Appraisal of Screening for Stomach Cancer

A report for the
UK National Screening Committee

June 2015

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Introduction

1. This report reviews screening for stomach cancer against the UK National Screening Committee (NSC) criteria for appraising the viability, effectiveness and appropriateness of a screening programme (NSC 2003). It is based on a literature search conducted by the NSC in November 2014. Full details of the search strategy are set out in Appendix A.

2. Stomach cancer is also known as gastric cancer. The development of stomach cancer is linked to the presence of *Helicobacter pylori* (*H. pylori*), which causes a chronic low-level inflammation of the stomach lining.

3. Screening for stomach cancer was previously reviewed against the NSC criteria in 2009 (Hillier & Fielder 2009). The current NSC policy is that screening for either gastric cancer or *H. pylori* are not recommended[1].

4. The previous review concluded that (Hillier & Fielder 2009):

   > "Overall, the potential harms outweigh the potential benefits of a national stomach cancer screening programme. The benefits of a programme would be identifying individuals with early stomach cancer and be able to treat the cancer at a curative stage. However, the UK has a low incidence of stomach cancer and there is a psychological harm to cause worry in a population whose actual risk of developing stomach cancer is low; the initial test is a procedure with radiation or endoscopy which is invasive, there is lack of evidence of effectiveness from randomised controlled trials and the programme is unlikely to be cost effective".

5. There are established national population-based screening programmes for stomach cancer in Japan (started in 1960) and Korea (started in 1999).

6. This current review focuses on four questions:

   - **Are any tests for Helicobacter pylori, or any other biomarkers or combinations of biomarkers, sufficiently valid for use in a population-based screening programme?**
   - **Is the likely trade-off known between benefit and harm from offering barium studies and/or endoscopy in a UK population-based screening programme, either as the initial screening test, or as the secondary screening test for individuals who test positive on a biomarker or combination of biomarkers?**
   - **Is there an adequate evidence base to inform the management of potentially malignant gastric lesions?**
   - **Are there any studies of the screening programme in Japan and Korea, providing data on mortality and morbidity outcomes?**

The Condition

7. The questions to be addressed in this review relate to the test, treatment and screening sections of the NSC criteria and are considered below. In this section we have updated the epidemiology data and briefly summarised key issues and conclusions on natural history from the previous NSC review but have not considered any further issues relating to the condition.

[1] The UK NSC recommendation on stomach cancer screening in adults - http://www.screening.nhs.uk/stomachcancer

The condition should be an important health problem

8. In 2011, around 7,100 people were diagnosed with stomach cancer in the UK (Cancer Research UK 2014).

9. The age-standarised five-year survival rate for stomach cancer is 18.9% (95%CI 18.0% to 19.9%), and the one-year survival rate is 41.8% (95% 41.6% to 42.1%). These rates have improved from 10.9% and 26.6% respectively in 1991 (Cancer Research UK 2014).

10. This criterion is met.

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

11. The UK age-standarised incidence rate for stomach cancer has steadily decreased since the early 1990s, from 14.1 per 100,000 in 1993 to 7.6 per 100,000 in 2011. However it is still the 11th most common cancer in UK men (age-standarised incidence rate 11.2 per 100,000 males) and the 15th most common cancer in UK women (age-standarised incidence rate 4.7 per 100,000 females). About 90% of new cases of stomach cancer occur in people aged 55 and over, and approximately 50% of cases are diagnosed in people aged 75 and over (Cancer Research UK 2014).

12. About 95% of cancers are adenocarcinomas, which can be intestinal or diffuse. Other malignant histologies include lymphomas and leiomyosarcomas (Cancer Research UK 2014).

13. The previous 2009 NSC review stated that “stomach cancer is a multifactorial disease with the recognised risk factors of *H. pylori* infection, genetic, environmental and nutritional factors” (Hillier & Fielder 2009). Of these risk factors, *H pylori* is linked to an estimated 32% of UK cases (Cancer Research UK 2014).

14. The previous 2009 NSC review stated that (Hillier & Fielder 2009):

> “Approximately 90% of stomach cancers are adenocarcinomas arising in the gastric mucosa. There is a stepwise progression from chronic inflammation of the mucosa which can slowly progress through the premalignant stages of atrophic gastritis, intestinal metaplasia, dysplasia and finally to adenocarcinoma.”

15. It was also stated that “the progression of premalignant gastric lesions to stomach cancer generally takes decades. It has been reported that early stage stomach cancer generally takes about 44 months to progress to an advanced stage” (Hillier & Fielder 2009).

16. The remaining criteria relating to ‘the condition’ are not considered further.

The Test

There should be a simple, safe, precise and validated screening test. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

17. The previous 2009 NSC review discussed five screening targets or techniques that had been explored for use in screening for stomach cancer, two of which (barium studies and

endoscopy) are recognised as validated tests for the screening programmes in Japan and Korea. These five screening targets or techniques were (Hillier & Fielder 2009):

- *Helicobacter pylori (H. pylori)*
- Serum pepsinogen
- Serum Gastrin-17
- Barium studies
- Endoscopy

18. Upper gastrointestinal endoscopy is the generally accepted gold standard for the diagnosis of stomach cancer (Hillier & Fielder 2009).

19. This current review focuses on two questions with regards to screening tests for stomach cancer. The second question concerns the trade-off between the benefit and harm from barium studies and/ or endoscopy and is considered below. The first question concerns tests for *H. pylori* and other biomarkers:

    - **Are any tests for *H. pylori*, or any other biomarkers or combinations of biomarkers, sufficiently valid for use in a population-based screening programme?**

H. pylori

20. The previous NSC review stated that "screening for *H.pylori* antibodies is problematic as it does not differentiate between chronic, non-atrophic gastritis and precancerous lesions" (Hillier & Fielder 2009).

