yet fully understood.

Criterion 6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

35. No defined or agreed test cut-off levels were identified in the literature.

Criterion 7: The test should be acceptable to the population

36. Replicating the Czoski-Murray et al. (2010) review, no evidence on appropriateness of tests to the population was identified in the literature.

Criterion 8: There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals

37. Anal cancer was included within the scope of the 2004 NICE cancer service guidance 'Improving Outcomes in Colorectal Cancers'. However, there is no policy on diagnostic investigation in the UK.
38. The Northwest Pennsylvania Rural AIDS Alliance of Clarion University of Pennsylvania has developed and implemented an anal Pap test screening policy, which provides an example of a diagnostic pathway to precursors of anal cancer. This is summarised in Table One below (taken from Ortozki and Kell, 2011, p541). Please note that it is based upon high risk groups and not the general population. Also note, this is based on the US Bethesda 2001 system where AIN is split in to three grades as opposed to 2, such as in the UK diagnostic system.

Table One: Screening pathway

Anal Cytology	HPV Test*	Recommendation
New	New	Await results
Negative	Negative	Annual screen
Negative	Positive	6 month rescreen
ASCUS	Negative	6 month rescreen
ASCUS	Positive	Refer for HR anoscopy
LSIL or HSIL	Negative or Positive	Refer for HR anoscopy

* Positive identifies at least 1 of 13 oncologic, high risk types.

Source: Ortoski and Kell, 2011

Criterion 9: If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out

39. This criterion is not applicable.

Criterion 10: There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

40. Localised anal cancers are commonly treated with chemoradiation (CRT), a combination of radiotherapy and chemotherapy. The standard chemoradiation regime is fluorouracil (5-FU), mitomycin and radiation (Abbas et al., 2010; Fraunholz et al. 2010). More advanced cancers can be treated with surgery and chemoradiation, with resection or salvage surgery (removal of the anus and rectum and permanent colostomy) reserved for persistent or recurrent disease (Robb, 2006; Uronis and Bendell, 2007; Bilimoria et al. 2008; Fesneau et al. 2010).

41. There has been an improvement in the treatment of anal cancer in the UK over recent decades and a reduction in anal cancer deaths (James, 2008). Improving survival rates, in England and Wales, have been attributed to improvements in disease staging, diagnosis technique or treatment (Jefferys et al. 2006).
42. Research has demonstrated a strong association between early disease stage, tumour size and treatment success (Czoski-Murray et al. 2010). In a study by Myerson et al. (2009) treatment success was specifically linked with T and N stage progression, with an 88.5% 5 year disease free survival rate at T1-T2NO, 70.1% for T3NO, and 52.7% for stage III. Bentzen et al. (2011) in an unselected national cohort study in Sweden between 2000-2007 has also concluded that (chemo) radiotherapy is satisfactory for patients with early-stage tumours. However, the authors highlight the need to improve results for patients with locally advanced disease.
43. The prognosis for rarer forms of anal cancers, such as melanoma, are less promising and due to the severity of these conditions the link between long term treatment success and disease progression at diagnosis is less clear. While very early diagnosis may provide better treatment outcomes, most anal melanomas present at an advanced (often metastatic) state, and long term survival even at stage II diagnosis is poor (Belli, et al., 2009; Singer and Much, 2006). Furthermore, while early diagnosis may improve anal cancer prognosis for more common conditions such as SCC, more research is needed to fully account for all the issues associated with different treatment pathways.
44. Highlighting the controversies around anal cancer treatment, Glynne-Jones, et al. (2011) has reported that a 'one-size-fits-all' approach for all stages of anal cancer is inappropriate, and early tumours are probably currently overtreated and progressed lesions might merit escalation of treatment. Franhoultz et al. (2006) also highlighted that the most effective treatment regime is yet to be found. Similar uncertainties have been put forward in the treatment of precursors to anal cancer (AIN): Herat, et al. (2007) argues that treatment approaches are not well validated, and that while successful treatment of anal intraepithelial neoplasia may reduce the risk of subsequent development of anal cancer, current therapies for this condition may be associated with treatment-related morbidity.
45. While the literature does indicate that early treatment improves the likelihood of successful treatment outcomes, more research is needed to fully understand this area.

