technically more difficult and requires considerable experience.

CQ. What are the indications for endoscopic submucosal dissection?

- (1) Tumors requiring endoscopic en bloc resection, for which the snare technique is difficult to use; (2) intramucosal tumors accompanied by submucosal fibrosis, induced by biopsy or peristalsis of the lesion; (3) sporadic localized tumors that occur as a result of chronic inflammation; and (4) local residual early carcinoma after endoscopic resection are among the indications for ESD (Recommendation none, level of evidence C).

Comment: The Colorectal ESD Standardization Implementation Working Group proposed a draft entitled Criteria of Indications for Colorectal ESD [31]. It specifically states that colorectal ESD is indicated for tumors requiring endoscopic en bloc resection when it is difficult to use the snare technique, such as LST-NG (especially the pseudo-depressed type), tumors with a type VI pit pattern, shallow submucosal invasive carcinoma, large depressed tumors, and large elevated lesions that are probably malignant (large nodular lesions such as LST-G). Other lesions such as intramucosal tumors accompanied by submucosal fibrosis induced by biopsy or peristalsis of the lesion, sporadic localized tumors that occur as a result of chronic inflammation such as ulcerative colitis, and local residual early carcinoma after endoscopic resection, are also included in the indications for ESD. A cure rate of 83–88 % has been reported using ESD for local residual early carcinoma after endoscopic resection [54, 55]. In Japan, colorectal ESD has been covered by national health insurance since April 2012. It is indicated in early colorectal carcinomas, early carcinomas that are 2–5 cm in diameter. However, there were no significant differences in the outcome of colorectal ESD between lesions 2–5 cm in diameter and those $\leq$5 cm in diameter based on a prospective cohort study by the Japan Gastroenterological Endoscopy Society (JGES). Considering payments by national health insurance, no limitations on lesion size have been required for colorectal ESD.

CQ. Is biopsy essential for choosing the therapeutic strategy for colorectal lesions?

- This will depend on the characteristics of individual lesions. It is acceptable to decide a therapeutic strategy for colorectal lesions without biopsy (Recommendation 2 [100 %], level of evidence C).

Comment: Endoscopic procedures, especially magnifying endoscopy such as pit pattern diagnosis or image-enhanced endoscopy, avoid unnecessary biopsy for colorectal tumors. Biopsy should not be performed in polypectomy or EMR, as it increases medical expenses. In addition, it is clinically insignificant to randomly obtain biopsies for protruding lesions, as most are adenoma or carcinoma in adenoma. However, biopsy for a lesion suspected to be T1 carcinoma may acceptable, since histological information is helpful for planning the therapeutic strategy. Biopsy for superficial lesions (flat or depressed lesions) should not be performed prior to endoscopic resection, as it causes false-positive non-lifting signs due to submucosal fibrosis after injection during EMR [56]. It is important to understand whether the lesion is indicated for endoscopic resection through standard or magnifying endoscopic observation.

CQ. How is the choice made from among polypectomy, EMR, and ESD for colorectal tumors?

- Polypectomy is indicated for pedunculated or semi-pedunculated polyps, and EMR is indicated for sessile polyps or superficial lesions. ESD is indicated for lesions requiring endoscopic en bloc resection, although the lesions cannot be resected en bloc by snare techniques (Recommendation 2 [100 %], level of evidence C).

Comment: The choice of technique for endoscopic resection should be based on tumor morphology and size. Polypectomy is normally indicated for pedunculated or adenomatous semi-pedunculated polyps, while EMR is suitable for sessile, semi-pedunculated, or superficial tumors that are likely to be carcinoma [6, 57]. ESD allows complete en bloc resection regardless of the size of the lesion [28, 31, 58, 59]. Colorectal ESD is thus indicated for lesions requiring endoscopic en bloc resection when it is difficult to use the snare technique [31]. Moreover, en bloc resection is particularly indicated for depressed tumors or pseudo-depressed-type LST-NGs, as these tumors have a high incidence of submucosal invasion [28, 29]. In contrast, piecemeal EMR is acceptable for LST-G homogenous-type, since it is associated with a very low incidence of submucosal invasion [31]. EMR or ESD should be preferred over polypectomy for suspected submucosal invasive (T1) carcinoma.

CQ. Does colorectal carcinoma incidence decrease by endoscopic removal of colorectal adenoma?

- It is generally believed that the incidence of colorectal carcinoma decreases following endoscopic removal of colorectal adenomas, at least in Western countries, although there is limited data in Japan (Recommendation none, level of evidence B).

Comment: In 1993, the National Polyp Study (NPS) Workgroup reported that endoscopic removal of all

colorectal adenomatous polyps is associated with a decrease in the incidence of colorectal carcinoma from 76 to 90 % [60]. Since then, endoscopic removal of all adenomas during colonoscopy was strongly recommended in Western countries. In contrast, some Japanese endoscopists have reported that endoscopic polypectomy of all adenomas (especially for diminutive polyps) may not be effective in decreasing the incidence of colorectal carcinoma. Moreover, there is limited data in Japan. Regarding this CQ, two issues should be considered, namely the prevalence of carcinoma based on the size of the lesions and the interval of surveillance after endoscopic polypectomy. Regarding the former, in 1995, Sawada and Hiwatashi reported that the prevalence of carcinoma in patients with diminutive (<5 mm) polyps was 1.2 % (98.8 % were benign adenoma) [61]. While this proportion appears to be higher than that reported in Western countries (0.03–0.05 %), this discrepancy may be related to differences in pathological definitions. Nonetheless, the prevalence of carcinoma in patients with diminutive polyps is rather low. On the other hand, a single screening/surveillance colonoscopy session may not identify all polyps. Moreover, there are many reports concerning the clinical importance of de novo carcinoma. We note that a single colonoscopy with polyp removal is not a flawless procedure, and in particular, poor bowel preparation may be associated with a lower reported incidence of colorectal carcinoma [62–64]. Based on these points, it can be assumed that carcinoma can be prevented by endoscopic removal of polyps.

CQ. How should surveillance colonoscopy be planned after endoscopic removal of colorectal adenoma?

- Follow-up colonoscopy should be performed within 3 years after polypectomy (Recommendation 2 [100 %], level of evidence B).

Comment: The National Polyp Study (NPS) Workgroup recommended an interval of at least 3 years after colonoscopic removal of newly diagnosed adenomatous polyps and follow-up examination [65]. According to the European guidelines [66] and modified US guidelines [67], the most suitable interval for surveillance colonoscopy is recommended based on the number of adenomas, maximum size of polyps, and histopathological findings (including the presence of high-grade dysplasia) of resected lesions. As general guidance, patients with several (in European guidelines: <4, in US guidelines <9) small adenomas (low-grade dysplasia) <10 mm should undergo surveillance colonoscopy at 3 years following polypectomy. In contrast, patients with only one or two small low-grade adenomas should undergo routine screening (i.e., FOBT) according to the European guidelines, and surveillance colonoscopy after 5–10 years according to the US guidelines. Moreover, according to these guidelines, patients with many adenomas (>10) or high-grade dysplasia (known as intramucosal cancer in Japan) should undergo more intensive surveillance colonoscopy. In Japan, the decision to follow these guidelines is uncertain because management of diminutive adenoma (<5 mm) has not been established. In brief, endoscopists in the West attempt to remove all adenomas, whereas there is no uniform Japanese approach (removal or follow-up) for diminutive adenomas, and controversy remains in Japan [68–72]. The present guidelines, therefore, recommend the following based on data from a retrospective study carried out by the Japan Polyp Study Workgroup [73]: "Follow-up colonoscopy should be performed within 3 years after polypectomy."

Acknowledgments This article was supported by a Grant-in-Aid from the JSGE. The authors thank Dr. Shiro Oka (Hiroshima University Hospital) and Dr. Toshiaki Tanaka (University of Tokyo) for great assistance for data collection, data analysis, and manuscript preparation.

Conflict of interest Any financial relationship with enterprises, businesses, or academic institutions in the subject matter or materials discussed in the manuscript are listed as follows; (1) those from which the authors, the spouse, partner or immediate relatives of the authors, have received individually any income, honoraria or any other types of remuneration; Ikagaku Co., Ltd., Abbvie Inc., Eisai Co., Ltd., Kyorin Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Company Limited., Mitsubishi Tanabe Pharma Corporation; and (2) those from which the academic institutions of the authors received support (commercial/academic cooperation); Asahi Kasei Medical Co., Ltd., Ajinomoto Pharmaceuticals Co., Ltd., Astellas Pharma Inc., AstraZeneca K.K., Abbvie Inc., Eisai Co., Ltd., MSD K.K., Otsuka Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Kyorin Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Jimro Co., Ltd., GeneCare Research Institute Co., Ltd., Suzuken Co., Ltd., Zeria Pharmaceutical Co., Ltd., Century Medical, Inc., Daiichi Sankyo Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Company Limited., Mitsubishi Tanabe Pharma Corporation, Chugai Pharmaceutical Co., Ltd., Toray Industries, Inc., Bristol-Myers Squibb Company, Yakult Honsha Co., Ltd., UCB Japan Co. Ltd.

Appendix

Members of the Working Committee who created and evaluated the "Evidence-based clinical guidelines for management of colorectal polyps", JSGE

Director Responsible

Mamoru Watanabe (Department of Gastroenterology and Hepatology, Tokyo Medical and Dental University)

Executive Committee

Chair: Shinji Tanaka (Department of Endoscopy, Hiroshima University Hospital)

Vice-Chair: Yusuke Saitoh (Digestive Disease Center, Asahikawa City Hospital)

Members: Takayuki Matsumoto (Division of Gastroenterology, Iwate Medical University), Takahisa Matsuda (Endoscopy Division, National Cancer Center Hospital), Yasushi Iwao (Center for Preventive Medicine, Keio University Hospital), Masahiro Igarashi (Department of Endoscopy, Cancer Institute Ariake Hospital), Yasumoto Suzuki (Coloproctology Center, Matsushima Clinic), Hiroshi Nishida (Occupational Health Center, Panasonic Health Insurance Organization), Toshiaki Watanabe (Department of Surgical Oncology, University of Tokyo), Tamotsu Sugai (Department of Molecular Diagnostic Pathology, Iwate Medical University).

Evaluation Committee

Chair: Ken-ichi Sugihara (Department of Surgical Oncology, Tokyo Medical and Dental University)

Vice-Chair: Osamu Tsuruta (Digestive Disease Center and GI Endoscopy, Kurume University Hospital)

Members: Ichiro Hirata (Department of Gastroenterology, Fujita Health University School of Medicine), Nobuo Hiwatashi (Department of Gastroenterology, Iwaki Kyoritsu General Hospital), Hiroshi Saito (Research Center for Cancer Prevention and Screening, National Cancer Center).