21. A systematic review and meta-analysis (Terasawa et al 2014) considered the performance of *H. pylori* serology and serum pepsinogen in prospective and retrospective cohort studies of apparently healthy adults. The search included papers published in English or Japanese up to December 2013 and studies that assessed test performance in asymptomatic participants of gastric screening programmes were considered eligible. Five studies assessing either the serum pepsinogen test, or *H. pylori* serology or both, included data that were used to calculate summary estimates of sensitivity and specificity (Table 1). All five studies were from Japan; two were workplace health check-ups and three were population-based health checks. The mean age of participants ranged from 45 to 57 years, mean follow-up ranged from 9.3 years to 12.3 years and the cancer incidence rate ranged from 111 to 260 per 100,000 person years. Results for H. pylori are presented in Table 1. Results for serum pepsinogen are presented separately below.

Table 1: Test performance for *H. pylori* to detect stomach cancer (Terasawa et al 2014)

Test	No. of studies (n)	Sensitivity	Specificity
H. pylori serology	3 studies[2] (n=9,960)	87% (95%CI 76% to 94%)	30% (95%CI 23% to 39%)

22. In Terasawa et al the follow-up periods and the method used to verify stomach cancer cases varied and included review of health records, cancer registry data and endoscopy with or without a biopsy following a positive screening result.

23. The 2014 review of studies on the performance of *H. pylori* reported a reasonable sensitivity (87%) but a low specificity (30%). A low specificity suggests that there would be a high number of false positives. For example, for every 100 people screened, 70 healthy people would screen positive but would not have the disease. This high level of

[2] One prospective workplace checkup and two retrospective population-based health checks

false positives would not be considered acceptable for a population-based screening programme.

Serum pepsinogen

24. The previous NSC review stated that "in a pooled analysis of Japanese studies that assessed about 300,000 people the sensitivity of serum pepsinogen was 77% and the specificity was 73% …. The low stomach cancer incidence in the UK means that the positive predictive value for serum pepsinogen testing will be low" (Hillier & Fielder 2009).

25. Serum PG consists of two types: PGI and PGII. PGI levels decrease with loss of fundic gland mucosa, whereas PGII remains constant. Therefore, a low PGI level or a low PGI/II ratio, or both, are good indicators of atrophic gastritis (Miki 2011).

26. The results for serum pepsinogen from Terasawa et al (2014) (described above) are presented in Table 2.

Table 2: Test performance for serum pepsinogen to detect stomach cancer (Terasawa et al 2014)

Test	No.of studies (n)	Sensitivity	Specificity
Serum pepsinogen	4 studies[3] (n=14,343)	57% (95%CI 49% to 65%)	76% (95%CI 69% to 81%)

27. Lomba-Viana et al (2012) assessed the performance of serum pepsinogen in a European population, described by the authors as a high-risk region (Portugal). Participants (n=13,118) were recruited through advertisement rather than through a population-based screening programme. They provided a blood sample and all who tested positive (PG1<70ng/ml and PGI/ PGII <3) were offered an annual endoscopy with a biopsy. A number of participants with consecutive negative test results were also offered an annual endoscopy. All participants receiving endoscopy were followed up for between three and five years.

Table 3: Test performance of serum pepsinogen to detect stomach cancer (Lomba-Viana et al 2012)

Participants	Results	Sensitivity	Specificity	Predictive values
N = 13,118 Median age 60 years (range 40 to 79)	Positive serum pepsinogen (SP) test: 446 (3.4%) Received endoscopy: 514 (274 following positive SP test; 240 following negative SP test) Cancer cases detected by endoscopy: 9 (6 following positive SP test; 3 following negative SP test)	67% (95%CI 63% to 71%)	47% (95%CI 43% to 51%)	PPV: 2% (95%CI 1% to 3%) NPV: 99% (95%CI 98% to 100%)

NPV – negative predictive value; PPV – positive predictive value

[3] Two prospective workplace checkups and two retrospective population-based health checks

28. In Lomba-Viana et al's study, although all participants with a positive serum pepsinogen result were offered an annual endoscopy, only 61% received the test. A number of participants with a negative serum test were also offered annual endoscopy and three cancer cases were detected. Both these factors mean it is possible that cases of stomach cancer were missed. This is the only study identified that relates to a European population, but the population studied was from a region of Portugal with a mean incidence of stomach cancer of 31 per 100,000 in 2006 and a high prevalence of *H. pylori* infection (84%), which limits the applicability of the findings to the UK context.

29. Mizuno et al (2009) explored the effectiveness of serum pepsinogen (PG) and barium meal X-ray (received simultaneously) in opportunistic screening of residents of a Japanese city. Participants with a PGI level of ≤30ng/ml and a PGI/ PGII ratio of ≤2.0, and participants with abnormal X-ray readings were advised to undergo oesophagogastroduodenoscopy (EGD). The results of individuals who received a follow-up test at the same organisation as the screening were recorded. Other screening participants were checked with the city's cancer registry. All participants were followed-up for one year after screening. In total, 493 participants (4.1%) had a positive serum pepsinogen screening test and 19 stomach cancer cases were identified, 13 through EGD and six through the registry.

30. The PG cut-off levels used by Mizuno et al identify the most severe gastric mucosal atrophy and the highest risk for developing gastric cancer. Cut-off levels of PGI ≤70ng/ml and PGI/PGII ≤3.0 have also been used in stomach cancer screening in Japan and Mizuno et al also reported test performance scores for these less stringent cut-off levels. The serum pepsinogen results are summarised in Table 4. The results for the barium meal x-ray test are considered separately below.