Criterion 11: There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

46. There is not an agreed policy covering which individuals should be offered treatment and the appropriate treatment to be given, however, anal cancer was included within the scope of the 2004 NICE cancer service guidance '*Improving Outcomes in Colorectal Cancers*'. Although it does not refer to those individuals that should receive treatment, it identifies the following as the primary treatment:

“Concurrent chemoradiotherapy, using mitomycin C, 5-fluorouracil and radiation, is appropriate for most patients. Other forms of treatment, such as surgical excision, may be considered by anal cancer multidisciplinary teams (MDTs), but surgery is usually reserved for salvage. There are still some areas of uncertainty about optimum treatment, and eligible patients should be encouraged to participate in trials such as the Cancer Research UK (CRUK) ACT 2 trial.” (p86)

Criterion 12: Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme

47. As stated in paragraph 41 above, anal cancer was included within the scope of the 2004 NICE cancer service guidance *Improving Outcomes in Colorectal Cancers*. The guidance recommends that *“all patients with anal cancer, including those who have undergone local excision, should therefore be referred to multi-disciplinary anal cancer teams which can provide specialist management.”* (p86)

Criterion 13: There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an “informed choice” (e.g. Down’s syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened

48. In line with the earlier reviews conducted by the MAS (2007) and Czoski-Murray et al. (2010), no such RCTs were identified in the literature that specifically related to screening and impact on morbidity or mortality.

Criterion 14: There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public

49. No evidence has been identified by the review team that is relevant to this criterion.

Criterion 15: The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)

50. No evidence was identified and therefore there is no update to the conclusions of Czoski-Murray et al. (2010): *“The screening process does not appear to present any physical harm; however, any psychological effects of anal cytology screening or pap smears have not been evaluated in the studies included in this review.”* (p70).

Criterion 16: The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource

51. Czoski-Murray et al. (2010) concluded that “the reference case cost-effectiveness model found that screening for anal cancer is very unlikely to be cost-effective. A key determinant of this finding was the low observed incidence of anal cancer in the UK population.” (p70)
52. This is also supported by the research of Gaisa et al. (2011) who critically reviewed the literature and conducted a comparative analysis/discussion of treatment modalities for anal HPV. Their conclusion was that cost effectiveness was apparent only for high risk groups (MSM): “Anal cytology screening for high-grade dysplasia has been shown to be sensitive and cost-effective in men who have sex with men; any abnormal anal cytology result should be followed with high-resolution anoscopy.” (p21)

Criterion 17. All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available

53. While there is an established and common method of treatment for anal cancer (see criterion 10), the literature and associated research remains focused on proving or confirming the long term effects and success of current treatment pathways or validating alternative approaches. In this context, the cost effectiveness of treatment methods remain very much in the backdrop, if at all mentioned, in the range of literature.
54. Regardless of its cost-effectiveness, there remains a range of controversies over the treatment options for anal cancers. In relation to anal melanoma, Heeney, 2011 states that there is “no convincing evidence to indicate that radical resection of primary anorectal melanoma is associated with improvement in local control or survival, and local excision is an acceptable treatment option”, and that “unfortunately prognosis for patients with this disease remains poor despite choice of treatment strategy with overall five year disease-free survival less than twenty percent in most studies.” (p27)
55. Similarly, regarding the more common types of anal cancer such as SCC, treatment options are often compromised by morbidity risk and other local side effects such as neutropenia and sepsis (Rabbani, 2010). As Zagar (2010) concluded, “definitive chemotherapy is fraught with considerable treatment-related morbidities. With the advent of intensity-modulated radiation therapy (IMRT), many oncologists are beginning to utilize this technology in the treatment of anal cancer in order to decrease these toxicities while maintaining similar treatment efficacy”. (p815)

Criterion 18: There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards

56. This has not been established for anal cancer although quality assurance guidelines for the screening of other cancers (such as cervical screening) will provide a model for their development.