The Japanese Society of Gastroenterology

President: Tooru Shimosegawa (Division of Gastroenterology, Tohoku University Graduate School of Medicine)

Former President: Kentaro Sugano (Jichi Medical University)

References

1. Yoshida M, Kinoshita Y, Watanabe M, JSGE clinical practice guidelines, et al. Standards, methods, and process of developing the guidelines. J Gastroenterol. 2014;. doi:10.1007/s00535-014-1016-1.
2. JSCCR Guidelines 2014 for the Treatment of Colorectal Cancer, published by Kanahara, Tokyo, 2014 (in Japanese, English version under preparation).
3. Tanaka S, Kashida H, Saito Y, et al. JGES Colorectal ESD/EMR Guidelines. Gastroenterol Endosc. 2014;56:1598–617 (in Japanese, English version under preparation).
4. Aldridge AJ, Simson JN. Histological assessment of colorectal adenomas by size. Are polyps less than 10 mm in size clinically important? Eur J Surg. 2001;167:777–81.
5. Ahlawat SK, Gupta N, Benjamin SB, et al. Large colorectal polyps: endoscopic management and rate of malignancy: does size matter? J Clin Gastroenterol. 2011;45:347–54.
6. Kudo S. Endoscopic mucosal resection of flat and depressed types of early colorectal cancer. Endoscopy. 1993;25:455–61.
7. Tanaka S, Oka S, Kaneko I, et al. Endoscopic submucosal dissection for colorectal neoplasia: possibility of standardization. Gastrointest Endosc. 2007;66:100–7.
8. Puli SR, Kakugawa Y, Gotoda T, et al. Meta-analysis and systematic review of colorectal endoscopic mucosal resection. World J Gastroenterol. 2009;15:4273–7.
9. Puli SR, Kakugawa Y, Saito Y, et al. Successful complete cure en-bloc resection of large non pedunculated colonic polyps by endoscopic submucosal dissection: a meta-analysis and systematic review. Ann Surg Oncol. 2009;16:2147–51.
10. Saitoh Y, Waxman I, West AB, et al. Prevalence and distinctive biological features of flat colorectal adenomas in a North American population. Gastroenterology. 2001;120:1657–65.
11. Saitoh Y, Iwashita A, Kudo S, et al. Result of project research [Management of colorectal diminutive lesions] in Japanese society for cancer for colon and rectum—guiding principle of endoscopic treatment for colorectal diminutive lesions with 5 mm or less. Stomach Intestine. 2009;44:1047–51 (in Japanese).
12. Tanaka S, Kaltenbach T, Chayama K, et al. High-magnification colonoscopy (with videos). Gastrointest Endosc. 2006;64:604–13.
13. Onoue K, Yamada H, Miyazaki T, et al. Natural history of colorectal diminutive polyps with 5 mm or less-prospective study. J Gastrointestinal Cancer Screen. 2008;46:729–34 (in Japanese with English abstract).
14. Toyonaga N, Nishino H, Suzuki Y, et al. Appropriate surveillance method after endoscopic resection of colorectal neoplasia. Gastroenterol Endosc. 2009;51:1121–8 (in Japanese with English abstract).
15. Gschwantler M, Kriwanek S, Langner E, et al. High-grade dysplasia and invasive carcinoma in colorectal adenomas: a multivariate analysis of the impact of adenoma and patient characteristics. Eur J Gastroenterol Hepatol. 2002;14:183–8.
16. Bretagne JF, Manfredi S, Piette C, et al. Yield of high-grade dysplasia based on polyp size detected at colonoscopy: a series of 2,295 examinations following a positive fecal occult blood test in a population-based study. Dis Colon Rectum. 2010;53:339–45.
17. Togashi K, Shimura K, Konishi F, et al. Prospective observation of small adenomas in patients after colorectal cancer surgery through magnification chromo colonoscopy. Dis Colon Rectum. 2008;51:196–201.
18. Bensen SP, Cole BF, Mott LA, et al. Colorectal hyperplastic polyps and risk of recurrence of adenomas and hyperplastic polyps. Polyps prevention study. Lancet. 1999;354:1873–4.
19. Laiyemo AO, Murphy G, Sansbury LB, et al. Hyperplastic polyps and the risk of adenoma recurrence in the polyp prevention trial. Clin Gastroenterol Hepatol. 2009;7:192–7.
20. Hasegawa S, Tsuruta O, Kawano H, et al. Endoscopic diagnosis of colonic serrated lesion—conventional endoscopic findings. Stomach Intestine. 2011;46:394–404 (in Japanese with English abstract).
21. Legget B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. Gastroenterology. 2010;138:2088–100.
22. Yoshimori K, Tsuruta O, Kawano H, et al. Serrated adenoma-endoscopic findings and treatment. Early Colorectal Cancer. 2006;10:291–6 (in Japanese with English abstract).
23. De Jesus-Monge WE, Gonzalez-Keelan MC, Cruz-Correa M. Serrated adenomas. Curr Gastroenterol Rep. 2009;11:420–7.
24. Matumoto T, Mizuno M, Shimizu M, et al. Clinico pathological features of serrated adenoma of the colorectum: comparison with traditional adenoma. J Clin Pathol. 1999;52:513–6.
25. Kashida H, Kudo S. New knowledge of colorectal polyp-concept, characters and diagnosis. J of Clinical and Experimental Medicine (IGAKU NO AYUMI) 2006 Supplement ver3:628–633 (in Japanese).
26. Uraoka T, Higashi R, Ohara N, et al. Endoscopic findings with magnification of serrated lesions in the colorectum. Stomach Intestine. 2011;46:406–16 (in Japanese with English abstract).
27. Kudo S, Lambert R, Allen JI, et al. Nonpolypoid neoplastic lesions of the colorectal mucosa. Gastrointest Endosc. 2008;68(Suppl):S3–47.
28. Saito Y, Fujii T, Kondo H, et al. Endoscopic treatment for laterally spreading tumors in the colon. Endoscopy. 2001;33:682–6.

29. Nishiyama H, Isomoto H, Yamaguchi N, et al. Endoscopic submucosal dissection for laterally spreading tumours of the colorectum in 200 consecutive cases. Surg Endosc. 2010;24:2881–7.
30. Uraoka T, Saito Y, Matsuda T, et al. Endoscopic indications for endoscopic mucosal resection of laterally spreading tumours in the colorectum. Gut. 2006;55:1592–7.
31. Tanaka S, Oka S, Chayama K. Colorectal endoscopic submucosal dissection: present status and future perspective, including its differentiation from endoscopic mucosal resection. J Gastroenterol. 2008;43:641–51.
32. Tanaka S, Haruma K, Oka S, et al. Clinicopathologic features and endoscopic treatment of superficially spreading colorectal neoplasms larger than 20 mm. Gastrointest Endosc. 2001;54:62–6.
33. Coverlizza S, Risio M, Ferrari A, et al. Colorectal adenomas containing invasive carcinoma: pathologic assessment of lymph node metastatic potential. Cancer. 1989;64:1937–47.
34. Kodahira S, Yao T, Nakamura K, et al. Submucosal invasive carcinoma of the colon and rectum with metastasis—analysis of 1,917 cases focused of sm invasion. Stomach Intestine. 1994;29:1137–42 (in Japanese).
35. Nakadoi K, Tanaka S, Kanao H, et al. Management of T1 colorectal carcinoma with special reference to criteria for curative endoscopic resection. J Gastroenterol Hepatol. 2012;27:1057–62.
36. Suh JH, Han KS, Kim BC, et al. Predictors for lymph node metastasis in T1 colorectal cancer. Endoscopy. 2012;44:590–5.
37. Son HJ, Song SY, Lee WY, et al. Characteristics of early colorectal carcinoma with lymph node metastatic disease. Hepatogastroenterology. 2008;55:1293–7.
38. Kim JH, Cheon JH, Kim TI, et al. Effectiveness of radical surgery after incomplete endoscopic mucosal resection for early colorectal cancers: a clinical study investigating risk factors of residual cancer. Dig Dis Sci. 2008;53:2941–6.
39. Tanaka S, Yokota T, Saito D, et al. Clinicopathologic features of early rectal carcinoma and indications for endoscopic treatment. Dis Colon Rectum. 1995;38:959–63.
40. Tanaka S, Haruma K, Oh-e H, et al. Conditions of curability after endoscopic resection for colorectal carcinoma with submucosally massive invasion. Oncol Rep. 2000;7:783–8.
41. Oka S, Tanaka S, Kanao H, et al. Mid-term prognosis after endoscopic resection for submucosal colorectal carcinoma: summary of a multicenter questionnaire survey conducted by the colorectal endoscopic resection standardization implementation working group in Japanese Society for Cancer of the Colon and Rectum. Dig Endosc. 2011;23:190–4.
42. Okabe S, Arai T, Maruyama S, et al. A clinicopathological investigation on superficial early invasive carcinomas of the colon and rectum. Surg Today. 1998;28:687–95.
43. Ueno H, Mochizuki H, Hashiguchi Y, et al. Risk factors for an adverse outcome in early invasive colorectal carcinoma. Gastroenterology. 2004;127:385–94.
44. Meining A, von Delius S, Eames TM, et al. Risk factors for unfavorable outcomes after endoscopic removal of submucosal invasive colorectal tumors. Clin Gastroenterol Hepatol. 2011;9:590–4.
45. Yoda Y, Ikematsu H, Matsuda T, et al. Long-term outcomes of submucosal invasive colorectal cancer. Stomach Intestine. 2011;46:1442–8 (in Japanese with English abstract).
46. Ikematsu H, Yoda Y, Matsuda T, et al. Long-term outcomes after resection for submucosal invasive colorectal cancers. Gastroenterology. 2013;144:551–9.
47. Tamura S, Nakajo K, Yokoyama Y, et al. Evaluation of endoscopic mucosal resection for laterally spreading rectal tumors. Endoscopy. 2004;36:306–12.
48. Luigiano C, Consolo P, Scaffidi MG, et al. Endoscopic mucosal resection for large and giant sessile and flat colorectal polyps: a single-center experience with long-term follow-up. Endoscopy. 2009;41:829–35.
49. Mannath J, Subramanian V, Singh R, et al. Polyp recurrence after endoscopic mucosal resection of sessile and flat colonic adenomas. Dig Dis Sci. 2011;56:2389–95.
50. Hurlstone DP, Sanders DS, Cross SS, et al. Colonoscopic resection of lateral spreading tumours: a prospective analysis of endoscopic mucosal resection. Gut. 2004;53:1334–9.
51. Saito Y, Fukuzawa M, Matsuda T, et al. Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection. Surg Endosc. 2010;24:343–52.
52. Terasaki M, Tanaka S, Oka S, et al. Clinical outcomes of endoscopic submucosal dissection and endoscopic mucosal resection for laterally spreading tumors larger than 20 mm. J Gastroenterol Hepatol. 2012;27:734–40.
53. Tanaka S, Terasaki M, Hayashi N, et al. Warning for unprincipled colorectal endoscopic submucosal dis- section: accurate diagnosis and reasonable treatment strategy. Dig Endosc. 2013;25:107–16.
54. Hurlstone DP, Shorthouse AJ, Brown SR, et al. Salvage endoscopic submucosal dissection for residual or local recurrent intraepithelial neoplasia in the colorectum: a prospective analysis. Colorectal Dis. 2008;10:891–7.
55. Kuroki Y, Hoteya S, Mitani T, et al. Endoscopic submucosal dissection for residual/locally recurrent lesions after endoscopic therapy for colorectal tumors. J Gastroenterol Hepatol. 2010;25:1747–53.
56. Dirschmid K, Kiesler J, Mathis G, et al. Epithelial misplacement after biopsy of colorectal adenomas. Am J Surg Pathol. 1993;17:1262–5.
57. Deyhle P, et al. A method for endoscopic electro resection of sessile colonic polyps. Endoscopy. 1973;5:38–40.
58. Kobayashi N, Saito Y, Uraoka T, et al. Treatment strategy for laterally spreading tumors in Japan: before and after the introduction of endoscopic submucosal dissection. J Gastroenterol Hepatol. 2009;24:1387–92.
59. Nakajima T, Saito Y, Tanaka S, et al. Current status of endoscopic resection strategy for large, early colorectal neoplasia in Japan. Surg Endosc. 2013;27:3262–70.
60. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med. 1993;329:1977–81.
61. Sawada T, Hiwatashi N, et al. Report from the workgroup of Ministry of Health. Labor Welf. 1995;H6:66–72 (in Japanese).
62. Igarashi M, Katsumata T. How to follow the residual colorectal polyps? (Chapter; How should we perform colorectal polypectomy? Edit: Tada S, Kudo S, Nihon Medical Center, Tokyo, 1997: 155–160 (in Japanese).
63. Nozaki R, Takagi K, Takano M, et al. Clinical investigation of colorectal cancer detected by follow-up colonoscopy after endoscopic polypectomy. Dis Colon Rectum. 1997;40:S16–22.
64. Nusko G, Hahn EG, Mansmann U. Risk of advanced metachronous colorectal adenoma during long-term follow-up. Int J Colorectal Dis. 2008;23:1065–71.
65. Winawer SJ, Zauber AG, O'Brien MJ, et al. Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. The National Polyp Study Work group. N Engl J Med. 1993;328:901–6.
66. Atkin WS, Valori R, Kuipers EJ, et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition- Colonoscopic surveillance following adenoma removal. Endoscopy. 2012;44(Suppl 3):S151–63.
67. Lieberman DA, Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a

consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2012;143:844–57.
68. Suzuki Y, Matsuike T, Nozawa H, et al. Treatment strategy for colorectal polyps and surveillance method by total colonoscopy. Ther Res. 1997;18:S362–5 (in Japanese).
69. Fukutomi Y, Moriwaki H, Nagase S, et al. Metachronous colon tumors: risk factors and rationale for the surveillance colonoscopy after initial polypectomy. J Cancer Res Clin Oncol. 2002;128:569–74.
70. Yamaji Y, Mitsushima T, Ikuma H, et al. Incidence and recurrence rates of colorectal adenomas estimated by annually repeated colonoscopies on asymptomatic Japanese. Gut. 2004;53:568–72.
71. Asano M, Matsuda Y, Kawai M, et al. Long-term outcome and surveillance after endoscopic removal for colorectal adenoma: from the viewpoint of the cases with multiple colorectal polyps. Dig Med. 2006;43:299–306 (in Japanese).
72. Kawamura T, Ueda M, Cho E. Surveillance after colonoscopic removal of adenomatous polyps. Dig Med. 2006;43:307–10 (in Japanese).
73. Matsuda T, Fujii T, Sano Y, et al. Five-year incidence of advanced neoplasia after initial colonoscopy in Japan: a multicenter retrospective cohort study. Jpn J Clin Oncol. 2009;39:435–42.

Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan Strategic Anti-cancer Randomized Trial (J-START): a randomised controlled trial

Noriaki Ohuchi, Akihiko Suzuki, Tomotaka Sobue, Masaaki Kawai, Seiichiro Yamamoto, Ying-Fang Zheng, Yoko Narikawa Shiono, Hiroshi Saito, Shinichi Kuriyama, Eriko Tohno, Tokiko Endo, Akira Fukao, Ichiro Tsuji, Takuhiro Yamaguchi, Yasuo Ohashi, Mamoru Fukuda, Takanori Ishida, for the J-START investigator groups

Summary

Background Mammography is the only proven method for breast cancer screening that reduces mortality, although it is inaccurate in young women or women with dense breasts. We investigated the efficacy of adjunctive ultrasonography.

Methods Between July, 2007, and March, 2011, we enrolled asymptomatic women aged 40–49 years at 42 study sites in 23 prefectures into the Japan Strategic Anti-cancer Randomized Trial (J-START). Eligible women had no history of any cancer in the previous 5 years and were expected to live for more than 5 years. Randomisation was done centrally by the Japan Clinical Research Support Unit. Participants were randomly assigned in 1:1 ratio to undergo mammography and ultrasonography (intervention group) or mammography alone (control group) twice in 2 years. The primary outcome was sensitivity, specificity, cancer detection rate, and stage distribution at the first round of screening. Analysis was by intention to treat. This study is registered, number UMIN000000757.

Findings Of 72 998 women enrolled, 36 859 were assigned to the intervention group and 36 139 to the control group. Sensitivity was significantly higher in the intervention group than in the control group (91·1%, 95% CI 87·2–95·0 *vs* 77·0%, 70·3–83·7; p=0·0004), whereas specificity was significantly lower (87·7%, 87·3–88·0 *vs* 91·4%, 91·1–91·7; p<0·0001). More cancers were detected in the intervention group than in the control group (184 [0·50%] *vs* 117 [0·32%], p=0·0003) and were more frequently stage 0 and I (144 [71·3%] *vs* 79 [52·0%], p=0·0194). 18 (0·05%) interval cancers were detected in the intervention group compared with 35 (0·10%) in the control group (p=0·034).

Interpretation Adjunctive ultrasonography increases sensitivity and detection rate of early cancers.

Funding Ministry of Health, Labour and Welfare of Japan.

Lancet 2016; 387: 341–48

Published Online November 4, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00774-6

See Comment page 313

Department of Surgical Oncology (Prof N Ohuchi PhD, A Suzuki PhD, Y-F Zheng PhD, Y N Shiono PhD, T Ishida PhD), **Department of Public Health** (Prof I Tsuji PhD), and **Department of Biostatistics** (Prof T Yamaguchi PhD), **Graduate School of Medicine, Tohoku University, Sendai, Japan; Department of Disaster-Related Public Health, International Research Institute of Disaster Science, Tohoku University, Sendai, Japan** (Prof S Kuriyama PhD); **Department of Environmental and Population Sciences, Graduate School of Medicine, Osaka University, Osaka, Japan** (Prof T Sobue MD); **Department of Breast Surgery, Miyagi Cancer Centre Hospital, Miyagi, Japan** (M Kawai PhD); **Department of Screening Assessment and Management, Research Centre for Cancer Prevention and Screening, National Cancer Centre, Tokyo, Japan** (S Yamamoto PhD, H Saito PhD); **Department of Radiology, Tsukuba Health Evaluation Centre, Tsukuba, Japan** (E Tohno PhD); **Department of Radiology, Higashi Nagoya National Hospital, Nagoya, Japan** (T Endo PhD); **Department of Public Health, Yamagata University School of Medicine, Yamagata, Japan** (Prof A Fukao PhD); **Department of Integrated Science and Engineering for Sustainable Society, Chuo University, Tokyo, Japan** (Prof Y Ohashi PhD); **and Department of Surgery,**

Introduction

The incidence of breast cancer continues to increase worldwide. Incidence remains highest in the USA and Europe, but has been increasing substantially in Japan and other Asian countries over the past three decades.[1–4] Early detection and access to optimum treatment are crucial to reduce mortality associated with breast cancer. Many countries have adopted national mammography screening programmes based on the results of randomised controlled trials (RCTs) done in developed countries. Although mammography is the only method that has evidence supporting mortality reduction for breast cancer, accuracy is reduced in women with high-density breast tissue and in young women.[5–7] Asian women characteristically have higher-density breasts than do women from other ethnic groups.[8–10] Consequently high accuracy is difficult to achieve with mammography screening alone. Furthermore, the age-specific incidence of female breast cancer in Asia peaks at age 40–49 years, whereas in western countries the peak is at age 60–70 years.[2] Asian countries must, therefore, take measures to address the accuracy of breast cancer screening in women aged 40–49 years.

Ultrasonography is one candidate to improve examination sensitivity because it can detect breast cancer at an early stage on the basis of the mass shape, even in the dense parenchyma of premenopausal women. Some clinical trials and observational studies have shown that mammography with adjunctive ultrasonography increased screening sensitivity and detection rates and lowered the frequency of interval cancers in women with dense breasts.[11–18] However, the addition of ultrasonography to mammography has substantially increased the number of false-positive findings.[17,19] Breast cancer screening including ultrasonography has not been assessed in RCTs in specified groups or for population screening and, therefore, its effect on detection of interval cancers cannot be estimated from published studies.[20–22] We did the Japan Strategic Anti-cancer Randomized Trial (J-START) to assess the efficacy of adjunctive ultrasonography in screening for breast cancer in Japanese women aged 40–49 years.

St Marianna University Breast and Imaging Centre, Kawasaki, Japan (M Fukuda PhD)

Correspondence to: Prof Noriaki Ohuchi, Department of Surgical Oncology, Tohoku University Graduate School of Medicine 1-1, Seiryo-machi, Aoba-ku, Sendai, Miyagi, 980-8574, Japan noriaki-ohuchi@med.tohoku.ac.jp

Methods

Participants

The design, standardisation of screening examinations, and study enrolment have been described in detail previously.[23,24] Briefly, between July, 2007, and March, 2011, we enrolled asymptomatic women in 42 study sites in 23 of 47 prefectures in Japan.[8,23] Eligible women were aged 40–49 years without a history of breast cancer, including in-situ cancer, or other cancers in the previous 5 years, and who had life expectancy of more than 5 years.

Trained clinical research coordinators or research staff obtained written informed consent from all women at each study site.[24] The study protocol was developed in accordance with the principles of the Declaration of Helsinki. We adhered strictly to the ethics guidelines for clinical studies issued by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare of Japan. Ethics approval was obtained from Tohoku University School of Medicine Research Ethics Committee and the Japan Anticancer Society.[23]

Randomisation and masking

We asked each study site to choose its method of allocation—individual RCT, cluster RCT, or non-RCT—on the basis of feasibility. According to the study protocol, sites that chose non-RCT would be excluded from the analysis. At cluster randomisation sites the clusters were balanced for numbers of participants. Deviations were defined in the statistical analysis plan (appendix).

See Online for appendix

Randomisation was done centrally by the Japan Clinical Research Support Unit, which was responsible for data management and trial operations, independently of Tohoku University. Women were randomised in a 1:1 ratio to receive screening by mammography plus ultrasonography, with or without clinical breast examination (intervention group) or mammography with or without clinical breast examination (control group) twice within a 2-year period. Allocation codes were kept in sealed envelopes that were sent to the principal investigators at each study site before randmisation. Screening allocations could not be masked for participants and study coordinators, but an independent panel that assessed outcomes was unaware of group assignment.