Table 4: Test performance of serum pepsinogen to detect stomach cancer (Mizuno et al 2009)

Participants	Cut-off level	Cancer cases detected by serum pepsinogen test	Sensitivity	Specificity	PPV
N = 12,120 Age range 15 to 84 (81% over 40 years)	PGI ≤30ng/ml; PGI/ PGII ratio of ≤2.0	7	36.8% (95%CI 15.2% to 58.5%)	96.0% (95%CI 95.6% to 96.3%)	1.4% (95%CI 0.38% to 2.46%)
	PG1≤70ng/ml; PGI/PGII ≤3.0	13	68.4% (95%CI 47.5% to 89.3%),	85.6% (95%CI 84.9% to 86.2%)	0.7% (95%CI 0.34% to 1.14%)

PPV – positive predictive value

31. The number of cancer cases detected by Mizuno et al was small and the confidence intervals are correspondingly wide.

32. Another population-based study explored the test performance of serum pepsinogen and gastrin-17 to identify pre-malignant gastric lesions in people aged 50 years or more in a high-incidence area in Iran (Shafaghi et al 2013). The results for serum pepsinogen are summarised in Table 5. The results for gastrin-17 are considered separately in the section below.

Table 5: Test performance of serum pepsinogen to detect pre-malignant lesions (Shafaghi et al 2013)

Participants	Positive screening test	Test	Sensitivity	Specificity	PPV
N = 1,390 Mean age 61.8	38.4% had at least one of three types of pre-malignant lesion (atrophy, metaplasia or dysplasia)	Serum pepsinogen[4] (cut-off level PGI<65.61; PGI/PGII <6.79)	PGI: 35.0% (95%CI 30.9% to 39.2%) PGI/PGII: 72.8% (95%CI 68.8% to 76.6%)	PGI: 74.7% (95%CI 71.5% to 77.5%) PGI/PGII: 61.8% (95%CI 58.4% to 65.1%)	PGI: 46.1% PG1/PGII: 54.2% 95% confidence intervals not reported

33. Shafaghi et al was a small study set in an area of Iran that was considered to have a high incidence of stomach cancer. Higher PPV scores were achieved, but unlike the other studies reported, this represents test performance to detect pre-malignant lesions rather than to detect stomach cancer.

34. The studies reporting the test performance of serum pepsinogen identified in the literature search for this review were smaller than the pooled analysis of Japanese studies identified in the 2009 review for the UKNSC. The sensitivity scores reported varied, but were lower than the 77% achieved in the previously reported pooled analysis. As in the previous NSC review, the evidence identified comes from areas with a higher incidence of stomach cancer than the UK. Despite this the positive predictive values (PPV) for stomach cancer, when reported, were 2% or less. If the same tests were used in the UK, where the incidence of stomach cancer is lower than the locations where the test was studied, the PPV would be even lower.

Gastrin-17

35. The previous NSC review concluded that (Hillier & Fielder 2009):

> "Although it [Gastrin-17] cannot be used as a single marker for gastric cancer it may be used in combination with other markers. The combination of pepsinogen and gastrin levels together with *H. pylori* antibody status has been reported as having a sensitivity and specificity of 89% and 93% in being able to identify and distinguish different types of atrophic gastritis".

36. The literature review for this update identified only one paper reporting the test performance of gastrin-17. Shafaghi et al (2013) explored the test performance of gastrin-17 to identify pre-malignant gastric lesions for people aged 50 years or more in a high-incidence area in Iran. The results are summarised in Table 6.

[4] In this study the results for PGI <65.61 and a PGI/PGII ratio of <6.79 were reported separately

Table 6: Test performance of gastrin-17 to detect pre-malignant lesions (Shafaghi et al 2013)

Participants	Positive screening test	Test	Sensitivity	Specificity	PPV
N = 1,390 Mean age 61.8	38.4% had at least one of three types of pre-malignant lesion (atrophy, metaplasia or dysplasia)	Gastrin-17 (cut-off level >2.49)	56.2% (95%CI 51.8% to 60.5%)	62.0% (95%CI 58.7% to 65.3%)	47.8% 95% confidence intervals not reported

PPV – positive predictive value

37. Important limitations of Shafagi et al's study are that it was set in an area considered to have a high incidence of stomach cancer, and it assessed test performance to detect pre-malignant lesions rather than stomach cancer. Whilst the PPVs reported are correspondingly higher, the sensitivity and specificity scores are not sufficient for use in a population screening programme.

38. No studies considering the combination of gastrin-7 with other markers were identified.

Other biomarkers

39. The literature review identified a study assessing the performance of monoclonal gastric cancer 7 antigen (MG7-Ag) in a screening programme (Zhang et al 2010).

40. Zhang et al (2010) evaluated MG7-Ag, as part of a screening programme in a rural Chinese population described as a high-risk population. The authors do not state the incidence of stomach cancer in the study area, but the age standardised incidence of stomach cancer was 22.7 per 100,000 in China in 2012[5].

41. All 2,710 participants in Zhang et al's study received an endoscopy as the primary screening test, with serum samples to detect MG7-Ag taken in addition. Biopsy samples were taken from five stomach sites[6] for all participants. Participants were aged 35 to 64 years (mean age 49.6±6.9) and people with a previous diagnosis of gastric cancer were excluded. The technicians assessing the MG7-Ag results were blinded to participant's histopathology results. Forty stomach cancer cases were detected. The sensitivity of MG7-Ag to detect stomach cancer was 77.5% and the specificity was 95.6% (95%CI and PPV not reported).

42. The test performance of MG7-Ag in a screening population suggests that this biomarker may be of interest as a potential option for screening, however its value in larger non-high-risk populations more generalisable to a UK screening population needs to be established.

[5] World Cancer Research Fund International. Stomach cancer statistics. http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/stomach-cancer-statistics

[6] Five biopsies were taken from standard stomach sites using the Updated Sydney System (Zhang et al 2010)

Summary

43. The additional studies identified in the literature search for this review do not provide sufficient evidence to change the conclusion of the previous NSC review. They suggest that there are currently no tests for *H.pylori*, or any other biomarkers or combinations of biomarkers that are sufficiently valid for use in a population-based screening programme. However, the performance of MG7-Ag may be of interest for further research.

44. The second question addressed in this review is:

    - **Is the likely trade-off known between benefit and harm from offering barium studies and/or endoscopy in a UK population-based screening programme, either as the initial screening test, or as the secondary screening test for individuals who test positive on a biomarker or combination of biomarkers?**

45. The previous NSC review reported a sensitivity of 70% to 90% and a specificity of 80% to 90% for barium studies using photofluorography. The review also noted that the detection rate can be low even in high incidence countries, giving the example of 770,710 individuals screened in Japan using barium meal examination with 364 (0.047%) asymptomatic stomach cancers detected (Hillier & Fielder 2009).

