Table 7 shows sensitivity and specificity when the cut-off point is moved according to the extent of cancer suspicion (A, B, C, D, E). When using high-density barium sulfate, the values for sensitivity were as follows: A: 13.70%, B: 27.40%, C: 50.68%, D: 84.93%, and E: 91.78%, and the values of specificity were as follows: A: 99.99%, B: 99.94%, C: 99.18%, D: 92.58%, and E: 91.43%. When using moderate-density barium sulfate, the values for sensitivity were as follows: A: 14.23%, B: 26.83%, C: 43.50%, D: 86.18%, and E: 92.28%, and the values for specificity were as follows: A: 99.99%, B: 99.93%, C: 99.17%, D: 92.19%, and E: 90.98%. The AUC value of high-density barium sulfate (0.935) was slightly higher than that of moderate-density barium sulfate (0.934); however, there was no significant difference in AUC values between moderate- and high-density barium sulfate ($P = 0.951$; Fig.1)

DISCUSSION

In the present study, the proportion of screenees for whom a workup examination was recommended (screening positives) was lower for high-density than for moderate-density barium sulfate. Specificity was higher for high-density than for moderate-density barium sulfate, but the difference was not remarkable. Sensitivity showed no significant difference between the two barium sulfates. The diagnostic validity of high-density and moderate-density barium sulfate screening was analyzed using AUC values. The findings of the present study indicate no significant difference in

diagnostic validity between the two barium sulfates.

The diagnostic validity of the screening tests was examined by follow-up with record linkage to the Cancer Registry. Cases of cancer detected within 1 year of the screening day were considered as cancer present at the time of screening, and the sensitivity and specificity were calculated.[31] Sensitivity and specificity are optimal measures for analyzing diagnostic validity, and are not dependent upon the prevalence of cancer. In addition, the ability of film reading to detect gastric cancer has been reported by Yatake et al.[31] using AUC analysis. The present study is the first to compare sensitivity, specificity, and AUC values between the two barium sulfates.

Previous studies of high-density barium sulfate revealed that it has a wider double-contrast range than that of conventional moderate-density preparations, and improved depiction of gastric cancer due to good barium adherence.[13] Furthermore, inadequate adhesion of barium to the gastric U (upper third) area[32] can be overcome using high-density barium sulfate.[10, 13] Many previous studies reported that image depiction ability of gastric mucosa was improved using high-density barium sulfate.[10, 33, 34–38] Because it has low viscosity and small volume, it is easy for screenees to drink.[9, 13–15, 34, 39, 40] Compared with moderate-density barium sulfate, its viscosity remains stable despite changes in barium temperature, and the pH and volume of gastric juice;[7, 8] the fluidity of high-density barium sulfate is excellent on fluoroscopic monitors.[9] Agglutination was found to be greater in high-density barium sulfate than in moderate-density barium sulfate in three reports,[10, 37, 38] as being equal in one report,[11] and as being less in two reports.[9, 35] Regarding outflow of barium sulfate to the outside of the stomach, this was found to be faster in high-density barium sulfate than

221 in moderate-density barium sulfate in two reports,[16,17] as being equal in two reports,[11,36] and as no
222 outflow in one report.[13] No significant difference has been found regarding gastric cancer detection
223 rate[19] between high- and moderate-density barium sulfates.[10,20–22,41,42] Regarding early gastric cancer
224 detection rate, four articles reported no significant differences[10,20–22] between the two preparations,
225 and three articles reported a significantly higher rate for high-density barium sulfate.[41–43] Yamamoto
226 et al. found no significant difference in radiation dose between screening conducted using high- and
227 moderate-density barium sulfate.[44,45] It has been reported that men aged 80 years and older have the
228 highest risk of mis-swallowing.[14,18] No significant difference in discharge time or discharge situation
229 has been found between the two barium sulfates.[13,15,46] Hamashima et al.[19] reported, "We could not
230 find any evidence on the excellence of gastric cancer screening using high-density barium sulfate
231 from the systematic review. Further appropriate research is obviously required to clarify the
232 diagnostic validity of the new method." The present study is the first in Japan to clarify sensitivity,
233 specificity, and AUC for gastric cancer screening with high-density barium sulfate.