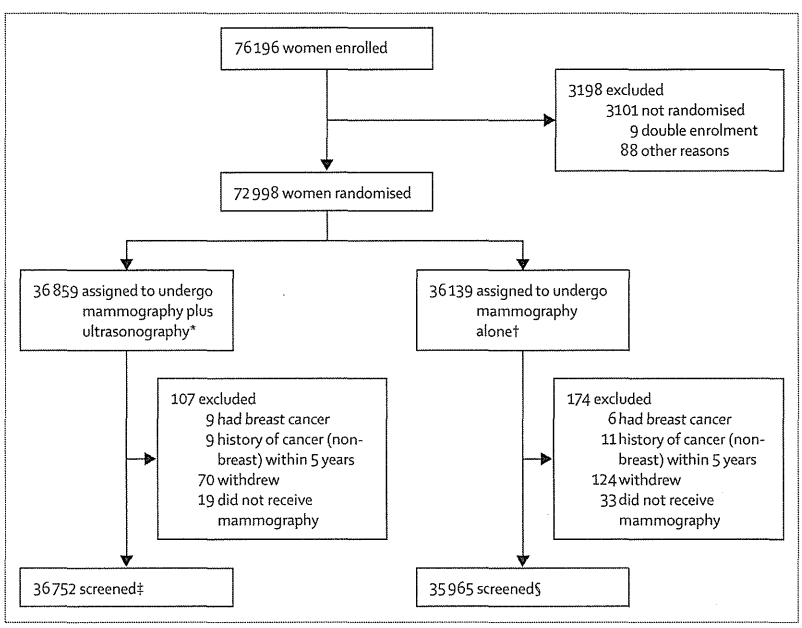


Figure: **Trial profile**

*26 434 enrolled in individual and 10 245 in cluster randomised controlled trials. †26 411 enrolled in individual 9278 in cluster randomised controlled trials. ‡Four women did not undergo ultrasonography. §Five women underwent ultrasonography.

Screening

Standard mammography and ultrasonography techniques were used at all participating facilities[23,24] and images were interpreted at each study site with double reading by two authorised physicians. Clinical examination was performed by physicians. Ultrasonography was done at each study site by trained clinical examiners, mostly clinical technologists, who had participated in a 2-day educational programme before screening started. The results were reassessed by physicians at the study sites, including radiologists and breast surgeons.

The independently assessed findings of mammography, ultrasonography, and clinical examination were classified into five categories that are used locally and internationally: 1, no findings; 2, benign; 3, probably benign but further assessment needed; 4, probably malignant; 5, malignant.[23,25–27] If further assessments were deemed necessary, results were taken to be positive if scores of 3 or higher were assigned. Mammography acquisition, practice, apparatus, and interpretation were certified by the Japan Central Organization on Quality Assurance of Breast Cancer Screening. Ultrasonography acquisition, practice, apparatus, and interpretation were certified by the Japan Association of Breast and Thyroid Sonology (JABTS).[24,28] Further details of screening methods are provided in the study protocol and in the appendix.

Follow-up

Breast cancers were diagnosed by assessment of first-round and second-round screening results or by a postal survey at the time of the second-round screening for women who did not attend. If data were incomplete, we used the Japan Clinical Research Support Unit to look up women's vital status from residential registers. To calculate the sensitivity of first-round screening, we defined screen-detected breast cancers as those categorised as 3–5 at the first round and interval cancers as those diagnosed between the first round and the second round of screening for which the initial category had been 1 or 2. All participants without breast cancer at either screening were followed up by assessment of screening records, questionnaire, and official cancer registry. Cases diagnosed after the second round of screening were not counted. Tumour stage was classified

with the Union for International Cancer Control Tumour Node Metastatic classification at referral hospitals and reported with histopathological findings.[29] A data and safety monitoring board was established to monitor the progress of the study every 6 months.

Statistical analysis

The primary outcome was sensitivity, specificity, cancer detection rate, and distribution of cancer stage at the first round of screening. The secondary outcome was rate of advanced breast cancers after the initial screening, but these data are not reported here. The sample size was calculated according to the hypothesis that adjunctive ultrasonography would improve screening sensitivity. We had shown previously that sensitivity of mammography screening was 71% in women aged 40–49 years, 85% in those aged 50–59 years, and 86% in those aged 60–69 years.[6] Therefore, we assumed that the sensitivity would increase from 71% to 86% by adding ultrasonography. We calculated that 130 confirmed cases of breast cancer would be needed to show this difference with 5% significance (two-sided) and 80% power and, therefore, that 42 500 women would need to be assigned to each group, based on prevalence of 0·003% among women aged 40–49 years.[6] We recruited 76 196 women, which, on the basis of the original calculation, would provide 75% statistical power to test the hypothesis. However, the incidence of breast cancer was expected to be higher than originally calculated, since the incidence in Japan is continuously increasing. Therefore, we estimated that the study would still have sufficient power to assess the primary endpoint, which was confirmed by the data monitoring committee after the second round of screening.

Analyses were done by intention to treat (appendix). There was no heterogeneity in the results between participants enrolled in individual and cluster RCTs (appendix), and the results are presented for all included women. First-round screening performance outcomes were assessed with generalised estimating equations with an exchangeable working correlation matrix and robust SEs. All tests were two-sided and significance was set at 5%. All statistical analyses were done with SAS version 9.2. This trial is registered, number UMIN000000757.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to most datasets and all summary estimates from each dataset, and had final responsibility for the decision to submit for publication.

Results

72 998 participants were randomised, of whom 36 859 were assigned to the intervention group and 36 139 to the control group (figure). 36 752 (99·7%) and 35 965 (99·5%), respectively, underwent screening. Data were unavailable for 1538 (2·1%) women at June 30, 2014. Baseline characteristics were similar in the two groups (table 1).

	All participants (n=72 717)	Intervention group (n=36 752)	Control group (n=35 965)
Age at randomisation (years)	44 (3·0)	44 (3·0)	44 (3·0)
Ever undergone breast cancer screening			
No	16 867 (23·2%)	8432 (22·9%)	8435 (23·5%)
Yes	55 838 (76·8%)	28 310 (77·0)	27 528 (76·5%)
Unknown or data missing	12 (<0·1%)	10 (<0·1%)	2 (<0·1%)
Time since most recent breast cancer screening (months)			
<12	11 460 (15·8%)	5882 (16·0%)	5578 (15·5%)
12–24	18 213 (25·1%)	9184 (25·0%)	9029 (25·1%)
25–36	14 096 (19·4%)	7128 (19·4%)	6968 (19·4%)
>36	10 802 (14·9%)	5531 (15·1%)	5271 (14·7%)
Unknown or data missing	18 146 (25·0%)	9027 (24·6%)	9119 (25·4%)
Method of most recent breast cancer screening			
Mammography			
No	16 303 (22·4%)	8285 (22·5%)	8018 (22·3%)
Yes	39 525 (54·4%)	20 023 (54·5%)	19 502 (54·2%)
Unknown or data missing	16 889 (23·2%)	8444 (23·0%)	8445 (23·5%)
Ultrasonography			
No	45 264 (62·3%)	22 849 (62·2%)	22 415 (62·3%)
Yes	10 564 (14·5%)	5459 (14·9%)	5105 (14·2%)
Unknown or data missing	16 889 (23·2%)	8444 (23·0%)	8445 (23·5%)
Clinical breast examination			
No	5247 (7·2%)	2635 (7·2%)	2612 (7·3%)
Yes	50 581 (69·6%)	25 673 (69·9%)	24 908 (69·3%)
Unknown or data missing	16 889 (23·2%)	8444 (23·0%)	8445 (23·5%)
Age at menarche (years)			
7–11	15 269 (21·0%)	7661 (20·9%)	7608 (21·2%)
12–13	41 682 (57·3%)	21 090 (57·4%)	20 592 (57·3%)
≥14	15 671 (21·6%)	7950 (21·6%)	7721 (21·5%)
Unknown or data missing	95 (0·1%)	51 (0·1%)	44 (0·1%)
Menopausal status			
Premenopausal	55 007 (75·7%)	27 742 (75·5%)	27 265 (75·8%)
Perimenopausal	13 394 (18·4%)	6775 (18·4%)	6619 (18·4%)
Postmenopausal	4272 (5·8%)	2208 (6·0%)	2064 (5·7%)
Unknown or data missing	44 (0·1%)	27 (0·1%)	17 (0·1%)
Number of preganancies			
0	8749 (12·0%)	4429 (12·0%)	4320 (12·1%)
1	8814 (12·1%)	4507 (12·0%)	4307 (12·3%)
2	25 225 (34·7%)	12 659 (34·9%)	12 566 (34·4%)
3–4	24 091 (33·1%)	12 237 (33·0%)	11 854 (33·3%)
5–10	3422 (4·7%)	1752 (4·6%)	1670 (4·8%)
Unknown or data missing	2416 (3·3%)	1168 (3·5%)	1248 (3·2%)
Number of pregnancies delivered			
Nulliparous	9506 (13·1%)	4858 (13·2%)	4648 (12·9%)
1	11 020 (15·2%)	5564 (15·1%)	5456 (15·2%)
2	32 142 (44·2%)	16 174 (44·0%)	15 968 (44·4%)
3	14 973 (20·6%)	7638 (20·8%)	7335 (20·4%)
4–8	2155 (3·0%)	1090 (3·0%)	1065 (3·0%)
Unknown or data missing	2921 (4·0%)	1428 (3·9%)	1493 (4·2%)

(Table 1 continues on next page)

	All participants (n=72 717)	Intervention group (n=36 752)	Control group (n=35 965)
(Continued from previous page)			
Age at first birth (years)			
<20	675 (0·9%)	354 (1·0%)	321 (0·9%)
20–24	9186 (12·6%)	4717 (12·8%)	4469 (12·4%)
25–29	23 365 (32·1%)	11 817 (32·2%)	11 548 (32·1%)
30–39	15 441 (21·2%)	7702 (21·0%)	7739 (21·5%)
40–49	430 (0·6%)	222 (0·6%)	208 (0·6%)
Unknown or data missing	23 620 (32·5%)	11 940 (32·5%)	11 680 (32·5%)
Ever breastfed children			
Yes	56 215 (77·3%)	28 432 (77·4%)	27 783 (77·3%)
No	14 974 (20·6%)	7587 (20·6%)	7387 (20·5%)
Unknown or data missing	1528 (2·1%)	733 (2·0%)	795 (2·2%)
Number of first-degree female relatives with breast cancer			
0	69 304 (95·3%)	34 988 (95·2%)	34 316 (95·4%)
1	3344 (4·6%)	1727 (4·7%)	1617 (4·5%)
>1	69 (0·1%)	37 (0·1%)	32 (0·1%)
Ever had breast surgery	1462 (2·0%)	754 (2·1%)	708 (2·0%)
Ever had benign neoplasm	917 (1·3%)	489 (1·3%)	428 (1·2%)
Ever had breast inflammation	538 (0·7%)	264 (0·7%)	274 (0·8%)

Data are mean (SD) or number (%).

Table 1: **Baseline characteristics**

The mean age of participants was 44·0 (SD 3·0) years. 3344 (4·6%) participants reported a history of breast cancer in first-degree female relatives and 917 (1·3%) reported having ever had one or more benign breast diseases.

Attendance at both screening visits was high (75%), and the proportion of participants not covered was 2%. The sensitivity of screening was higher in the intervention group than in the control group (p=0·0004), but specificity was lower (p<0·0001, table 2). Mammography alone detected notably more cancers in the control group than in the intervention group, but ultrasonography alone detected 67 cases (table 2).

Screening-detected cancers were more frequently clinical stage 0 and I in the intervention group than in the control group (144 [71·3%] *vs* 79 [52·0%], p=0·0194; table 3). The frequency of breast cancers of clinical stage II or worse did not differ significantly between groups. 48 (78%) of 61 cancers detected by ultrasonography alone were stage 0–I. The screening detection rate overall was increased by 0·17% (95% CI 0·08–0·27) in the intervention group (p=0·0003).