46. Although endoscopy is generally accepted as the gold standard for the diagnosis of stomach cancer, the conclusion from the previous NSC review regarding endoscopy was that:

    > "It is still not sufficient to justify its use for routine screening. It is an unpleasant procedure that carries the risk of haemorrhage and perforation with a reported mortality of 0.0008% and a morbidity of 0.432%."

47. The literature search for this current review identified several retrospective reviews and prospective studies which considered the sensitivity and specificity of endoscopy or barium studies in a screening population. The test performance scores reported by these studies are summarised in Appendix Table B1 for information. As several large studies reporting test performance were identified, only studies with more than 1,000 participants are included, however smaller studies were checked for any information regarding potential harms associated with endoscopy or barium meal x-ray. The sensitivity and specificity scores reported were similar in the three studies that assessed endoscopy, with sensitivity scores ranging from 59% to 69% and specificity scores ranging from 96% to 98%.Confidence intervals were not reported in one study and were wide in another. The three studies that assessed barium studies had more variation in the sensitivity scores, which ranged from 13% to 68% but similar specificity scores, ranging from 90% to 94%. Only one of these studies reported 95% confidence intervals, which were wide. All the studies were set in Japan or Korea, both of which have a higher incidence of stomach cancer than the UK. However, the overall number of cancer cases detected was low, representing less than 1% of the population screened in all but one of the studies (in the remaining study it was 2%).

48. Only one study reported potential harms associated with endoscopy or barium x-ray. Yao et al (2014) reported that of 1,094 patients receiving endoscopy as part of a screening programme, two patients discontinued the endoscopy due to a severe vomiting reflex. No adverse events were observed in the 1,092 patients who completed endoscopy. We did not identify any studies that have looked at the trade-off between the benefits and harms from offering barium studies and/ or endoscopy in a UK population-based screening programme as an initial or secondary screening test.

49. The known risks associated with endoscopy were discussed in the previous review. The literature review did not identify any studies that further considered the harms of endoscopy or barium studies when used in population screening programmes.

50. Table C1 in Appendix C provides estimates of the number of cancer cases that might be identified and the potential mortality and morbidity that might be expected in screening for stomach cancer using endoscopy as the initial screening test in a general UK population aged 40 years and above. This suggests that from a UK population of 100,000 we would expect 15 cases of stomach cancer, of which 10 might be detected and 5 missed using screening with endoscopy as the initial test. There would be 3,900 false positive results, 430 people would experience significant morbidity as a result of endoscopy, and one person might be killed by the endoscopy.

51. Table C2 in Appendix C provides estimates of the number of cancer cases that might be identified and the potential mortality and morbidity that might be expected in screening for stomach cancer using the biomarker MG7-Ag as the initial screening test, with endoscopy reserved for those with a positive MG7-Ag result. This suggests that from a UK population of 100,000 we would expect 15 cases of stomach cancer, of which 3 might be missed by MG7-Ag, and a further 4 would be missed despite proceeding to endoscopy after a positive MG7-Ag result. The estimated number of people undergoing endoscopy would be 4,411. Among them 8 cases of stomach cancer would be detected, there would be 172 false positive endoscopy results, 19 people would experience significant morbidity as a result of endoscopy, and no one would be killed by the endoscopy.

52. The estimates in Tables C1 and C2 should be regarded as highly speculative, because the test performance data are from single studies conducted in high-risk, non- UK populations.

Summary

53. Two specific questions about screening tests for cancer have been addressed in this update. However, this has not changed the overall conclusion that there is not a simple, safe, precise and validated screening test for stomach cancer in the UK. This criterion is therefore still not met.

54. The remaining NSC criteria relating to testing for stomach cancer are not considered further at this time.

The Treatment

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

55. The previous 2010 NSC review cited NICE guidance as stating that "for patients whose stomach cancer is diagnosed at a stage that is amenable to surgical treatment, the options include open or laparoscopic gastrectomy" (Hillier & Fielder 2009).

56. The question posed for this review with respect to the treatment of stomach cancer is:

- **Is there an adequate evidence base to inform the management of potentially malignant gastric lesions?**

57. The literature search for this review identified a 2013 Cochrane review on the surveillance of gastric intestinal metaplasia for the prevention of gastric cancer (O'Connor et al 2013). The stated objective of this review was to "see whether or not endoscopic or biochemical surveillance of patients with gastric intestinal metaplasia (GIM) could result in increased detection of dysplasia and gastric cancer to decrease gastric cancer mortality". The studies of interest were randomised controlled trials comparing surveillance versus no surveillance and including populations where GIM was diagnosed through population based screening or opportunistically through a symptomatic service, and with ongoing surveillance for at least five years. The Cochrane review authors did not identify any randomised controlled trials on the utility of surveillance. The authors did however acknowledge potential ethical constraints to running randomised controlled trials in this area and suggested that prospective cohort studies of patients undergoing surveillance[7] are needed which could then be compared to overall population data from cancer registries (O'Connor et al 2013).

58. The literature search did not identify any further studies on the management of potentially malignant gastric lesions published after the date of the Cochrane review.

59. We did not identify any studies to suggest that there is an adequate evidence base to inform the management of potentially malignant gastric lesions. This criterion is not currently met.

60. The remaining NSC criteria relating to the treatment of stomach cancer are not considered further at this time.

[7] Powered to detect a variance in tumour nodes metastasis status at diagnosis and also of gastric cancer mortality (O'Connor et al 2013)

The Screening Programme

There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity

61. The specific question posed for this review with respect to stomach cancer screening programmes is:

    - **Are there any studies of the screening programme in Japan and Korea, providing data on mortality and morbidity outcomes?**

62. The previous 2010 NSC review did not identify any randomised controlled trials assessing the effectiveness of screening for stomach cancer. The 2010 review did identify four case control studies from Japan which showed a decline in the incidence of, and mortality from stomach cancer in those who had been screened, ranging from 40-60% (these results were statistically significant). Five large prospective studies that defined death from stomach cancer as an endpoint mostly reported a reduced relative risk, suggesting a protective effect for screening. However the results were inconsistent and some did not reach statistical significance (Hillier & Fielder 2009).