Criterion 19. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme

57. This has not been established for anal cancer and is not covered in the evidence review.

Criterion 20. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice

58. This criterion was not discussed in the literature sourced. Several of the cancer charities provide evidence based information regarding anal cancer testing and treatment on their websites.

Criterion 21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public

59. This criterion was not discussed in the literature and in addition the sensitivity of testing and screening intervals continues to be investigated.

Criterion 22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members

60. This criterion is not applicable.

Conclusions

61. Rates of anal cancer have increased in recent decades, particularly amongst those identified as being at a higher risk, but it remains a rare form of cancer across the general population with only 916 registrations of new cases in 2010. It is more common amongst women and increases with age. Other groups with higher levels of risk include, women with a history of genital dysplasia, men who have sex with men, HIV-positive men and women, and finally people with immunosuppression such as post-transplant patients. Although anal cancer is generally accepted to have a

natural history similar to that of cervical cancer, understanding of it is still underdeveloped.

62. Screening methods for anal cancer include anal-rectal cytology and high-resolution anoscopy. Variable sensitivity and specificity rates have been reported in the research to date. There is no research on the acceptability of these tests to the general public although the literature does not suggest that they are not considered safe. The research to date indicates that the benefits of screening to survival rates are not yet fully understood. Much is still unknown about this cancer and the development of it.
63. HPV is a known cause of anal cancer, with research showing that the quadrivalent HPV vaccine (currently offered to females to prevent cervical cancer) offers protection against the high risk types of HPV. The HPV vaccine provides an important primary prevention tool against anal cancer, with the vaccination of females offering vaccine conferred benefits to males. There is some discussion in the literature of extending the vaccination programme to males but there are considerable concerns relating to the benefit of taking this approach.
64. There is still much that is unclear and it is difficult to assess how a general population screening programme would provide a cost effective approach and benefit.

Implications for policy

65. Based on the evidence provided, further research is required before the NSC's criteria for assessing the need for a population screening programme can be met. The Czoski-Murray et al. (2010) review for the HTA stated that: *"It is clear that many of the criteria for assessing the need for a population screening programme have not been met for anal cancer. There is limited knowledge about the epidemiology and natural history of the disease, along with a paucity of good-quality evidence concerning the effectiveness of screening for anal cancer. The absence of such data, combined with the possible reluctance of high-risk groups to attend an anal cancer screening programme, makes introduction of population-based screening for anal cancer difficult."* (p73). This review of evidence supports the HTA finding.

Implications for research

66. Further research is required to improve understanding of anal cancer. The research to date has focused on groups of a higher risk of anal cancer with less known about those that develop anal cancer in the general population. In addition, further research should aim to provide:
 - More detailed understanding of the variation in sensitivity and specificity of screening tests;
 - Economic evaluation of potential screening programmes to determine the cost effectiveness of the tests;

- An understanding of whether the test is acceptable to the general public and high risk groups;
- Understanding of the benefits of screening to survival rates, incidence and mortality; and,
- Understanding of the impact of the HPV vaccine on anal cancer rates.

Appendix One: literature search strategy

1. The UK NSC conducted a literature search on anal cancer screening, and related issues, during 2011-12. Sources searched included: Medline; Embase; Cochrane Library; PsycINFO; Cinahl; BNI; and, Web of Science. A summary of the search areas, terms and results provided to the SERIO by the UK NSC, are shown below:

Epidemiology of anal cancer:

- exp Anus Neoplasms/ (4295)
- anus neoplasm\$.tw. (3)
- neoplasm\$, anus.tw. (0)
- anal neoplasm\$.tw. (20)
- neoplasm\$, anal.tw. (3)
- anal cancer\$.tw. (950)
- cancer\$, anal.tw. (30)
- cancer of anus.tw. (2)
- anus cancer\$.tw. (12)
- cancer of the anus.tw. (94)
- anal squamous carcinoma.tw. (18)
- circumanal gland neoplasm\$.tw. (1)
- exp Anal Gland Neoplasms/ (161)
- neoplasm\$, anal gland.tw. (0)
- anal gland neoplasm\$.tw. (0)
- neoplasm\$, circumanal gland.tw. (0)
- neoplasm\$, perianal gland.tw. (0)
- perianal gland neoplasm\$.tw. (2)
- OR/1-18 (4566)
- exp Epidemiology/ (18954)
- exp Natural History/ (532)
- epidemiolog\$.ti. (83427)
- inciden\$.ti. (75909)
- prevalen\$.ti. (72095)
- Incidence/ (150210)
- Prevalence/ (156226)
- OR/20-26 (445783)
- 19 AND 27 (316)
- limit 28 to yr="2006 -Current" (149)

The test:

- anal cytologic screening.tw. (5)
- anoscopy.tw. (186)
- anal cytology.tw. (115)

- liquid based cytology.tw. (651)
- Mass Screening/ (72995)
- Occult Blood/ (3914)
- Sigmoidoscopy/ (4021)
- Colonoscopy/ (15321)
- mass screening.tw. (4136)
- occult blood.tw. (3505)
- Diagnostic Tests, Routine/ (5866)
- diagnos\$.tw. (1420349)
- diagnosis/ (16201)
- diagnostic us\$.tw. (3257)
- "reproducibility of results"/ (226284)
- Observer Variation/ (27177)
- di.fs. (1776582)
- sigmoidoscop\$.ti,ab. (3438)
- colonoscop\$.ti,ab. (15573)
- reproducibility of results.ti,ab. (625)
- observer variation\$.ti,ab. (866)
- OR/30-50 (2808407)
- exp Anus Neoplasms/ (4295)
- anus neoplasm\$.tw. (3)
- neoplasm\$, anus.tw. (0)
- anal neoplasm\$.tw. (20)
- neoplasm\$, anal.tw. (3)
- anal cancer\$.tw. (950)
- cancer\$, anal.tw. (30)
- cancer of anus.tw. (2)
- anus cancer\$.tw. (12)
- cancer of the anus.tw. (94)
- anal squamous carcinoma.tw. (18)
- circumanal gland neoplasm\$.tw. (1)
- exp Anal Gland Neoplasms/ (161)
- neoplasm\$, anal gland.tw. (0)
- anal gland neoplasm\$.tw. (0)
- neoplasm\$, circumanal gland.tw. (0)
- neoplasm\$, perianal gland.tw. (0)
- perianal gland neoplasm\$.tw. (2)
- exp Precancerous Conditions/ (33935)
- preneoplastic condition\$.tw. (105)
- Papillomavirus Infections/ (12421)
- human papillomavirus\$.ti,ab. (19042)

- infectious human wart virus\$.ti,ab. (0)
- human wart virus, infectious.ti,ab. (0)
- papilloma virus, human.ti,ab. (2)
- anal cytological abnormalit\$.ti,ab. (8)
- anal human papillomavirus disease\$.ti,ab. (2)
- anal squamous intraepithelial neoplasia.ti,ab. (3)
- anal high grade squamous intraepithelial lesion\$.ti,ab. (9)
- high-grade anal squamous intraepithelial lesion\$.ti,ab. (5)
- OR/52-81 (59275)
- exp Cohort Studies/ (1154051)
- Prognosis/ (315160)
- exp Mortality/ (244466)
- exp morbidity/ (311219)
- morbidity.ti,ab. (202462)
- mortality.ti,ab. (383786)
- (natural adj history).ti,ab. (31892)
- prognos\$.ti,ab. (307358)
- course.ti,ab. (375503)
- predict\$.ti,ab. (759606)
- "Outcome Assessment (Health Care)"/ (41035)
- outcomes\$1.ti,ab. (292752)
- (inception adj cohort\$1).ti,ab. (1205)
- disease progression/ (82906)
- exp survival analysis/ (146834)
- OR/83-97 (3127891)
- 51 AND 82 AND 98 (7564)

Method filter:

- guideline\$.ti,ab. (151373)
- Health Planning Guidelines/ (3602)
- recommendation\$.ti,ab. (119348)
- randomized controlled trial/ (322346)
- Random Allocation/ (73538)
- (random* adj5 (alloca* or assign* or control*)).tw. (193067)
- double-blind method/ or single-blind method/ (128556)
- exp clinical trial/ (668016)
- (clinical adj5 trial*).tw. (182336)
- ((singl* or doubl* or trebl* or tripl*) adj5 (blind* or mask*)).tw. (115825)
- Placebos/ (30603)
- (placebo* or random*).tw. (642703)
- Research Design/ (65177)
- "review"/ or evaluation studies/ (1830510)
- exp Longitudinal Studies/ (757854)

- (compar* adj5 (report* or stud* or trial*)).tw. (354832)
- meta-analysis/ (32082)
- "Review Literature as Topic"/ (4127)
- systematic review.tw. (28865)
- meta-analys?s.tw. (39656)
- OR/100-119 (3845926)

Cost-effectiveness:

- exp "Patient Acceptance of Health Care"/ (140438)
- exp "Costs and Cost Analysis"/ (161933)
- cost\$.ti. (70491)
- (cost\$ adj2 (effective\$ or util\$ or benefit\$ or minimi\$)).ab. (71274)
- (economic\$ or pharmaco economic\$ or pharmoco-economic\$).tw. (126435)
- Quality-Adjusted Life Years/ (5419)
- quality adjusted life.tw. (4660)
- (qaly\$ or qald\$ or qale\$ or qtime\$).tw. (3895)
- disability adjusted life.tw. (911)
- daly\$.tw. (923)
- Health Status Indicators/ (17486)
- (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short from thirtysix or short form thirty six).tw. (12761)
- (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1186)
- (sf12 or sf 12 or short from 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2380)
- (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or s hortform sixteen or short form sixteen).tw. (19)
- (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short from twenty).tw. (343)
- (euroqol or euro qol or eq5d or eq 5d).tw. (2762)
- (hql or hqol or h qol or hrqol or hr qol).tw. (5757)
- (hye or hyes).tw. (51)
- health\$ year\$ equivalent\$.tw. (37)
- health utilit\$.tw. (843)
- (hui or hui1 or hui2 or hui3).tw. (741)
- disutil\$.tw. (171)
- rosser.tw. (70)
- quality of wellbeing.tw. (7)
- qwb.tw. (150)
- willingness to pay.tw. (1711)
- standard gamble\$.tw. (595)
- time trade off.tw. (619)
- time tradeoff.tw. (192)

- tto.tw. (479)
- exp Models, Economic/ (8429)
- *Models, Theoretical/ (32998)
- *Models, Organizational/ (4071)
- economic model\$.tw. (1397)
- Markov Chains/ (7700)
- markov\$.tw. (10636)
- Monte Carlo Method/ (16480)
- monte carlo.tw. (23801)
- exp Decision Theory/ (8633)
- (decision\$ adj2 (tree\$ or analy\$ or model\$)).tw. (10349)
- OR/121-161 (574010)

Cost-effectiveness of screening technologies:

- 120 OR 162 (4226787)
- 99 AND 163 (4171)
- limit 164 to yr="2006 -Current" (1676)

The treatment:

- exp Anus Neoplasms/ (4295)
- anus neoplasm\$.tw. (3)
- neoplasm\$, anus.tw. (0)
- anal neoplasm\$.tw. (20)
- neoplasm\$, anal.tw. (3)
- anal cancer\$.tw. (950)
- cancer\$, anal.tw. (30)
- cancer of anus.tw. (2)
- anus cancer\$.tw. (12)
- cancer of the anus.tw. (94)
- anal squamous carcinoma.tw. (18)
- circumanal gland neoplasm\$.tw. (1)
- exp Anal Gland Neoplasms/ (161)
- neoplasm\$, anal gland.tw. (0)
- anal gland neoplasm\$.tw. (0)
- neoplasm\$, circumanal gland.tw. (0)
- neoplasm\$, perianal gland.tw. (0)
- perianal gland neoplasm\$.tw. (2)
- OR/166-184 (4566)
- exp Therapeutics/ (3006842)
- treatment\$.ti,ab. (2614106)
- therap\$.ti,ab. (1544587)
- exp Radiotherapy/ (121658)
- radiotherap\$.ti,ab. (99594)