18 interval cancers (0·05%, 95% CI 0·03–0·07) were diagnosed in the intervention group, compared with 35 (0·10%, 0·07–0·13) in the control group. Thus ultrasonography was associated with a decrease of 0·05% in interval cancers (appendix). 128 (70%) of 184 cancers

	Confirmed breast cancer		No breast cancer		Status unknown	Total
	Number of participants	Sensitivity (95% CI)*	Number of participants	Specificity (95% CI)†		
Intervention group (n=36 752)						
MG+, US–, CBE+/–	41	..	1876	..	11	1928 (5·2%)
MG+, US+, CBE+/–	76	..	424	..	5	505 (1·4%)
MG–, US+, CBE+/–	67	..	1865	..	18	1950 (5·3%)
Total MG+	117	57·9% (51·0–64·8)	..	..	0	117 (<0·01%)
Total US+	143	70·8% (64·0–77·0)	..	..	0	143 (<0·01%)
Total CBE+	46	22·8% (17·2–29·2)	..	..	0	46 (<0·01%)
Only MG+	34	16·8% (11·7–22·0)	..	..	0	34 (<0·01%)
Only US+	61	30·2% (23·9–36·5)	1765	..	0	61 (<0·01%)
Only CBE+	0	NA	262	..	2	264 (0·7%)
Any positive	184‡	91·1% (87·2–95·0)	4427§	..	36	4647 (12·6%)
All negative	18¶	..	31 420‖	87·7% (87·3–88·0)	667	32 105 (87·4%)
Control group (n=35 965)						
MG+, CBE+/–	109	71·7% (63·8–78·7)	2576	..	17	2702 (7·5%)
MG–, CBE+	8	5·3% (2·3–10·1)	439	..	4	451 (1·3%)
Only MG+	72	47·4% (39·4–55·3)	..	..	0	72 (<0·01%)
Total CBE+	45	29·6% (22·4–36·9)	..	..	0	45 (<0·01%)
Either positive	117‡	77·0% (70·3–83·7)	3015§	..	21	3153 (8·8%)
Both negative	35¶	..	31 963‖	91·4% (91·1–91·7)	814	32 812 (91·2%)

Percentages might not total 100% due to rounding. MG=mammography. US=ultrasonography. CBE=clinical breast examination. NA=not applicable. *p=0·0004 for proportion difference between groups. †p<0·0001 for proportion difference between groups. ‡Screening-detected breast cancers. §False positive. ¶Interval breast cancers. ‖True negative.

Table 2: Results of first round of screening

	Clinical stage*					Total	Stage 0–I	Stage II or worse
	0	I	II	III or IV	Data missing			
Intervention group (n=36 752)								
MG+, US–, CBE+	3 (1·5%)	2 (1·0%)	2 (1·0%)	0	0	7 (3·5%)	5 (2·5%)	2 (1·0%)
MG+, US–, CBE+/–	20 (10·0%)	10 (5·0%)	3 (1·5%)	0	1 (0·5%)	34 (16·8%)	30 (14·9%)	3 (1·5%)
MG+, US+, CBE+	5 (2·5%)	16 (7·9%)	10 (5·0%)	2 (1·0%)	0	33 (16·3%)	21 (10·4%)	12 (5·9%)
MG+, US+, CBE–	15 (7·4%)	21 (10·4%)	5 (2·5%)	2 (1·0%)	0	43 (21·3%)	35 (17·3%)	8 (4·0%)
MG–, US+, CBE+	2 (1·0%)	3 (1·5%)	1 (0·5%)	0	0	6 (3·0%)	5 (2·5%)	1 (0·5%)
MG–, US+, CBE–	9 (4·5%)	39 (19·3%)	10 (5·0%)	1 (0·5%)	2 (1·0%)	61 (30·2%)	48 (23·8%)	13 (6·4%)
MG–, US–, CBE+	0	0	0	0	0	0	0	0
MG–, US–, CBE–	1 (0·5%)	8 (4·0%)	8 (4·0%)	1 (0·5%)	0	18 (8·9%)	9 (4·5%)	9 (4·5%)
Only MG+	40 (19·8%)	51 (25·3%)	21 (10·4%)	4 (2·0%)	1 (0·5%)	117 (57·9%)	91 (45·1%)	25 (12·4%)
Only US+	28 (13·8%)	81 (40·1%)	27 (13·4%)	5 (2·5%)	2 (1·0%)	143 (70·8%)	109 (54·0%)	32 (15·8%)
Only CBE+	10 (4·9%)	21 (10·4%)	13 (6·4%)	2 (1·0%)	0	46 (22·8%)	31 (15·4%)	15 (7·4%)
Any positive	51 (25·2%)	93 (46·0%)	32 (15·8%)	5 (2·5%)	3 (1·5%)	184 (91·1%)	144 (71·3%)	37 (18·3%)
Relative sensitivity (US/MG)	0·70	1·59	1·29	1·25	2·00	1·22	..	..
Control group (n=35 965)								
MG+, CBE+	2 (1·3%)	14 (9·2%)	19 (12·5%)	2 (1·3%)	0	37 (24·3%)	16 (10·5%)	21 (13·8%)
MG+, CBE–	28 (18·4%)	28 (18·4%)	15 (9·9%)	1 (0·7%)	0	72 (47·4%)	56 (36·8%)	16 (10·3%)
MG, CBE+	1 (0·7%)	6 (4·0%)	1 (0·7%)	0	0	8 (5·3%)	7 (4·6%)	1 (0·7%)
Both negative	8 (5·3%)	17 (11·2%)	9 (5·9%)	1 (0·7%)	0	35 (23·0%)	25 (16·5%)	10 (6·6%)
MG+	30 (2·0%)	42 (27·6%)	34 (22·4%)	3 (2·0%)	0	109 (71·7%)	72 (47·4%)	37 (24·3%)
CBE+	3 (1·3%)	20 (13·2%)	20 (13·2%)	2 (1·3%)	0	45 (29·6%)	23 (15·1%)	22 (14·5%)
Either positive	31 (2·0%)	48 (31·6%)	35 (23·0%)	3 (2·0%)	0	117 (77·0%)	79 (52·0%)	38 (25·0%)
Relative sensitivity (CBE/MG)	0·1	0·48	0·59	0·67	0	0·41	..	..

Data are number (%), unless otherwise indicated. MG=mammography. US=ultrasonography. CBE=clinical breast examination. *Based on the Union for International Cancer Control Tumour Node Metastases classification, seventh edition.

Table 3: **Distribution of clinical stages of breast cancer**

detected in the intervention group were invasive, compared with 86 (74%) of 117 in the control group; 16 (89%) of 18 and 27 (77%) of 35 of interval cancers, respectively, were invasive (table 4).

Further assessment was recommended for 4647 particpants in the intervention group compared with 3153 in the control group (table 5). The number of biopsies done owing to the first round of screening was higher in the intervention group than in the control group. There were no complications or adverse events associated with mammography and ultrasonography throughout the screening period.

Discussion

Mammography with adjunctive ultrasonography was associated with a significantly higher detection rate of breast cancer than mammography alone. The main strength of this study is that it differed from previous studies in several important ways (panel). Our study design enabled recruitment at multiple centres to ensure a large study population with good adherence and a follow-up rate of 98%, which was sufficient quality compared with the populations in previous studies.[17] Attendance at both screening visits was high and surgical outcomes after recall were independently reviewed. Our original target sample size was 85 000 for the overall study population, based on the number of cases needed to detect a difference between groups and expected prevalence. Our final results are based on a sample of 72 717 women, but, because the number of cases of breast cancer was 354, the study had sufficient power to detect a clinically meaningful difference in sensitivity.

Sensitivity was higher in the intervention group than in the control group because of a lower number of interval cancers (18 *vs* 35) and because 67 additional cases were detected by ultrasonography. In the intervention group, 78% of breast cancers detected by ultrasonography alone were clinical stage 0–I, and most were invasive and node negative. These findings are similar to those in previous studies where ultrasonography detected breast cancers at early and preclinical stages.[11,13,14,17] The difference between the intervention and control groups in the total number of breast cancers detected (202 *vs* 152) might be explained by the ability of ultrasonography to depict additional cancers, which is supported by our finding of fewer interval cancers in the intervention group (18 *vs* 35). No breast cancers were detected by clinical examination alone in the intervention group. By contrast, eight breast

	Intervention group (n=36752)						Control group (n=35965)			
	Screen-detected cancers					Interval cancers (n=18)	Screen-detected cancers			Interval cancers (n=35)
	Total (n=184)	MG+ and US+ (n=76)	Only MG+ (n=41)	Only US+ (n=67)	Only CBE+ (n=0)		Total (n=117)	Only MG+ (n=109)	Only CBE+ (n=8)	
Time since initial screening (months)										
≤12	169 (92%)	70 (92%)	37 (90%)	62 (93%)	0	5 (28%)	109 (93%)	102 (94%)	7 (88%)	7 (20%)
>12	15 (8%)	6 (8%)	4 (10%)	5 (8%)	0	13 (72%)	8 (7%)	7 (6%)	1 (13%)	28 (80%)
Histopathological cancer type*										
Non-invasive†	53 (29%)	20 (26%)	23 (56%)	10 (15%)	0	2 (11%)	31 (27%)	30 (28%)	1 (13%)	8 (23%)
Invasive‡	128 (70%)	56 (74%)	17 (42%)	55 (82%)	0	16 (89%)	86 (74%)	79 (73%)	7 (88%)	27 (77%)
Unknown or data missing	3 (2%)	0	1 (2%)	2 (3%)	0	0	0	0	0	0
Size of invasive tumours on histology (mm)										
Mean (SD)	15·3 (12·6)	17·5 (14·3)	11·4 (8·9)	14·2 (11·5)	0	15·3 (8·1)	15·1 (8·7)	15·2 (8·9)	14·3 (5·9)	17·7 (8·0)
25th percentile	9·0	10·0	6·0	9·0	0	10·0	9·0	8·0	9·0	12·0
75th percentile	16·0	18·0	14·0	16·0	0	21·0	20·0	21·0	17·0	21·0
Node status of invasive cancers										
Negative	101 (79%)	41 (73%)	13 (77%)	47 (86%)	0	10 (63%)	54 (63%)	47 (60%)	7 (100%)	17 (63%)
Positive	23 (18%)	13 (23%)	2 (12%)	8 (15%)	0	6 (38%)	29 (34%)	29 (37%)	0	10 (37%)
Unknown or data missing	4 (3%)	2 (4%)	2 (12%)	0	0	0	3 (4%)	3 (4%)	0	0

Data are number (%), unless otherwise indicated. MG=mammography. US=ultrasonography. CBE=clinical breast examination. Percentages might not total 100% due to rounding. *Based on the International Classification of Diseases, tenth edition. †Including ductal carcinoma in situ and lobular carcinoma in situ. ‡Including invasive ductal carcinoma and special type.