63. No randomised controlled trials on the effectiveness of screening were identified in the literature search for this current review. The literature search did identify two studies which provided data on mortality or morbidity outcomes from screening.

64. Gong et al (2014) compared the clinical outcomes of 327 patients who received screening by upper endoscopy and were diagnosed with stomach cancer at one healthcare centre in South Korea, with outcomes for 663 patients who were diagnosed with stomach cancer at the outpatient clinic of the same healthcare centre[8]. The clinical outcomes for the two groups are summarised in Table 7.

Table 7: Clinical outcomes for screening and outpatient groups (Gong et al 2014)

	Screening group (n=327)	Outpatient group (n=663)	p-value
Mean follow-up (months)	70.7± 41.5	55.9± 45.4	Not reported
Number of deaths	61 (18.7%)	309 (46.6%)	Not reported
Symptomatic	44.3%	61.4%	<0.001
Endoscopic classification	EGC: 70.9% AGC:29.1%	EGC: 43.9% AGC: 56.1%	<0.001
Proportion resectable tumour[9]	95.1%	78.1%	<0.001
Treatment (resection)	Surgical: 70.6% Endoscopic: 14.4%	Surgical: 64.3% Endoscopic: 8.3%	<0.001
Stage at diagnosis	Stage 1: 75.1% Stage 2: 10.9% Stage 3: 8.9% Stage 4: 5.1%	Stage 1: 48.0% Stage 2: 13.7% Stage 3: 17.8% Stage 4: 20.2%	<0.001
Five-year overall survival	82.4%	56.3%	<0.001

AGC - Advanced gastric cancer; EGC - early gastric cancer

[8] The National Cancer Screening Programme in South Korea recommends that individuals over 40 years old undergo gastric cancer screening every two years. Endoscopy is also widely performed during self-financed routine health check-ups (Gong et al 2014).

[9] Tumours were considered resectable if there was no evidence of distant metastasis and invasion or encasement of major vascular structures (Gong et al 2014).

65. Table 7 shows that the clinical outcomes, including five year survival rate, were statistically significantly better for the screening group than for the outpatient group. This was a small retrospective study. The survival rates estimated in this non-randomised study design are also susceptible to lead time bias, in which survival may appear to improve but only as a result of earlier detection, not as a result of changing the course of the disease through earlier detection.

66. A community–based case-control study (Hamashima et al 2013) evaluated the reduction in mortality from stomach cancer in five Japanese cities that had offered annual endoscopic screening to individuals aged over 40 for at least five years, and had local cancer registries. These cities had higher mortality rates for stomach cancer than other cities in Japan. Participation in screening was reported to be about 25% (Hamashima et al 2013). Examination of the registries identified 410 case subjects who had died of stomach cancer. Patients who were less than 39 years old or over 80 years old at the time of diagnosis were excluded. The controls (n=2,292) were identified from resident lists for each city and were matched by sex, birth year (±3 years) and residence in the area of the city. Odds ratios were calculated for the likelihood of a reduction in mortality for cases and controls having participated in screening within 12, 24, 36 and 48 months before the case subject was diagnosed with stomach cancer.

67. Hamashima et al reported a 30% reduction in stomach cancer mortality for endoscopic screening compared with no screening within 36 months before the date of diagnosis, but comparisons at 12, 24 and 48 months were not statistically significant. These results are presented in Table 8.

Table 8: Results from Hamashima et al 2013

Months before the date of diagnosis	Odds ratio
12	0.97 (95%CI 0.66 to 1.41)
24	0.70 (95%CI 0.49 to 1.01)
36	0.70 (95%CI 0.49 to 0.99)
48	0.71 (95%CI 0.51 to 1.01)

68. A limitation of this study was that screening history was identified from participant lists for community-based screening. Any screening that took place opportunistically or as part of a regular workplace health check would not have been identified. It is also possible that the apparent protective effect of screening could be an artefact caused by healthy volunteer bias, in which people who are at lower risk of developing or dying from stomach cancer are more likely to volunteer for screening.

69. The literature search identified one study, (Gong et al 2014) comparing clinical outcomes from patients diagnosed with stomach cancer following screening with patients diagnosed at an outpatient clinic, and a community based case-control study (Hamashima et al 2013) evaluating reduction in stomach cancer mortality in five Japanese cities that offered annual screening. Both reported a reduction in mortality with screening, however both studies had limitations. The sample sizes were fairly small and neither study excluded patients with symptoms. In Hamashima et al's study a significant reduction in mortality was only observed at one of the four time points considered. It cannot be assumed that the results from the studies on Korean or Japanese populations can be generalised to a UK population, because the incidence rates of stomach cancer are higher in Korea and Japan than in the UK (e.g. crude incidence rate in Korea in 2012 was 86.8 and 41.1 per 100,000 person-years for men and women respectively (Gong et al 2014)).

Summary

70. The current review has identified limited evidence of outcomes of screening programmes in Japan and Korea in response to a specific question. However, it cannot be assumed that results from these studies can be generalised to a UK population, because Korea and Japan have higher incidence rates of stomach cancer than the UK. Overall this criterion of identifying evidence of morbidity and mortality outcomes from high quality RCTs of screening programmes remains unmet.

Implications for Policy

71. The questions posed for this review are considered in turn below:

- **Are any tests for *H. pylori*, or any other biomarkers or combinations of biomarkers, sufficiently valid for use in a population-based screening programme?**

72. The additional studies identified in the literature search for this review do not provide sufficient evidence to change the conclusion of the previous NSC review and suggest that there are currently no tests for *H. pylori*, or any other biomarkers or combinations of biomarkers that are sufficiently valid for use in a population-based screening programme. However, the performance of MG7-Ag may be of interest for further research.