- chemotherap\$.ti,ab. (232926)
- surger\$.ti,ab. (667732)
- OR/185-191 (5794411)
- 184 AND 192 (2391)
- 120 AND 193 (972)
- limit 194 to yr="2006 -Current" (329)

Screening programmes or policies:

- exp Anus Neoplasms/ (4295)
- anus neoplasm\$.tw. (3)
- neoplasm\$, anus.tw. (0)
- anal neoplasm\$.tw. (20)
- neoplasm\$, anal.tw. (3)
- anal cancer\$.tw. (950)
- cancer\$, anal.tw. (30)
- cancer of anus.tw. (2)
- anus cancer\$.tw. (12)
- cancer of the anus.tw. (94)
- anal squamous carcinoma.tw. (18)
- circumanal gland neoplasm\$.tw. (1)
- exp Anal Gland Neoplasms/ (161)
- neoplasm\$, anal gland.tw. (0)
- anal gland neoplasm\$.tw. (0)
- neoplasm\$, circumanal gland.tw. (0)
- neoplasm\$, perianal gland.tw. (0)
- perianal gland neoplasm\$.tw. (2)
- OR/196-213 (4566)
- screening program\$.ti,ab. (17053)
- Mass Screening/ (72995)
- mass screening\$.ti,ab. (4238)
- cancer screening\$.ti,ab. (14109)
- screening programme\$.ti,ab. (5942)
- screening polic\$.ti,ab. (590)
- screening\$.ti,ab. (275803)
- screening campaign\$.ti,ab. (453)
- OR/215-222 (300582)
- 214 AND 223 (243)
- 163 AND 224 (134)
- limit 225 to yr="2006 -Current" (87)

2. A total number of 5,479 studies were located. Following a flittering exercise to check for duplication, a total of 3,884 abstracts remained. These were filtered further by the UK NSC for relevance to the screening of anal cancer, which narrowed the literature base into 456 studies relating to general population screening and 267 studies on screening amongst high risk groups.

3. The inclusion criteria used by the UK NSC for the first filtering exercise included:

- Epidemiology of anal cancer
- Epidemiology of HPV with reference to anal cancer
- HPV vaccination if referring to anal cancer prevention
- HPV as a cause of anal cancer
- Screening technologies (the test)
- Testing for HPV or anal lesions as a screen
- Treatment
- Screening

4. The exclusion criteria used for the first filtering exercise included:

- Colorectal, gastrointestinal, rectal cancers/neoplasms etc. (unless it also included anal)
- Recurrent cancers
- Metastatic cancers
- Any other cancer at any other location in the body (unless it also included anal)

5. The UK NSC provided SERIO with the filtered abstracts in May 2012. SERIO then conducted a further filtering process to select the most relevant literature to the screening criteria. Article titles were first reviewed for relevance with abstracts being reviewed where the title did not provide enough information. Articles were excluded from the review if they:

- Were focused on low sample sizes (<50);
- Were focused on studies based at less than three institutions (therefore not reflecting wider population studies); and
- Purely focused on high risk groups.

6. Studies were included in the review if they:

- Contained population incidence, effectiveness of screening, health outcomes and treatment of anal cancer;
- Were based on general population studies – particularly if using randomised control techniques;
- Prospectively tested new ways of detecting anal cancer; or,
- Specifically matched any aspect of the UK NSC screening criteria.

7. In addition to reviewing the abstracts provided to the review team by the NSC, SERIO conducted a grey literature search to ensure that all relevant literature was accessed. The team used combinations of word associate with, and including 'anal cancer', in an online search engine. A cut of date of 2006 was used to focus the findings, and literature was only accessed if English was the language used. Apart from the results including a range of non-official and official websites, the majority were that which was already cited in the NSC's reference list. Only a small number of additional papers were located, and were of minimal relevance to the review.

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