Table 4: **Histological findings**

	Total (n=72717)	Intervention group (n=36752)	Control group (n=35965)
Recalled after first-round screening	7800 (10·7%)	4647 (12·6%)	3153 (8·8%)
Biopsy done*	2320 (3·2%)	1665 (4·5%)	655 (1·8%)
Fine-needle aspiration	1662 (2·3%)	1227 (3·3%)	435 (1·2%)
Core needle biopsy	583 (0·8%)	407 (1·1%)	176 (0·5%)
Vacuum-assisted biopsy	225 (0·3%)	137 (0·4%)	88 (0·2%)
Surgical biopsy†	66 (0·1%)	42 (0·1%)	24 (0·1%)

Data are number (%). *When clinically indicated, participants might have undergone two or more types of biopsy. †14 (33%) in the intervention group and four (17%) in the control group had breast cancers diagnosed.

Table 5: **Need for biopsy on the basis of first-round screening**

cancers were detected by this method in the control group, which suggests that ultrasonography could replace clinical examination.

The use of adjunctive ultrasonography was associated with a 0·17% overall increase in the screening detection rate. This difference seems to be in accordance with the conclusions of a review which showed that ultrasonography detected an additional 0·03–0·77% of cancers.[17] Of note, though, is that the studies assessed were of heterogeneous design and that particpants were mostly mammography negative, had heterogeneously or extremely dense breasts, and that family history was mixed: some included only first-degree relatives, some included broader family members, one separated *BRCA* mutations from other family history, and some combined family and personal history of breast cancer.[17] Our study design enabled comparison of incidence of interval cancers, which was lower in the intervention group than in the control group. Berg and colleagues[12] and Corsetti and colleagues[13,14] had previously shown low interval cancer rates in women screened with adjunctive ultrasonography. All women in those studies, however, underwent ultrasonography screening and the effect could not be quantified. Our results, therefore, extend these findings.

Specificity was lower in the intervention group than in the control group. This finding is disadvantageous for young women. The first reason for low specificity was the separate categorisation of the mammographic and ultrasound images, which inevitably led to an increased recall rate and reduced specificity. Combined assessment might improve specificity. The JABTS and Japan Association of Breast Cancer Screening (JABCS) have proposed guidelines for combined categorisation from mammographic and ultrasound images.[30] If these guidelines are verified, the recall rate is likely to decrease in routine breast cancer screening programmes. Another reason for low specificity is that ultrasonography can detect some lesions that are not visible on mammography in women with dense breasts. A study in Japan reported that the recall rate of mammography screening among 33924 women aged 40–49 years was 9·9%.[31] The recall rate in our study, however, was lower (8·8%) and within

Panel: Research in context

Systematic review

In 2013, Gartlehner and colleagues[20] reported the results of a systematic review and meta-analysis of mammography plus breast ultrasonography versus mammography alone for breast cancer screening in women at average risk. We searched MEDLINE (OVID), the Cochrane database (CCTR, DARE, and CDSR), and Embase from September, 1977, to November, 2014. The last search was done on Nov 22, 2014. We modified the search strategy of Gartlehner and colleagues, using the keywords "breast neoplasms", "breast cancer", "screening", "mammography", "ultrasound", and "randomised controlled trial" to identify whether any additional randomised controlled trials had been done since this review. Except for J-START reports, we did not identify any appropriate, completed studies. Houssami and Ciatto[21] had reviewed the use of adjunctive ultrasonography for breast screening, but the studies were restricted to women with dense breasts, and no study had used a randomised controlled design. Therefore, we decided to do a randomised controlled trial to compare screening approaches.

Interpretation

Adjunctive ultrasonography was associated with a significantly higher detection rate of breast cancer than mammography alone. Thus, ultrasonography could offer a low-cost way to increase sensitivity and detection rates of early cancers in women with dense breast tissue. Additionally, because stage I breast cancers are more likely to be correctly diagnosed than stage 0 cancers and have better survival than more advanced tumours, this distribution supports the potential for reduction of mortality or incidence of advanced breast cancer. Long-term studies are needed to assess these outcomes.

the target range of routine screening mammography (less than 11%).

To keep screening-associated harm to a minimum is very important.[19,32,33] Kasahara and colleagues[31] reviewed harm associated with screening mammography in 144 848 women in the general population in Japan, and compared the data with those from the Breast Cancer Surveillance Consortium (BCSC) and the JABCS in 2013.[31] Fine-needle aspiration cytology was used in 1·61% of cases in JABCS (no data are available from BCSC) and biopsies, including core needle, vacuum-assisted, and open surgical methods, were used in 0·93% of cases in the BCSC and 0·69% in the JABCS. In our study, the rates for both these assessments were about twice as high, at 3·34% for fine-needle aspiration and 1·59% for biopsies, but the detection rate was also around twice as high (0·50% in our intervention group *vs* 0·26% in BCSC and 0·28% in JABCS). Ultrasonography-guided histological examination is easier, more accurate, and more reliable than clinical observation of the lesions alone, and is the main reason for the increased biopsy rate. In Japan, fine-needle aspiration cytology is preferred to core needle biopsy for lesions thought to be benign, and lesions are histologically assessed when aspiration cytology is negative. Fine-needle aspiration is less harmful than core needle biopsy or surgery, and an increase in biopsy rate might raise the cancer yield, which means that harm overall might be almost equal to that with mammography screening alone.

An important limitation of this study is that sensitivity and specificity were calculated with the data from the first round of screening. Since characteristics of breast cancer, such as distribution of tumour size or sojourn time, would differ between the first and later rounds of screening, our findings cannot be extended beyond the first round.

Irrespective of ethnic origin and Asian versus non-Asian countries, about 60% of women in their 40s are estimated to have dense breasts.[8–10,19] In this study, 57·7% of the women were classified as having dense breasts (scores of 3 or 4 in the American College of Radiology Breast Imaging Reporting and Data System[34]) and will be reported in more detail in the future. Our study makes an important contribution to understanding of the efficacy of adjunctive ultrasonography in breast cancer screening of women aged 40–49 years and provides generalisable data. Ultrasonography could offer a low-cost way to increase sensitivity and detection rates of early cancers in women with dense breasts. Long-term follow-up is needed to assess whether the combined approach could reduce the frequency of advanced breast cancers at detection and breast cancer mortality.

Contributors

NO, TS, SY, and IT designed this study. NO, AS, TS, HS, ET, TE, AF, IT, MF, and TI did the literature search. NO, AS, MK, Y-FZ, YNS, and TI collected the data from the study sites. NO, TS, SY, Y-FZ, SK, AF, IT, TY, and YO planned the statistical analysis and analysed and interpreted the data. NO, AS, TS, MK, SY, Y-FZ, YNS, HS, SK, ET, TE, YO, MF, and TI drafted the paper. MK and Y-FZ did the systematic review. All authors contributed data and reviewed the drafts of the report. NO is the guarantor.

Declaration of interests

We declare no competing interests.

Acknowledgments

This study was support by the third Comprehensive Control Research for Cancer programme of the Japanese Ministry of Health, Labour and Welfare (grant number H18-Senryaku-001, H23-Shitei-002, H25-Shitei-005).

References

1 Green M, Raina V. Epidemiology, screening and diagnosis of breast cancer in the Asia-Pacific region: current perspectives and important considerations. *Asia Pac J Clin Oncol* 2008; **4**: S5–13.

2 Leong SP, Shen ZZ, Liu TJ, et al. Is breast cancer the same disease in Asian and Western countries? *World J Surg* 2010; **34**: 2308–24.

3 Youlden DR, Cramb SM, Yip CH, Baade PD. Incidence and mortality of female breast cancer in the Asia-Pacific region. *Cancer Biol Med* 2014; **11**: 101–15.

4 Matsuda A, Matsuda T, Shibata A, et al. Cancer incidence and incidence rates in Japan in 2008: a study of 25 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. *Jpn J Clin Oncol* 2014; **44**: 388–96.

5 Maskarinec G, Pagano I, Chen Z, Nagata C, Gram IT. Ethnic and geographic differences in mammographic density and their association with breast cancer incidence. *Breast Cancer Res Treat* 2007; **104**: 47–56.

6 Suzuki A, Kuriyama S, Kawai M, et al. Age-specific interval breast cancers in Japan: estimation of the proper sensitivity of screening using a population-based cancer registry. *Cancer Sci* 2008; **99**: 2264–67.

7 Nelson HD, Tyne K, Naik A, et al. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. *Ann Intern Med* 2009; **151:** 727–37, W237–42.

8 Ishihara S, Taira N, Kawasaki K, et al. Association between mammographic breast density and lifestyle in Japanese women. *Acta Med Okayama* 2013; **67:** 145–51.

9 Dai H, Yan Y, Wang P, et al. Distribution of mammographic density and its influential factors among Chinese women. *Int J Epidemiol* 2014; **43:** 1240–51.

10 Bae JM, Shin SY, Kim EH, Kim YN, Nam CM. Distribution of dense breasts using screening mammography in Korean women: a retrospective observational study. *Epidemiol Health* 2014; **36:** e2014027.

11 Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27825 patient evaluations. *Radiology* 2002; **225:** 165–75.

12 Berg WA, Blume JD, Cormack JB, et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. *JAMA* 2008; **299:** 2151–63.

13 Corsetti V, Houssami N, Ghirardi M, et al. Evidence of the effect of adjunct ultrasound screening in women with mammography-negative dense breasts: interval breast cancers at 1 year follow-up. *Eur J Cancer* 2011; **47:** 1021–26.

14 Corsetti V, Houssami N, Ferrari A, et al. Breast screening with ultrasound in women with mammography-negative dense breasts: evidence on incremental cancer detection and false positives, and associated cost. *Eur J Cancer* 2008; **44:** 539–44.

15 Nothacker M, Duda V, Hahn M, et al. Early detection of breast cancer: benefits and risks of supplemental breast ultrasound in asymptomatic women with mammographically dense breast tissue. A systematic review. *BMC Cancer* 2009; **9:** 335.

16 Hooley RJ, Greenberg KL, Stackhouse RM, Geisel JL, Butler RS, Philpotts LE. Screening US in patients with mammographically dense breasts: initial experience with Connecticut Public Act 09-41. *Radiology* 2012; **265:** 59–69.

17 Scheel JR, Lee JM, Sprague BL, Lee CI, Lehman CD. Screening ultrasound as an adjunct to mammography in women with mammographically dense breasts. *Am J Obstet Gynecol* 2015; **212:** 9–17.

18 Chae EY, Kim HH, Cha JH, Shin HJ, Kim H. Evaluation of screening whole-breast sonography as a supplemental tool in conjunction with mammography in women with dense breasts. *J Ultrasound Med* 2013; **32:** 1573–78.

19 Sprague BL, Stout NK, Schechter C, et al. Benefits, harms, and cost-effectiveness of supplemental ultrasonography screening for women with dense breasts. *Ann Intern Med* 2015; **162:** 157–66.

20 Gartlehner G, Thaler K, Chapman A, et al. Mammography in combination with breast ultrasonography versus mammography for breast cancer screening in women at average risk. *Cochrane Database Syst Rev* 2013; 4: CD009632.

21 Houssami N, Ciatto S. The evolving role of new imaging methods in breast screening. *Prev Med* 2011; **53:** 123–26.

22 Irwig L, Houssami N, Armstrong B, Glasziou P. Evaluating new screening tests for breast cancer. *BMJ* 2006; **332:** 678–79.