- **Is the likely trade-off known between benefit and harm from offering barium studies and/or endoscopy in a UK population-based screening programme, either as the initial screening test, or as the secondary screening test for individuals who test positive on a biomarker or combination of biomarkers?**

73. We did not identify any studies that considered the likely trade-off between the benefit and harm from offering barium studies and/or endoscopy in a UK population-based screening programme as the initial or secondary screening test. The known risks associated with endoscopy were discussed in the previous review. Only one study was identified from the current literature search which reported any harms associated with endoscopy, and no studies were identified that give estimates for the morbidity and mortality with screening using barium x-ray.

74. A modelling exercise conducted for this review estimated that from a UK population of 100,000 people aged 40 and above we would expect 15 cases of stomach cancer, of which 10 might be detected and 5 missed using screening with endoscopy as the initial test. There would be 3,900 false positive results of which 430 people would experience significant morbidity and one person might die as a result of the endoscopy procedure.

75. If the biomarker MG7-Ag were used as the initial screening test, with endoscopy reserved for those with a positive MG7-Ag result, of the 15 cases of stomach cancer 3 might be missed by MG7-Ag, and a further 4 would be missed despite proceeding to endoscopy after a positive MG7-Ag result. The estimated number of people undergoing endoscopy would be 4,411. Among them 8 cases of stomach cancer would be detected, there would be 172 false positive endoscopy results, 19 people would experience significant morbidity as a result of endoscopy, and no one would be killed by the endoscopy. These estimates should be regarded as highly speculative, because the test performance data for MG7-Ag are from a single study conducted in a high-risk, non- UK population

- **Is there an adequate evidence base to inform the management of potentially malignant gastric lesions?**

76. We did not identify any studies to suggest that there is an adequate evidence base to inform the management of potentially malignant gastric lesions.

- **Are there any studies of the screening programme in Japan and Korea, providing data on mortality and morbidity outcomes?**

77. Two studies reporting a reduction in mortality with screening were identified, but both were limited by small sample sizes and neither study excluded patients with symptoms. One was a case-control study that compared outcomes between screen-detected stomach cancer and symptomatically-detected stomach cancer; it is known that this study design is susceptible to lead time bias, in which survival may appear to improve but only as a result of earlier detection, not as a result of changing the course of the disease through earlier detection. The other study compared the screening history of people who died from stomach cancer with the screening history of healthy controls. The apparent protective effect of screening could be an artefact caused by healthy volunteer bias, in which people who are at lower risk of developing or dying from stomach cancer are more likely to volunteer for screening. Japan and Korea have a higher incidence of stomach cancer than the UK and it cannot be assumed that the results from the studies on Korean or Japanese populations can be generalised to a UK population.

78. The 2010 NSC review concluded that the potential harms outweighed the potential benefits of a national stomach cancer screening programme. We did not identify sufficient evidence to change this conclusion.

Implications for Research

79. A small study evaluating MG7-Ag as part of a screening programme in a high risk population reported reasonably high sensitivity and specificity scores. Further larger studies assessing the performance of MG7-AG as a screening test would be of interest. If these support the initial promising results for MG7-AG, it is possible that a randomised controlled trial of screening using MG7-AG as the initial test, and endoscopy for those with a positive MG7-AG result would be worthwhile. However, the dilemma would remain of how to manage the large numbers of potentially malignant gastric lesions that would be detected in the screening arm of such a trial.

80. Large cohort studies on the management of potentially malignant gastric lesions would be of interest due to the difficulties of running randomised controlled trials in this area.

Appendix A

NSC stomach cancer literature search, Bazian, October 2014

BACKGROUND

The last UK NSC review (2010) drew attention to:

- The low prevalence of stomach cancer in the UK, the lack of a clear marker for screening (helicobacter pylori is a candidate but its natural history and relationship to the development of adenocarcinoma is problematic in terms of screening. Not all infections lead to cancer and the infection tends to clear during the progression to cancer so there could be both false positives and false negatives)
- Candidate tests for early gastric cancer are invasive (endoscopy) or expose a low risk population to radiation (photofluorography). There are issues relating to their practicality and reliability.

An update review should focus on:

- Epidemiology of gastric cancer and h. pylori (UK if possible)
- Natural history (e.g. the role of h. pylori and perhaps any novel biomarkers)
- Tests for stomach cancer – photofluorography and endoscopy seem to the main ones but the last review covered a few (serum pepsinogen + / - h pylori, gastrin 17). Although these tests were ruled out last time it would be worth looking to see if there are papers which would justify reconsideration
- The screening programme, it might be useful to review papers on the experience of screening in Korea and Japan.

This literature search should start in January 2009, and cover the below headings.

- The condition (epidemiology and natural history)
- The test
    - Photofluorography, and endoscopy
    - Serum pepsinogen + / h pylori, gastrin 17
      –these tests were previously ruled out, are there any new papers reappraising them?
- Treatment
- Screening programme in Japan and Korea

SOURCES SEARCHED: Medline and Medline In-process; Embase; Cochrane Library (CDSR, CENTRAL, DARE, HTA, NHS EDD)

DATES OF SEARCH: January 2009 – October 2014.

The PICO (Population, Intervention, Comparison, Outcome) framework used to develop the search strategy.