234 The present study contains some limitations. First, the study was observational and the
235 subjects were not randomly assigned to receive high-density or moderate-density barium sulfate.
236 There was a significant difference in the sex and age distributions (all subjects) of screenees between
237 the high-density and moderate-density barium sulfate ($P< 0.05$). When sensitivity and specificity of
238 the two density barium sulfates were calculated by sex (male, female) and age group (≥60, <60),
239 sensitivity was higher for the moderate-density barium sulfate test than for the high-density test when
240 calculated for males, and higher for the high-density barium sulfate test than for the moderate-density

241 test when calculated for females. Sensitivity was higher for the moderate-density barium sulfate test
242 than for the high-density test by age (<60), and higher for the high-density barium sulfate test than
243 for the moderate-density test by age (≥60); however, the difference found for sensitivity was not
244 significant. This finding does not contradict the conclusions of the present study. A significant
245 difference was found for specificity, but the individual values for specificity showed no remarkable
246 differences. Trends regarding sex (male, female) and age group (≥60, <60) were much the same as
247 those in the subjects. The significant difference observed in specificity between the two barium
248 sulfate groups may have arisen because of the large number of subjects. Briefly, the large sample size
249 reduces the confidence interval to a significant difference. In addition, there is no clinical meaning in
250 the value of specificity alone; evaluation of diagnostic validity should analyze both sensibility and
251 specificity. Second, the results of the 1-year follow-up with record linkage to the Osaka Cancer
252 Registry were defined as the gold standard in the present study. The degree of completeness of the
253 Osaka Cancer Registry should be treated with caution, and a second standard should be developed in
254 addition to the 1-year follow-up. However, we consider that comparability was retained between the
255 two barium sulfate densities because the same follow-up methods were used and because of the
256 criteria for false negatives in the two groups. Third, it is the most important to guarantee the
257 comparability of 2 groups for comparing testing methods. In this study, the difference in the
258 diagnostic ability between the 19 radiological technologists and 20 radiologists was unclear, and the
259 comparability could not be guaranteed. However, since the same radiological technologists carried
260 out radiography using both the new and conventional methods, the same radiologists read the

radiograms, and the percentages of those who were involved in the examination using both methods were nearly the same, the effect of the difference in the diagnostic ability on the results of this study would be small.

This result is considered to reflect the improved depiction ability and fast passage of barium in the new method, although additional radiography has been actively conducted at the Screening Center when using both the conventional and new methods. The amount of barium within the stomach may be less in the new high-density barium sulfate method due to the small volume of barium swallowed and fast outflow from the stomach; accordingly, the radiographic technologists are required to rapidly turn and roll the screenees to obtain the films before the barium is lost. It will take some time before we can confirm that the diagnostic validity of the new method is better than that of the conventional method.

CONCLUSION

Specificity showed no remarkable differences between the two barium sulfates. Sensitivity showed no significant differences, and AUC value analysis revealed no significant differences between moderate- and high-density barium sulfate in screening for gastric cancer. Both screening tests with high-density and moderate-density barium sulfate showed similar validity in terms of sensitivity, specificity, and ROC curves. We consider that moderate- and high-density barium sulfate should

281 both be recommended for use in X-ray screening for gastric cancer.

282

283

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285

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Table 1. Sex and age distribution of screenees

	High-density barium sulfate				Moderate-density barium sulfate			
Age	Male	(%)	Female	(%)	Male	(%)	Female	(%)
<29	68	(0.2)	46	(0.2)	79	(0.2)	40	(0.1)
30–39	3,246	(11.1)	875	(4.6)	2,129	(4.4)	3,194	(4.2)
40–49	9,760	(33.4)	4,681	(24.5)	8,845	(18.3)	12,573	(16.7)
50–59	9,977	(34.1)	6,771	(35.4)	12,449	(25.8)	26,966	(35.8)
60–69	4,618	(15.8)	5,131	(26.9)	17,538	(36.4)	25,903	(34.4)
70–79	1,371	(4.7)	1,485	(7.8)	6,618	(13.7)	6,146	(8.2)
>80	183	(0.6)	124	(0.7)	588	(1.2)	429	(0.6)
Total	29,223	(100.0)	19,113	(100.0)	48,246	(100.0)	75,251	(100.0)