23 Ohuchi N, Ishida T, Kawai M, Narikawa Y, Yamamoto S, Sobue T. Randomized controlled trial on effectiveness of ultrasonography screening for breast cancer in women aged 40–49 (J-START): research design. *Jpn J Clin Oncol* 2011; **41:** 275–77.

24 Ishida T, Suzuki A, Kawai M, et al. A randomized controlled trial to verify the efficacy of the use of ultrasonography in breast cancer screening aged 40–49 (J-START): 76–196 women registered. *Jpn J Clin Oncol* 2014; **44:** 134–40.

25 Ohuchi N, Yoshida K, Kimura M, et al. Improved detection rate of early breast cancer in mass screening combined with mammography. *Jpn J Cancer Res* 1993; **84:** 807–12.

26 Ohuchi N, Yoshida K, Kimura M, et al. Comparison of false negative rates among breast cancer screening modalities with or without mammography: Miyagi trial. *Jpn J Cancer Res* 1995; **86:** 501–06.

27 Duijm LE, Guit GL, Zaat JO, Koomen AR, Willebrand D. Sensitivity, specificity and predictive values of breast imaging in the detection of cancer. *British J Cancer* 1997; **76:** 377–81.

28 Tohno E, Takahashi H, Tamada T, Fujimoto Y, Yasuda H, Ohuchi N. Educational program and testing using images for the standardization of breast cancer screening by ultrasonography. *Breast Cancer* 2012; **19:** 138–46.

29 Sobin LH, Gospodarowicz MK, Wittekind C, eds. TNM classification of malignant tumours, 7th edn. Chichester: Wiley-Blackwell, 2010.

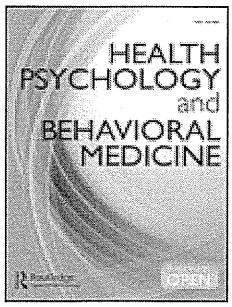
30 Tohno E, Ueno E, Watanabe H. Ultrasound screening of breast cancer. *Breast Cancer* 2009; **16:** 18–22.

31 Kasahara Y, Kawai M, Tsuji I, et al. Harms of screening mammography for breast cancer in Japanese women. *Breast Cancer* 2013; **20:** 310–15.

32 US Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2009; **151:** 716–26, W-236.

33 Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. *Lancet* 2012; **380:** 1778–86.

34 Sickles EA, D'Orsi CJ, Bassett LW, et al. ACR BI-RADS® Mammography. In: D'Orsi CJ, Sickles EA, Mendelson EB, et al. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System, 4th edn. Reston, VA: American College of Radiology, 2003.



Routledge
Taylor & Francis Group

Health Psychology and Behavioral Medicine
An Open Access Journal

ISSN: (Print) 2164-2850 (Online) Journal homepage: http://www.tandfonline.com/loi/rhpb20

The relationship between obtaining fecal occult blood test and beliefs regarding testing among Japanese

Toshiatsu Taniguchi, Kei Hirai, Kazuhiro Harada, Yoshiki Ishikawa, Miwa Nagatsuka, Jun Fukuyoshi, Hirokazu Arai, Yuri Mizota, Seiichiro Yamamoto, Hiroshi Saito & Daisuke Shibuya

To cite this article: Toshiatsu Taniguchi, Kei Hirai, Kazuhiro Harada, Yoshiki Ishikawa, Miwa Nagatsuka, Jun Fukuyoshi, Hirokazu Arai, Yuri Mizota, Seiichiro Yamamoto, Hiroshi Saito & Daisuke Shibuya (2015) The relationship between obtaining fecal occult blood test and beliefs regarding testing among Japanese, Health Psychology and Behavioral Medicine, 3:1, 251-262, DOI: 10.1080/21642850.2015.1084473

To link to this article: http://dx.doi.org/10.1080/21642850.2015.1084473

Published online: 12 Sep 2015.

Health Psychology & Behavioural Medicine, 2015
Vol. 3, No. 1, 251–262, http://dx.doi.org/10.1080/21642850.2015.1084473

Taylor & Francis
Taylor & Francis Group

The relationship between obtaining fecal occult blood test and beliefs regarding testing among Japanese

Toshiatsu Taniguchi[a*], Kei Hirai[b], Kazuhiro Harada[c], Yoshiki Ishikawa[d], Miwa Nagatsuka[e], Jun Fukuyoshi[f], Hirokazu Arai[g], Yuri Mizota[h], Seiichiro Yamamoto[i], Hiroshi Saito[j] and Daisuke Shibuya[k]

[a]Tottori Seikyo Hospital, 458 Suehiroonsenn-cho, Tottori-shi, Tottori 680-0841, Japan; [b]Department of Complementary and Alternative Medicine, Graduate School of Medicine, Osaka University, Sunren Honbu B-2F2-1 Yamadaoka, Suita-shi, Osaka 565-0871, Japan; [c]Section for Physical Function Activation, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka-machi, Obu-shi, Aichi 474-8511, Japan; [d]Department of Health and Social Behavior, School of Public Health, The University of Tokyo, Bunkyo-ku, C:1-8-3 Dougenzaka, Shibuya-ku, Tokyo 150-0043, Japan; [e]National Hospital Organization Osaka Medical Center, 2-1-14 Houzenzaka, Chuo-ku, Osaka-shi, Osaka 540-0006, Japan; [f]Cancer Scan, 1-8-3 Dougenzaka, Shibuya-ku, Tokyo 150-0043, Japan; [g]Department of Psychology, Faculty of Letters, Hosei University: 2-17-1 Fujimi, Chiyoda-ku, Tokyo 102-8160, Japan; [h]Public Health Policy Research Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1, Tukiji, Chuo-ku, Tokyo 104-0045, Japan; [i]Public Health Policy Research Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1, Tukiji, Chuo-ku, Tokyo 104-0045, Japan; [j]Screening Assessment & Management Division, National Cancer Center, 5-1-1 Tukiji, Chuo-ku, Tokyo 104-0045, Japan; [k]Cancer Detection Center, Miyagi Cancer Society, 5-7-30 Uesugi, Aoba-ku, Sendai-shi, Miyagi, Japan

(*Received 18 April 2015; accepted 15 August 2015*)

Purpose: We examined the relationship between fecal occult blood test (FOBT) screening behavior and beliefs regarding FOBT screening in order to formulate effective measures to improve FOBT screening rates. *Method:* In June 2010, we conducted a cross-sectional questionnaire survey of 600 randomly selected individuals aged 40–60 years who were registered participants of Refine, which was an internet research company to cooperate with this study. We assessed CRC knowledge, perceived risk of CRC, perceived severity of CRC, concern for CRC, beliefs of FOBT screening, FOBT screening behavior, and demographic variables. *Result:* There were 592 valid responses (from 294 males and 298 females; mean age 53.96 ± 8.39) in the final analysis. A total of 266 (44.9%) underwent FOBT in the year preceding the survey. Factor analysis relating to the beliefs of obtaining FOBT demonstrated five factors ($\alpha = 0.829$) including: (1) *perceived barrier*, (2) *subjective norms*, (3) *low importance*, (4) *descriptive norms*, and (5) *non-necessity. Descriptive norms* were found to be a promoting factor (OR = 1.18, CI = 1.09–1.28), and *perceived barrier* (OR = 0.88, CI = 0.84–0.94) and *low importance* (OR = 0.91, CI = 0.82–0.99) were inhibiting factors of FOBT screening behavior. *Conclusion:* This study suggests the following three actions can effectively improve the cancer screening rate: (1) promotion of public awareness that everyone should be regularly screened for cancer, (2) informing the public about the ease of obtaining FOBT, and (3) promotion of the importance of FOBT.

*Corresponding author. Email: tt.m04126e@gmail.com

Keywords: colorectal cancer; CRC screening behavior; FOBT; beliefs of FOBT

1. Introduction

While the global colorectal cancer (CRC) incidence is increasing, the incidence in Japan has had a particularly large recent increase (Center, Jemal, & Ward, 2009). It is widely accepted that early detection and treatment of CRC can improve prognosis, and that fecal occult blood testing (FOBT) and colonoscopy significantly decrease CRC mortality rates (Lee et al., 2007; Levin et al., n.d.; Nancy et al., 2009; Rex, Johnson, Lieberman, Burt, & Sonnenberg, 2000; Saito et al., 1995; Zauber et al., 2012). CRC screening guidelines in Japan recommend a yearly FOBT (a 2-day immunochemical FOBT) as the first stage of CRC screening in people over 40 years of age. The government notifies the eligible individuals with a recommendation to undergo FOBT for CRC screening, which includes the description of how and where to receive the FOBT kit and the price of the kit. Then the eligible individuals are expected to contact the predetermined hospital to receive the FOBT kit, collect the samples, and submit it to the clinic for testing (Tomotaka et al., 2005). The cost of FOBT varies depending on the municipality of residence, but the municipality partially bears the cost, which in turn lowers the cost born by the eligible individual to less than 1000 JPY (about 8 USD). However, a recent research shows that the CRC screening rate in Japan remains low at under 30% (Matsuda et al., 2012), which needs to be increased in order to raise awareness of CRC screening. It is clear that improving the CRC screening rate is essential to prevent CRC-related deaths strongly. It is also essential to clarify what psychological factor affects the screening behavior.

Several previous studies have described predictors associated with CRC screening behavior, including high income, education level, health insurance (Liang, Phillips, Nagamine, Ladabaum, & Haas, 2006; Rawl et al., 2005), physician and family recommendations, fear and knowledge of CRC, and health literacy (de Bosset, Atashili, Miller, & Pignone, 2008; Manne et al., 2002; Ng, Tan, Teo, Seah, & Phua, 2007; Peterson, Dwyer, Mulvaney, Dietrich, & Rothman, 2007). Then predictors of whether or not a person follows guidelines of FOBT screening include age, type of medical insurance, recommendation from a healthcare provider, knowledge of CRC and FOBT (procedure, importance of FOBT, and cancer curability), and perceived discomfort of collecting stool samples (de Bosset et al., 2008; Jones, Devers, Kuzel, & Woolf, 2010; Liang et al., 2006; Manne et al., 2002; Matsuda et al., 2012; Ng et al., 2007; Peterson et al., 2007; Rawl et al., 2005). In Japan, these predictors have been researched in gastric and breast cancer screening behavior. Research of cancer screening predictors regardless of the cancer type revealed an association between targets' behavior and demographic factors such as age, income, medical insurance, regularity of hospital visits, and education background (Watanabe, 2003). Gastric cancer screening research based on the Health Belief Model (Janz & Becker, 1984) described a negative correlation between 'seriousness' and 'barriers' (Tsubono, Fukao, Hisamichi, Sugawara, & Hosokawa, 1993). Additionally, a similar survey targeting breast cancer patients indicated that 'barrier of screening', 'low importance', and 'subjective norms' influence screening behavior (Nagatsuka, Arai, & Hirai, 2009; Seki et al., 2011).

It has been believed that extremely low awareness toward CRC and its screening programs results in the present status of screening participation. However, factors influencing CRC screening behavior have never been investigated in Japan. Knowledge of the current CRC screening situation and identification of modifiable cognitive factors including individual attitudinal factors are essential to formulate effective measures to improve screening rates. The purpose of this study is to examine the relationship between FOBT screening behavior and beliefs relating to FOBT.