Population	Stomach cancer
Intervention	
Non-interventional aspects	Screening, tests (including photofluorography, endoscopy, serum pepsinogen + / h pylori, gastrin 17), diagnostic accuracy, epidemiology, natural history
Comparator	n/a
Outcome	n/a
Study types	SRs, RCTs, diagnostic accuracy and epidemiological studies

MEDLINE SEARCH STRATEGY:
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

1 Stomach Neoplasms/ (76973)
2 (stomach adj4 cancer).ti,ab. (8916)
3 (stomach adj4 neoplas$).ti,ab. (675)
4 (stomach adj4 (tumor$ or tumour$)).ti,ab. (3147)
5 (gastric adj4 cancer).ti,ab. (40085)
6 (gastric adj4 neoplas$).ti,ab. (1706)
7 (gastric adj4 (tumor$ or tumour$)).ti,ab. (7208)
8 Helicobacter pylori/ (29750)
9 "h. pylori".ti,ab. (21710)
10 helicobacter pylori.ti,ab. (32363)
11 Helicobacter Infections/ (25720)
12 (helicobacter adj2 infection).ti,ab. (11450)
13 ((stomach or gastric) adj5 (pre-cancer$ or precancer$ or adenocarcinoma$ or carcinoma$ or metaplasia$ or dysplasia$ or malignan$ or pre-malignan$ or premalignan$)).ti,ab. (28715)
14 or/1-13 (124591)
15 Mass Screening/ (85470)
16 Early Detection of Cancer/ (9227)
17 Early Diagnosis/ (14267)
18 screen$3.ti,ab. (493841)
19 ((early adj3 diagnos$) or detect$).ti,ab. (1763503)
20 Population Surveillance/ (47679)
21 surveillance.ti,ab. (110624)
22 (test or tests or testing).ti,ab. (1604249)
23 exp Enzyme-Linked Immunosorbent Assay/ (129174)
24 enzyme linked immunosorbent assay.ti,ab. (58671)
25 ELISA.ti,ab. (118081)
26 exp Hematologic tests/ (214356)
27 exp Serologic Tests/ (168779)
28 (endoscop$ or photofluorography or "serum pepsinogen" or "gastrin 17").ti,ab. (148824)
29 exp Biological markers/ (663502)
30 marker$.ti,ab. (531066)
31 exp Risk factors/ (596646)
32 or/15-31 (5130680)
33 14 and 32 (51554)
34 limit 33 to (english language and yr="2009 -Current") (13860)
35 Meta-Analysis as Topic/ (14498)
36 meta analy$.tw. (70989)
37 metaanaly$.tw. (1422)
38 Meta-Analysis/ (53746)
39 (systematic adj (review$1 or overview$1)).tw. (60798)
40 exp "Review Literature as Topic"/ (8062)
41 35 or 36 or 37 or 38 or 39 or 40 (136473)
42 cochrane.ab. (34517)
43 embase.ab. (33462)
44 (psychlit or psyclit).ab. (932)
45 (psychinfo or psycinfo).ab. (14230)
46 (cinahl or cinhal).ab. (11602)
47 science citation index.ab. (2194)
48 bids.ab. (388)
49 cancerlit.ab. (606)
50 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 (59779)
51 reference list$.ab. (10934)
52 bibliograph$.ab. (12600)
53 hand-search$.ab. (4357)
54 relevant journals.ab. (801)
55 manual search$.ab. (2605)

56 51 or 52 or 53 or 54 or 55 (27984)
57 selection criteria.ab. (21636)
58 data extraction.ab. (11275)
59 57 or 58 (31146)
60 Review/ (1967812)
61 59 and 60 (20604)
62 Comment/ (620408)
63 Letter/ (876809)
64 Editorial/ (373673)
65 animal/ (5528317)
66 human/ (14003717)
67 65 not (65 and 66) (3983385)
68 62 or 63 or 64 or 67 (5326104)
69 41 or 50 or 56 or 61 (171769)
70 69 not 68 (161076)
71 Randomized Controlled Trials as Topic/ (98934)
72 Randomized Controlled Trial/ (397350)
73 Random Allocation/ (83684)
74 Double-Blind Method/ (131770)
75 Single Blind Method/ (20379)
76 Clinical trial/ (499976)
77 clinical trial, phase i.pt. (15207)
78 clinical trial, phase ii.pt. (24380)
79 clinical trial, phase iii.pt. (9942)
80 clinical trial, phase iv.pt. (1014)
81 controlled clinical trial.pt. (90496)
82 randomized controlled trial.pt. (397350)
83 multicenter study.pt. (186769)
84 clinical trial.pt. (499976)
85 exp Clinical Trials as Topic/ (293325)
86 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 (1083293)
87 (clinical adj trial$).tw. (233576)
88 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (136345)
89 Placebos/ (33945)
90 placebo$.tw. (168332)
91 randomly allocated.tw. (18117)
92 (allocated adj2 random$).tw. (20776)
93 87 or 88 or 89 or 90 or 91 or 92 (449267)
94 86 or 93 (1242326)
95 case report.tw. (214025)
96 Letter/ (876809)
97 Historical Article/ (311185)
98 95 or 96 or 97 (1389984)
99 94 not 98 (1211246)
100 exp "Sensitivity and Specificity"/ (440249)
101 sensitivity.tw. (565924)
102 specificity.tw. (342357)
103 ((pre-test or pretest) adj probability).tw. (1401)
104 post-test probability.tw. (380)
105 predictive value$.tw. (72590)
106 likelihood ratio$.tw. (9797)
107 100 or 101 or 102 or 103 or 104 or 105 or 106 (1092432)
108 Epidemiology/ (11790)
109 Incidence/ (184509)
110 exp Mortality/ (291971)
111 exp disease progression/ (126189)
112 (ep or di or mi or mo or pc or sn).fs. (4829193)
113 (incidence or epidemiolog* or mortality or prevention or "natural history").ti,ab. (1508857)
114 108 or 109 or 110 or 111 or 112 or 113 (5598251)
115 34 and 70 (544)
116 34 and 99 (1193)
117 34 and 107 (1680)

118 34 and 114 (7561)
119 115 or 116 or 117 or 118 (8801)

Similar searches also carried out in EMBASE and Cochrane Library.

The search generated more than 11,000 hits, with 9,400 records after de-duplication. The sifting process excluded animal studies, conference abstracts, editorials, letters, comment, news, case report and studies about multiple cancers.