Cochran–Mantel–Haenszel test

Age and sex distribution between the two barium sulfates: $P < 0.05$

Table 2. Comparison of results of screening for the two barium sulfates

Result	High-density	(%)	Moderate-density	(%)	*P* value
Total screenees	48,336		123,497		
Those who were recommended for workup tests	4,201	(8.7)	11,341	(9.2)	0.001
Those who underwent workup tests	3,596	(85.6)	9,849	(86.8)	0.044
Gastric cancer detected	62	(0.13)	207	(0.17)	0.064
Early gastric cancer detected	39	(62.9)	140	(67.6)	0.489

Chi-square test

High-density: High-density barium sulfate
Moderate-density: Moderate-density barium sulfate

Table 3. Comparison of results of follow-up for all subjects

Screening		Cancer		
		Present	Absent	Total
High-density barium sulfate	Positive	67	4,134	4,201
	Negative	6	44,129	44,135
	Total	73	48,263	48,336
Moderate-density barium sulfate	Positive	227	11,114	11,341
	Negative	19	112,137	112,156
	Total	246	123,251	123,497

Period: Between January 1, 2000 and December 31, 2002

Table 4. Comparison of results of follow-up by sex (male, female) and age (≥60, <60)

Screening		Sex						Age					
		Male cancer			Female cancer			≥60 cancer			<60 cancer		
		Present	Absent	Total	Present	Absent	Total	Present	Absent	Total	Present	Absent	Total
High-density barium sulfate	Positive	53	2,640	2,693	14	1,494	1,508	42	1,439	1,481	25	2,695	2,720
	Negative	5	26,525	26,530	1	17,604	17,605	1	11,430	11,431	5	32,699	32,704
	Total	58	29,165	29,223	15	19,098	19,113	43	12,869	12,912	30	35,394	35,424
Moderate-density barium sulfate	Positive	146	5,580	5,726	81	5,534	5,615	181	6,169	6,350	46	4,945	4,991
	Negative	9	42,511	42,520	10	69,626	69,636	14	50,858	50,872	5	61,279	61,284
	Total	155	48,091	48,246	91	75,160	75,251	195	57,027	57,222	51	66,224	66,275

Period: Between January 1, 2000 and December 31, 2002

Table 5. Performance value of screening for the two barium sulfates for all subjects

	High-density	Moderate-density	*P* value
Sensitivity (%)	91.78	92.28	0.890
Specificity (%)	91.43	90.98	0.003

Chi-square test

High-density: High-density barium sı

Moderate-density: Moderate-density barium sulfate

Table 6. Performance value of screening for the two barium sulfates by sex (male, female) and age (≥60, <60)

	Sex						Age					
	Male			Female			≥60			<60		
	High	Moderate	*P* value	High	Moderate	*P* value	High	Moderate	*P* value	High	Moderate	*P* value
Sensitivity (%)	91.38	94.19	0.461	93.33	89.01	0.611	97.67	92.82	0.236	83.33	90.20	0.365
Specificity (%)	90.95	88.40	0.000	92.18	92.64	0.031	88.82	89.18	0.231	92.39	92.53	0.397

Chi-square test

High: High-density barium sulfate

Moderate: Moderate-density barium sulfate

Table 7. Sensitivity and specificity for the two barium sulfates by extent of cancer suspicion

	High-density barium sulfate		Moderate-density barium sulfate	
Cut-off point	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
A	13.70	99.99	14.23	99.99
B	27.40	99.94	26.83	99.93
C	50.68	99.18	43.50	99.17
D	84.93	92.58	86.18	92.19
E	91.78	91.43	92.28	90.98

Extent of cancer suspicion

A: Definitely cancer

B: Probably cancer

C: Possibly cancer

D: Suspicious of a benign lesion

E: Workup tests for confirmation

Figure legends

Fig. 1 Area under ROC curve (AUC) analysis of high- and moderate-density barium sulfate.

Extent of cancer suspicion

A: Definitely cancer

B: Probably cancer

C: Possibly cancer

D: Suspicious of a benign lesion

E: Workup tests for confirmation