2. Method

2.1. *Participants and survey design*

A population-based cross-sectional survey targeting regional residents was conducted through the internet in late June 2010. We requested registered participants of Refine, which was an internet research company to cooperate with this study. As numerical standards of participation of CRC screening (FOBT) are set for the populationaged 40–69, the age eligibility for this study was 40–69 years of age. In addition, we excluded from the study people with histories of CRC or ulcerative colitis, or who are involved in the healthcare industry, the pharmaceutical industry, or medical equipment manufacturing and distribution. We then extracted 600 participants as eligible candidates after equalizing the number of candidates in each age and gender group.

2.2. *Ethical considerations*

We commissioned an internet research company to perform the survey, and our researchers did not meet the participants in person. We converted the collected private information and response data into ID numbers to make each candidate anonymous. The first page of the questionnaires clearly described that the personal identifiable information would not be disclosed, and the collected data would only be used for this study and would be disposed of after a certain period. This study was approved by the Ethics Committee of Osaka University, Graduate School of Human Science.

2.3. *Measures*

We created a questionnaire with reference to the established theoretical models of health behavior including the Health Belief Model (Janz & Becker, 1984), the Theory of Planned Behavior (Ajzen, 1991), Trans-theoretical Model (Prochaska & Velicer, 1997), and social cognitive theory (Bandura, 1998) in previous studies (Subramanian, Klosterman, Amonkar, & Hunt, 2004), all of which can be used to assess CRC screening behavior. We created the questionnaire for this study after discussions involving graduate students majoring in psychology, researchers of medical psychology, medical social workers, and clinical psychologists. We modified the questionnaire items used by previous studies in Western populations as some items were considered unsuitable for Japanese culture.

2.3.1. *Background variables*

Demographics and health: The variables recorded for demographics and health were (1) age and gender, (2) smoking habits, (3) drinking habits, (4) exercising habits, (5) cancer insurance, (6) familial history of CRC, and (7) regularity of hospital visits.

CRC knowledge: Thirteen items testing CRC knowledge were asked including the nature of CRC morbidity and mortality, risk of CRC morbidity, and CRC screening tests. We developed these items with reference to our previous studies (Nagatsuka et al., 2009; Seki et al., 2011). Subjects were asked whether they already had knowledge of each item (I already know/I did not know), and the answers were subjected to a CRC knowledge assessment.

Exposure to CRC screening information: The information source for CRC knowledge screening consisted of 10 variables including TV commercials, magazines, and direct mails from public administrations. We asked participants how often they have been exposed to these information sources, and the result was measured using a 6-point Likert scale (1 = never seen, 6 = frequently seen).

2.3.2. *Psychological variables*

Perceived risk of CRC: Perceived risk has been assessed in many studies (Janz & Becker, 1984). In this study, 3 items were used with reference to previous studies (Liang et al., 2006; Seki et al., 2011): (1) personal risk for CRC in males in the same age group measured with a 3-point Likert scale (*1 = lower, 3 = higher*); (2) personal risk for CRC in females in the same age group measured with a 3-point Likert scale (*1 = lower, 3 = higher*); and (3) a 0–100 scale rating of lifetime risk of CRC morbidity.

Perceived severity: In this assessment, we used two items with reference to the gastric cancer severity assessment by Tubono (Tsubono et al., 1993): (1) If you are diagnosed with CRC, how curable do you think it is? (1 = almost incurable, 5 = absolutely curable) and (2) How much easier is it to cure CRC than to cure other illnesses? (1 = much more difficult, 5 = much easier).

CRC worry: Four items with referenced to Lerman et al. (1991) were used to assess the degree of CRC worry. These items include an assessment of degree of worry about undergoing CRC screening and its impact on mood and daily life. The items were measured by a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree).

Beliefs of FOBT: Twenty-two items about beliefs regarding undergoing FOBT were developed with reference to three previous studies (Liang et al., 2006; Matsuda et al., 2012; Vernon, Myers, & Tilley, 1997). These items were constructed on the assumption of four psychological factors including *perceived barrier, low importance, subjective norm,* and *descriptive norm.* We modified *perceived barrier* and *low importance*, which were confirmed to be valid in previous studies about breast cancer screening in Japan (Seki et al., 2011), to make them suitable for CRC screening. We also adopted *subjective norm* and *descriptive norm* as questionnaire items because they are reportedly associated with CRC screening behavior (Sieverding, Matterne, & Ciccarello, 2010). Participants were presented with an item: 'Read each question about thoughts and environment that may exist assuming that you are undergoing an FOBT, and choose a number that corresponds to your response', which measured the level of agreement using a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree).

Self-efficacy: Self-efficacy is one of the main predictors of health behaviors (Bandura, 2004), and previous studies that investigated the predictors of screening behavior have adopted self-efficacy (Galvin, Fu, Nguyen, Glasheen, & Scharff, 2008; Salz et al., 2009). In this study, we adopted eight items that were used by Togari, Yamazaki, Koide, and Miyata (2006) in an assessment of self-efficacy for health management, for example, 'I think I can manage my health well' and 'I usually manage my health well'. The level of agreement on the items was measured by a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree).

2.3.3. *Outcome variable*

Current FOBT-screening behavior: FOBT was used for CRC screening in this study because FOBT is generally considered as the standard for CRC screening in Japan. We explained the details of the FOBT procedure in the space above the question to provide an understanding of the correct way to take the test. Furthermore, since yearly FOBT screening is recommended, we provided a simple question: 'Have you done FOBT in the past year?' to assess current FOBT screening behavior.

2.4. *Statistical analyses*

Initially, we checked ceiling effect and floor effect of 22 items regarding beliefs of FOBT. Secondly, we employed the maximum likelihood method and the promax rotation method to analyze an exploratory factor. After extracting the factor structure, we performed the confirmatory

factor analysis using the maximum likelihood method to test whether the extracted factor structure fitted the data. Then, we calculated the total score of each subscale and performed univariate logistic regression analyses to assess the association between the FOBT screening state and each independent variable. Finally, we performed multiple logistic regression analyses to assess the association between beliefs of FOBT screening and FOBT screening behavior. The choice of moderator variables was made with reference to a p value of less than 0.25 in bivariate analysis results. For all analyses, we analyzed dates using the two-tailed test, with p value of less than .05 considered statistically significant. A likelihood ratio test determined statistical significance of predictors for multiple logistic regression analyses. SPSS for Windows 17.0J was used for all statistical analyses except for the confirmatory factor analysis, for which AMOS 14.0J was used.

3. Result

3.1. *Background of participants*

Of 600 participants, 592 (294 males and 298 females) responded to the questionnaire completely (98.7% response rate). The mean age of participants was 53.96 ± 8.39 years (range 40–69). A summary of other variables is presented in Table 1. Table 2 shows the results of CRC knowledge. The most unacknowledged item was 'CRC is the second most common cancer among Japanese' (16.6%). On the other hand, 'Most people are cured if the CRC is detected early' (77.0%) was the most acknowledged item. Finally, 266 participants (44.9%) underwent FOBT in the past year. We found a significant difference only in those subjects in their 60s, and also noticed that more males tended to get the FOBT than females ($\chi^2 = 4.50$, $p = .047$).

3.2. *Beliefs of FOBT*

Initially, we specified skewed items in the 22 items used to assess the beliefs regarding FOBT. Although a slight occurrence of floor effects was observed during the assessment of four items

Table 1. Demographics and health states ($n = 592$).

	% or mean(SD)
Demographics	
Age	54.0(8.39)
Gender	
Male	49.7
Female	50.3
Region of residence	
Hokkaido/Tohoku	7.1
Kanto	42.7
Hokuriku/Chubu	14.4
Kinki	21.8
Chugoku/Shikoku	6.9
Kyushu/Okinawa	7.1
Health states	
Cancer insurance	51.2
Familial history of CRC	13.0
Smoking habits	46.5
Drinking habits	62.8
Exercising habits	32.6
Regular hospital visit	40.4
Exposed information	21.8(8.8)

Table 2. Result of CRC knowledge.

Items	Already knew	%
Most people are cured if the colorectal cancer is detected early	456	77.0
The first screening test to detect a colorectal cancer is a stool test (FOBT)	411	69.4
A colorectal cancer with symptoms accompanied by bloody stool is already advanced in many cases	366	61.8
The risk for colon cancer is high if there is a family history of colon cancer	342	57.8
A colonoscopy is carried out when the FOBT result is positive	341	57.6
A lifestyle is related to the cause of colon cancer	337	56.9
A colorectal cancer is a preventable disease	273	46.1
The risk of a colon cancer increases as the age advances	247	41.7
Colorectal cancer is a disease resulting from an expanding malignant growth in the colon and the rectum	225	38.0
A colorectal cancer is the second most common cancer among Japanese	98	16.6

categorized in *Subjective norms*, we considered these items important in this study and decided to use them in the subsequent analysis. We then yielded a 5-factor structure to analyze the exploratory factor of the 22 items by using the maximum likelihood method and the promax rotation method. We deleted items with a factor loading of less than 0.4, then reanalyzed 20 items and determined a 5-factor structure. We interpreted these subscales as: (1) *Perceived barrier*, (2) *Subjective norms*, (3) *Low importance*, (4) *Descriptive norms*, and (5) *Non-necessity*. Calculating internal consistency (Cronbach's alpha coefficients) of this scale indicated that the coefficient alpha was .829 for the total score. Alpha ranged from .61 for *Non-necessity* to .92 for *Subjective norms* for this subscale (Table 3). Additionally, we determined the validity of this scale by adopting the confirmatory factor analysis using the maximum-likelihood method. We obtained adequate fit index as the result of a confirmatory factor analysis regarding the models of these five factors: chi-square (df = 163) = 665.78, $p < .001$; GFI = 0.89; AGFI = 0.86; RMSEA = 0.072.

3.3. *Relationship between beliefs of FOBT and FOBT-screening behavior.*

Results of univariate logistic analysis indicated that *Perceived barrier* (OR = 0.83, 95% CI = 0.80–0.86), *Subjective norm* (OR = 1.07, 95% CI = 1.03–1.11), *Low importance* (OR = 0.75, 95% CI = 0.70–0.80), and *Descriptive norm* (OR = 1.31, 95% CI = 1.22–1.41) were associated with Beliefs of FOBT (OR = 1.02, 95% CI = 0.96–1.10). Then we conducted a multiple logistic regression analysis, which indicated that predictors of FOBT screening were *Perceived barrier* (OR = 0.87, 95% CI = 0.84–0.92), *Low importance* (OR = 0.91, 95% CI = 0.84–0.99), and *Descriptive norm* (OR = 1.18, 95% CI = 1.09–1.28) (Table 4).

4. Discussion

Despite the fact that FOBT is part of the recommended CRC screening in Japan, the screening rate remains low. An effective measure is needed to raise the CRC screening rate in Japan. In this study we intended to elucidate the relationship between FOBT screening behavior and beliefs of FOBT, both of which are manipulative variables.

Firstly, we extracted *Perceived barrier* and *Low importance* as inhibiting factors of FOBT screening behavior. *Perceived barrier* consisted of inconvenient operating hours of medical institutions performing FOBT, waiting time, and cost. *Perceived barrier* shows an association with structural barriers such as cost and unsuitable screening hours that are revealed in this study,