Databases and sites searched	**Dates searched**	**Number of hits**
MEDLINE	2009-21/10/2014	8801
EMBASE	2009-21/10/2014	1631
Cochrane Database Syst Rev	2009-22/10/2014	7
Cochrane CENTRAL	2009-22/10/2014	574
CRD – DARE	2009-22/10/2014	59
CRD - HTA	2009-22/10/2014	14
Cochrane – NHS EED	2009-22/10/2014	29
Total number of hits		**11116**
Total number after de-duplication		**9576**
Total number after first appraisal		**715**

715 references were passed to the reviewer for consideration.

Appendix B

Table B1: The sensitivity and specificity of endoscopy and barium x-ray

Study	Patients	Positive screening results	Stomach cancer cases	Sensitivity	Specificity	PPV
Choi et al (2011) Retrospective review of a Korean national screening database for people who received at least one **endoscopy** as part of an endoscopic screening programme, 2002 - 2005 Stomach cancer diagnoses ascertained from the Korean Central Cancer Registry up to 12 months after the screening Korea	Participants in a national screening programme Average-risk population aged 40 years and over N=765,813	32,589[10]	2,074	69.4% (95%CI 66.4% to 72.4%)	96.1% (95%CI 95.9% to 96.3%)	6.36% 95% confidence intervals not reported
Yao et al (2014) Multicentre prospective uncontrolled feasibility study of patients undergoing routine screening **endoscopy** using magnifying endoscopy with narrow-band imaging at seven centres, 2009 - 2010	Patients receiving screening at each centre. Median age 66 (range 30 to 90) N=1,094	371	20	60.0% (95%CI 38.5% to 81.5%)	98.0% (95%CI 96.5% to 100%)	PPV 3.2% 95% confidence intervals not reported

[10] Results are presented from the first endoscopy within the study period regardless of any previous stomach cancer screening

Cancer diagnosis based on results of histopathology Japan						
Lee et al (2010) Retrospective review of **upper gastrointestinal x-ray and upper endoscopy** recipients as part of the Korean National Screening Programme, 2002-2004 Stomach cancer diagnoses ascertained through the Korea Central Cancer Registry up to 12 months after screening Korea	Participants in the national screening programme X-ray: N=1,067,378 Endoscopy: N = 436,268	X-ray: 109,070 Endoscopy: 17,146	X-ray: 892 Endoscopy: 1,041	X-ray: 42.1% Endoscopy: 59.0% 95% confidence intervals not reported	X-ray: 89.8% Endoscopy: 96.3% 95% confidence intervals not reported	X-ray: 0.8% Endoscopy: 0.61% 95% confidence intervals not reported
Mizuno et al (2009) Prospective study on the effectiveness of **barium meal x-ray** in opportunistic screening of residents in one city Participants with abnormal x-ray advised to have endoscopy and all participants followed up for 12 months through the city's cancer registry Japan	City residents, age range 15 to 84 years (81.4% over 40 years old) N=12,120	728	19	68.4% (95%CI 47.5% to 89.3%)	94.1% (95%CI 93.7% to 94.5%)	1.8% (95%CI 0.82% to 2.75%)

Yamamoto et al (2010) Retrospective review of participants in a screening programme in one city who received either a **high-density[11] or medium density barium meal x-ray**, 2000-2001 Participants followed up for 12 months through the city's cancer registry Japan	Residents of one city About 99% of participants in each group were aged 30-79 years High density: N = 48,336 Medium density: N = 123,497	High density: 4,201 Medium density: 11,341	High density: 62 Medium density: 207 A further 25 cases identified through the city register (5 high density; 20 medium density)	High density: 13.7% Medium density: 14.23% 95% confidence intervals not reported	High density: 99.99% Medium density: 99.99% 95% confidence intervals not reported	High density: 2.2% Medium density: 0.26% 95% confidence intervals not reported

PPV – positive predictive value

[11] High-density barium sulphate was recommended for stomach cancer screening in a 2005 Japanese guideline. It is described as easier for drinkers to swallow and permits superior depiction of the gastric mucosa. Its disadvantages are described as rapid outflow from the stomach and a higher incidence of mis-swallowing (Yamamoto et al 2010).

Appendix C

The data blow provides an estimate of the number of cancer case that might be identified, and the number of potential mortality and morbidity cases that might be expected in screening for stomach cancer using endoscopy, with or without prior screening using the biomarker MG7-Ag, in a general UK population.

Table C1: Estimated benefits and harms of screening for stomach cancer using endoscopy as the initial screening test

Number of people screened using endoscopy	100,000
Number of people with stomach cancer in the screened population	15
Number of cases detected by endoscopy	10
Number of cases missed by endoscopy	5
Number of false positives from endoscopy	3,900
Number of people with morbidity from endoscopy	430
Number of people killed by endoscopy	1

Table C2: Estimated benefits and harms of screening for stomach cancer using endoscopy as the secondary screening test for individuals who test positive on MG7-Ag

Number of people screened using MG7-Ag	100,000
Number of people with stomach cancer in the screened population	15
Number of cases missed by initial MG7-Ag screening	3
Number of people proceeding to endoscopy following a positive MG7-Ag screening result	4,411
Number of cases detected by endoscopy	8
Number of cases missed by endoscopy	4
Number of false positives from endoscopy	172
Number of people with morbidity from endoscopy	19
Number of people killed by endoscopy	0

Assumptions used in Appendix C:
Incidence of stomach cancer in people aged 40 and over = 15.2/100,000 (UK 2011age-standardised incidence rate for all ages = 7.6/100,000, doubled to provide an estimate of the incidence for persons aged 40 years and over)
Sensitivity of MG7-Ag = 77.5% (Zhang et al (2010)
Specificity of MG7-Ag = 95.6% (Zhang et al (2010)
Sensitivity of endoscopy = 69.4% (Choi et al 2011)
Specificity of endoscopy = 96.1% (Choi et al 2011)
Morbidity from endoscopy = 0.43% (2009 NSC review)
Mortality from endoscopy = 0.0008% (2009 NSC review)

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